EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

23 March 2017
EMA/CHMP/232746/2017
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Trumenba

Common name: meningococcal group b vaccine (recombinant, adsorbed)

Procedure No. EMEA/H/C/004051/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

4CMenB	Multicomponent meningococcal serogroup B vaccine
ABC	Active Bacterial Core
AE	adverse event
AlPO4	aluminum phosphate
ANSM	Agence Nationale de Sécurité du Medicament
Anti-TPO	anti-thyroid peroxidise
AS	active substance
CC	Clonal complex
CFR	Code of Federal Regulation
CFU	Colony forming units
cHAP	ceramic hydroxyapatite chromatography
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
cLIA	competitive Luminex immunoassay
CPP	critical process parameter
CRM197	cross-reactive material-197
CSR	clinical study report
dTAP	low-dose diphtheria, tetanus, and low-dose acellular pertussis vaccine
e-diary	electronic diary
EIP	Evaluable Immunogenicity Population
EU	European Union
EVA	ethylvinylacetate
FDA	Food and Drug Administration
fH	Factor H
fHBP	factor H binding protein (referring to the bacterial lipoprotein expressed on surface of *N meningitidis*)
FMEA	Failure Modes and Effects Analysis
FP	finished product
GCP	Good Clinical Practice
GD	Gestation day
GMR	geometric mean ratio
GMT	geometric mean titer
HAV	hepatitis A virus vaccine
HCP	host cell protein
HPV	human papilloma virus vaccine
hSBA	serum bactericidal assay using human complement
ICD	informed consent document
ICH	International Conference on Harmonisation
IgA	Immunoglobulin A
IgG	Immunoglobulin G
IM	Intramuscular
IMAC	Immobilized metal affinity chromatography
IMD	invasive meningococcal disease
IPC	in process control
IPT-C	in process test for control
IPT-M	in process test for monitor
IPV	inactivated poliomyelitis virus vaccine
ISE	integrated summary of efficacy
ISS	integrated summary of safety
IVRA	in vitro antigenicity assay
iTT	intent-to-treat
IEX-HPLC	Ion-exchange high performance liquid chromatography
LAL	Limulus amoebocyte lysate assay
LCI	lower bound confidence interval
LLOQ	lower limit of quantitation
LOD	limit of detection
LOS	lipooligosaccharide
LP2086	lipoprotein 2086 (referring to the recombinant fHBP or fHBP vaccine antigen)
LXA	Luminex assay
MAA	marketing authorization application

MAC	membrane attack complex
MAE	medically attended adverse event
MCB	master cell bank
MCC	meningococcal serogroup C conjugate
MCV4	quadrivalent meningococcal polysaccharide conjugate vaccine, Menactra
MedDRA	Medical Dictionary for Regulatory Activities
MFI	Mean fluorescence intensity
mITT	modified intent-to-treat
MLST	multi-locus sequence type
MnB	*Neisseria meningitidis* serogroup B
MnC	*Neisseria meningitidis* serogroup C
MnW	*Neisseria meningitidis* serogroup W
MnY	*Neisseria meningitidis* serogroup Y
MPSV4	meningococcal polysaccharide vaccine
MRI	magnetic resonance imaging
NA	not applicable or not available
NaCl	sodium chloride
NCA	National Competent Authority
NDCMCs	newly diagnosed chronic medical conditions
NOEL	No observed effect level
NOR	normal operating range
OMV	outer membrane vesicle
PAR	proven acceptable range
PIP	Pediatric Investigation Plan
Por A	porin A
Por B	porin B
PPD	Post-partum day
PPV	positive predictive value
PS80	polysorbate 80
PT	preferred term
RCDC	reverse cumulative distribution curve
rLP2086	recombinant lipoprotein 2086
RR	respiratory rate
RP-HPLC	reverse phase high performance liquid chromatography
RPT	rabbit pyrogenicity test
rSBA	serum bactericidal assay using baby rabbit serum as complement source
SAE	serious adverse event
SAP	statistical analysis plan
SBA	serum bactericidal assay
SD	standard deviation
SEC-HPLC	size exclusion chromatography (high performance liquid chromatography)
SOC	System organ class
SUSAR	suspected unexpected serious adverse reaction
Tdap	tetanus, low-dose diphtheria, and low-dose acellular pertussis vaccine
TSH	thyroid stimulating hormone
UFDF	ultrafiltration and diafiltration
URTI	upper respiratory tract infection
US	United States
WCB	working cell bank
WFI	water for injection
WHO	World Health Organization

1. Background information on the procedure

1.1. Submission of the dossier

The Applicant Pfizer Limited submitted on 22 April 2016 an application for marketing authorisation to the European Medicines Agency (EMA) for Trumenba, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004.

The Applicant applied for the following indication:

Trumenba is indicated in individuals 10 years and older for active immunisation to prevent invasive meningococcal disease caused by Neisseria meningitidis serogroup B.

See section 5.1 for information on protection against specific group B strains.

Dosing of Trumenba should be determined taking into consideration the risk of invasive meningococcal B disease by each country or region. The use of this vaccine should be in accordance with official recommendations.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application. The Applicant indicated that *Neisseria meningitidis* serogroup B bivalent lipoprotein (recombinant lipidated fHbp (factor H binding protein) subfamily A and B) was considered to be a new active substance.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on Applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0304/2015 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0304/2015 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the Applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

New active Substance status

The Applicant requested the active substance, *Neisseria meningitidis* serogroup B bivalent lipoprotein (recombinant lipidated fHbp (factor H binding protein) subfamily A and B) contained in the above medicinal product to be considered as a new active substance, as the Applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

Scientific Advice

The Applicant received Scientific Advice from the CHMP on 23 October 208, 19 November 209, 20 January

2011, 19 May 2011, 19 July 2012 and 23 April 2015. The Scientific Advice pertained to insert quality, non-clinical and clinical aspects of the dossier.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Johann Lodewijk Hillege Co-Rapporteur: Kristina Dunder

- The application was received by the EMA on 22 April 2016.
- The procedure started on 19 May 2016.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 4 August 2016. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 4 August 2016. The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on 18 August 2016.
- During the meeting on 15 September 2016, the CHMP agreed on the consolidated List of Questions to be sent to the Applicant.
- The Applicant submitted the responses to the CHMP consolidated List of Questions on 22 November 2016.
- The Rapporteurs circulated the Joint Assessment Report on the Applicant's responses to the List of Questions to all CHMP members on 6 January 2017.
- During the PRAC meeting on 12 January 2017, the PRAC agreed on the PRAC Assessment Overview and Advice to CHMP.
- During the CHMP meeting on 26 January 2017, the CHMP agreed on a List of Outstanding Issues to be addressed in writing by the Applicant.
- The Applicant submitted the responses to the CHMP List of Outstanding Issues on 20 February 2017.
- The Rapporteurs circulate the Joint Assessment report on the Applicants responses to the List of Outstanding 8 March 2017.
- The Rapporteurs circulated an updated report on the Applicants responses on 16 March 2017.
- During the meeting on 20-23 March 2017, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Trumenba on 23 March 2017.

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Trumenba is intended for active immunisation to prevent invasive meningococcal disease caused by *Neisseria meningitidis* serogroup B in individuals 10 years and older.

N. meningitidis is an obligate human pathogen that colonizes the upper respiratory tract and in some individuals can cause serious, life-threatening disease. Transmission with *N. meningitidis* is via contact with droplets from the upper respiratory tract, typically resulting in colonization and asymptomatic carriage in otherwise healthy individuals. Under certain instances, that are not well understood, *N. meningitidis* is capable of invading the human host, leading to bacteraemia which then manifests as life-threatening invasive meningococcal disease.

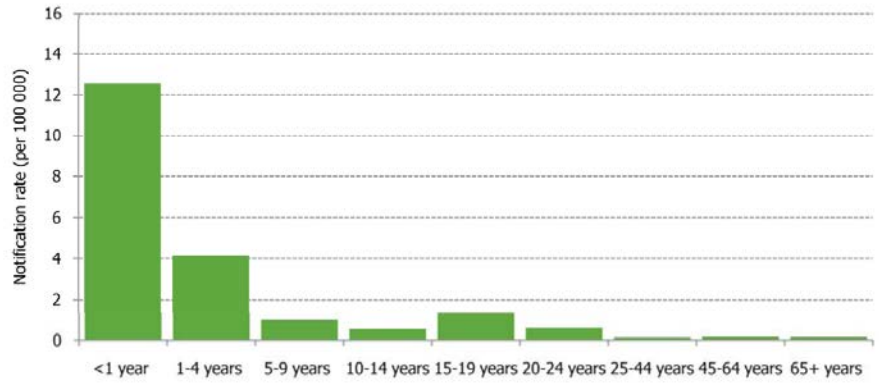
2.1.2. Epidemiology and risk factors, screening tools / prevention

Of the 12 identified serogroups of *N. meningitidis*, 6 (A, B, C,W,X and Y) are responsible for virtually all meningococcal diseases globally. In Europe, meningococcal disease has been declining in general over the past decade. This decline can be attributed, in part to the introduction of meningococcal serogroup C conjugate vaccine programs; however invasive meningococcal disease caused by *N. meningitidis* serogroup B (MnB) has also declined. In 2007, overall meningococcal rates were 3.76 per 100,000 in Ireland and 2.50 per 100,000 in the United Kingdom but had decreased to 1.31 in Ireland and 1.36 in the United Kingdom by 2012.

Endemic Disease

MnB is a significant cause of endemic meningococcal disease worldwide, which can occasionally occur in outbreaks of limited duration or as prolonged epidemics. In Europe approximately 60-72% of Invasive Meningococcal Disease (IMD) cases since 2000 have been attributed to MnB. Similar to overall meningococcal disease, the greatest burden of MnB disease in Europe occurs in children <5 years of age (peak incidence in England and Wales has been reported in infants under 5 months of age) with another peak of disease occurring in adolescents and young adults (Figure 1).

Figure 1. Age-Group-Specific Notification Rates (per 100 000) of Serogroup B Invasive Meningococcal Disease, 2009



Population data: Eurostat
Contributing countries: Austria, Belgium, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Lithuania, Malta, Netherlands, Norway, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden and the United Kingdom.

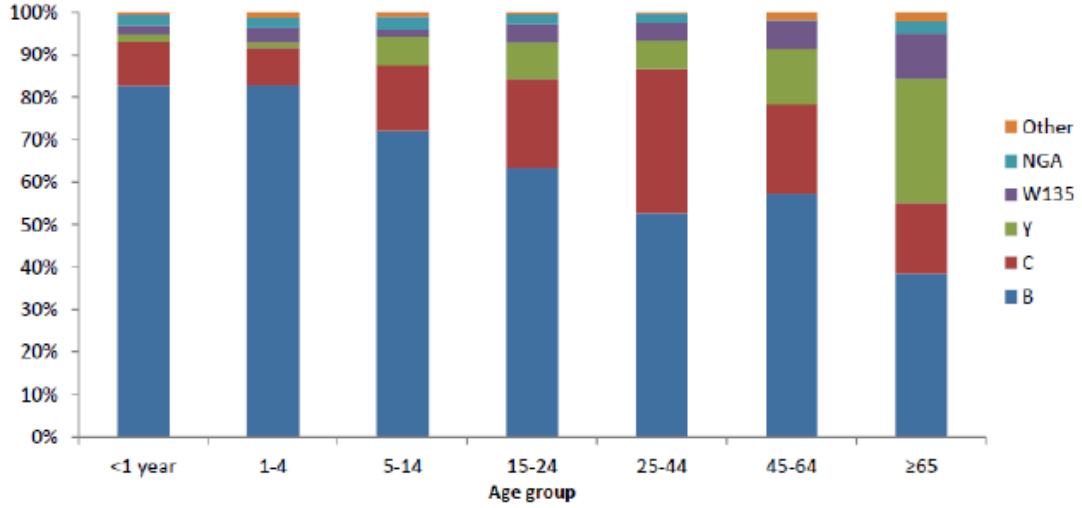
In 2009, the incidence of disease in 15-19 year old individuals in Europe was reported to be 1.7 per 100,000. During the 2013/2014 epidemiological year in England, 75 MnB cases were observed in those aged 10 to 24 years old (17% of the total MnB cases), with the majority (56%) of cases observed in children less than 5 years of age.

The peak in incidence in adolescents and young adults is believed to be due to increased social mixing and exposure to new strains of *N. meningitidis* while in closed, crowded communities such as classrooms, dormitories, and military institutions, and due to the higher frequency of risk behaviours such as smoking. It is also thought that these behaviours and environmental risks contribute to the observation that adolescents and young adults have peak carriage rates of meningococci. As seen with the introduction of MnC conjugate vaccination programs, adolescents and young adults are an important target population for vaccination if the objective is to interrupt transmission of meningococci.

Meningococcal disease incidence in older individuals tends to be lower than that observed in infants, young children and young adults. The disease incidence in the EU during 2012 in those aged 45 to 64 years and 65 years above was approximately 0.2-0.5 per 100,000, compared to infants and young children where incidence is around 5 per 100,000 or young adults (aged 15 to 24 years) where it is approximately 1 per 100,000.

It has been reported that there is greater diversity in the serogroups responsible for meningococcal disease in older age groups. Data from the EU/EEA region (Figure 2), for the distribution of serogroups by age, show that while serogroups B and C are the main cause of disease in infants, young children, and young adults, in those aged 45 years and above disease rates caused by other serogroups, such as W and Y, are increased.

Figure 2. Rates of Confirmed Invasive Meningococcal Disease Reported Cases by Age and Serogroup, EU/EEA, 2012



Source: Country reports; NGA: non-groupable.; 'Other' includes confirmed cases reported as serogroup 'other' (n=15), as serogroup A (n=12), serogroup 29E (n=3) and serogroup Z (n=1). The specific codes are kept for the most common serogroups. Others are the remaining/other groupable serogroups that should be reported.

Overall, while the incidence of endemic disease has decreased in all age groups and is currently at a relatively low level globally, MnB disease can be devastating.

Hyperendemicity

As compared to the relatively low national rate, hyper-endemic or persistently high levels of MnB disease have been reported in some regions of Europe and the US. For example, in the past 10 to 12 years higher

disease rates have been observed in two regions in France. In the city of Dieppe, in the Seine-Maritime department between 2003-2006 the incidence of MnB disease was observed to be 8.6 per 100,000, and between 2008-2009 in the Landes department, the annual incidence was 3 per 100,000 which was five times the national average. A period of hyper-endemic MnB disease was found in the Netherlands starting in 1982 and peaking in 1993 when the rate reached 3.43 per 100,000 but then subsequently decreased to 0.39 per 100,000 in 2012.

Outbreaks

MnB can cause protracted outbreaks, despite use of chemoprophylaxis with ciprofloxacin and promotion of control measures. Over the past 10 years several outbreaks have been recorded in Europe in various settings including kindergarten classes, nursery schools and a family cluster. Several outbreaks at US universities have also been observed.

Carriage

Predicting an individual's risk of contracting IMD is difficult. Humans are the only known reservoir for *N. meningitidis*. While approximately 10% of the population carries the bacterium in their oropharynx, most remain asymptomatic. Though infants have the highest risk of disease, carriage of *N. meningitidis* is infrequent in infants. Carriage rates increase through childhood, peak in late adolescence, and decline in older adults. The highest rates of carriage are observed in adolescents and young adults, often notable among individuals living in university and college dormitories and military barracks, making these groups important targets for implementation of a preventive vaccination strategy.

The temporal trends in meningococcal disease and serogroup epidemiology make it difficult to predict a person's risk of IMD and disease rates in a population. Meningococcal disease epidemiology is dynamic, unpredictable, and can rapidly change. Surveillance of meningococcal disease requires robust systems to fully elucidate the dynamic nature of the disease and carriage strain epidemiology. The collection of both serological (serogrouping) and molecular (multilocus sequence type [MLST], Clonal Complexes) information has been useful in informing on trends for different serogroups and hyper-invasive lineages of meningococci. For MnB, it has been critical to collect additional information on non-capsular antigen expression to understand the diversity of strains that cause MnB disease. This has included determination of Porin A (PorA), Porin B (PorB), FetA and lipooligosaccharide (LOS) immunotypes. Epidemiological databases use these markers to provide an overview by region and country of MnB strain diversity at the molecular level.

Studies have confirmed that most MnB meningococci express an fHBP variant and that all fHBP variants can be classified into 1 of 2 immunologically distinct subfamilies (subfamily A or B). Significant differences in age group and regional differences in the distribution of fHBP variants expressed by MnB disease strains have been noted.

The majority (70%) of invasive MnB isolates studied by the sponsor express subfamily B fHBP variants, but this subfamily distribution does change as a function of age. Approximately 80% of invasive isolates from patients 10-25 years of age express subfamily B fHBP variants, while the prevalence of fHBP subfamily A and B variants is equivalent among isolates from patients <1 year and > 65 years of age. By way of comparison, nearly 83% of carriage isolates studied from individuals 10-25 years of age express fHBP variants from subfamily A.

Further, isolates lacking the fHBP gene have been identified but are rare, and are estimated to represent 0.04% of all the isolates that caused disease in England, Wales, and Northern Ireland over a 35-year period. Similar strains have not been identified in other countries.

MLST analysis of MnB diversity has been used for both routine surveillance but also in investigations of outbreaks. Because the distribution and expression of fHBP variants does not correlate with MLST or

clonal complex types for MnB, initiatives to predict the impact of new MnB vaccines will require surveillance programs to monitor the epidemiology of fHBPs.

Immune response

Protection against meningococcal infection is mediated by antibody and/or complement recognition of bacterial cell surface constituents such as capsular polysaccharide or outer membrane proteins leading to activation of the classical and/or alternative complement pathways. Both pathways result in the formation of a membrane attack complex (MAC) that is directly responsible for bacterial destruction. The bactericidal mechanism can be described as follows:

1. anti-meningococcal antibody binds to the target bacteria;
2. complement component C1q binds to the Fc portion of the bound immunoglobulin;
3. the classical complement cascade is initiated, ultimately resulting in the formation of a membrane attack complex late in the cascade by complement components C5-C9; and
4. insertion of the membrane attack complex into the meningococcal membrane resulting in bacterial cell lysis

2.1.3. Clinical presentation

MnB disease has a sudden onset and fast progression, even in healthy individuals. Patients may initially present with a nonspecific febrile illness characterized by headache and fatigue but then progress to severe illness within 24 hours. Early stages of meningococcal disease are therefore difficult to diagnose, especially if the disease occurs in the absence of a known outbreak. The median time from the onset of disease to presentation of an adolescent patient to a general practitioner is approximately 19 hours. This is important because IMD manifests itself most often as meningitis and/or septicaemia, which can be rapidly fatal within 24 to 48 hours or result in permanent significant clinical sequelae in those who survive. Approximately 70% to 85% of all patients who present with sepsis or purpura fulminans (a manifestation of sepsis) will die within 24 hours of presentation in the absence of antibiotic therapy. IMD can also result in profound neurologic abnormalities and evidence of disseminated infection in multiple organs, including ischemia of limbs that can require amputation.

2.1.4. Management

IMD is treated with antibiotics. The case fatality ratio of IMD remains high (10% to 15%) even with appropriate antibiotic treatment, and of those who survive, 11% to 19% will experience long-term sequelae such as neurological impairment, hearing loss, renal failure, or skin, digit and limb loss. Additionally, long term academic learning impairment (22.6%) and deficits in executive function and memory can occur in up to 36% of survivors.

For prevention of IMD, antimicrobial chemoprophylaxis can be used to prevent transmission from infected individuals to close contacts. However the cornerstone of prevention is represented by vaccines. In Europe, licensed meningococcal conjugate vaccines are available for the prevention of disease due to serogroup C alone or serogroups A, C, W and Y (quadrivalent). However, the use of conjugate vaccine technology is not possible for MnB because its capsular polysaccharide, polysialic acid, exhibits structural similarity to polysialic acid structures on human neuronal cells. As a result, the MnB capsular polysaccharide is poorly immunogenic and potentially capable of eliciting the production of autoantibodies. In order to provide sufficient breadth of immune coverage against diverse MnB strains that cause disease, non-capsular surface antigens must be carefully selected to identify candidates with conserved sequences that are immunogenic and expressed by most strains.

Outer membrane vesicle (OMV) based vaccines have been successfully deployed to control clonal epidemics or hyper-endemic MnB disease. MeNZB is an example of an OMV vaccine designed to respond to the MnB epidemic in New Zealand. However, the protective bactericidal immune response to OMV vaccines is largely directed against surface accessible loops of the porin protein PorA and these loops are antigenically variable. While OMV vaccines are able to elicit a protective immune response to invasive strains that express PorA sequences homologous to the PorA sequences in the vaccine, bactericidal activity is narrow in spectrum and not suitable to protect against the diversity of MnB disease isolates. Therefore there was a need for MnB vaccines that would provide broad protection against the diversity of strains that are circulating in Europe and elsewhere.

In 2013, Bexsero was approved in the EU for prevention of MnB disease in individuals 2 months of age and older. Bexsero is based on three proteins: i) factor H binding protein (fHBP), ii) Neisseria adhesin A (NadA) and iii) NHBA or 287. To increase the potency of the immune response and to facilitate large-scale vaccine manufacturing, the fHBP protein has been combined with the accessory protein GNA2091 (936), and the 287 protein has been combined with GNA1030 (953), to create two fusion proteins. In addition the vaccine also contains OMV derived from the New Zealand epidemic strain. It is thought that this combination will ensure a broad immune response to MnB strains.

Bivalent rLP2086 (Trumenba) and Bexsero were recently approved in the US to prevent MnB disease in adolescents aged 10 to 25 years of age.

2.1.5. About the product

Trumenba is a bivalent recombinant lipoprotein 2086 vaccine (bivalent rLP2086) that consists of 2 purified recombinant lipoprotein 2086 (rLP2086) antigens, i.e. 1 protein antigen from each of the factor H binding protein (fHBP) subfamilies (A and B). The antigens are fHBP variants identified from *N. meningitidis* serogroup B (MnB) strain M98250771 (variant A05, subfamily A) and strain CDC1573 (variant B01, subfamily B). fHbp is found on the surface of meningococcal bacteria and is essential for bacteria to avoid host immune defences. fHbps segregate into two immunologically distinct subfamilies, A and B, and >95% of serogroup B strains express fHbps from either subfamily. Trumenba also contains aluminium phosphate, which is a known adjuvant but which in this case functions as formulation stabiliser.

Bivalent rLP2086 prevents serogroup B disease by inducing broadly protective bactericidal antibody responses against serogroup B strains. Bactericidal antibodies act in concert with human complement to kill meningococci. This process is measured in vitro with serum bactericidal assay using human complement (hSBA) for serogroup B. A positive response in SBA is a presumptive correlate of protection from meningococcal disease.

The proposed indication of bivalent rLP2086 is:

Trumenba is indicated for active immunisation of individuals 10 years and older to prevent invasive meningococcal disease caused by Neisseria meningitidis serogroup B.

See section 5.1 for information on the immune response against specific serogroup B strains.

The use of this vaccine should be in accordance with official recommendations.

The proposed posology is:

Primary series

2 doses (0.5 ml each) administered at a 6 month interval (see section 5.1).

3 doses: 2 doses (0.5 ml each) administered at least 1 month apart, followed by a third dose at least 4 months after the second dose (see section 5.1).

Booster doses

A booster dose should be considered following either dosing regimen for individuals at continued risk of invasive meningococcal disease (see section 5.1).

Type of Application and aspects on development

The CHMP did not agree to the Applicant's request for an accelerated assessment as the product was not considered to be of major public health interest. This was based primarily on the availability of an alternative MenB vaccine on the European market, for which no shortages are affecting public health programmes. Although it was considered that it would be beneficial to have an additional vaccine available, this in itself was not considered sufficient to justify an urgent medical need or to consider the bivalent rLP2086 vaccine a product of major public health interest.

The Applicant obtained scientific advice from the CHMP on six occasions. These advices addressed quality and clinical issues. The use of in vitro serum bactericidal assays (SBA, see also further below) with human complement as a surrogate measure of efficacy was accepted, because the incidence of MnB in Europe is very low and a clinical efficacy trial would not be possible. The selection of 4 primary MnB strains used for Phase 3 SBA analyses was accepted as well as the assessment of functional and protective immune response with the 4 primary MnB test strains as a 4-fold increase from baseline (pre-existing titre) in immune responses measured in hSBA (SBA with human serum). The assessment of 10 additional MnB test strains was accepted as secondary endpoint, among which there should be sufficient strains with low expression of fHbp.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as a suspension for injection containing 60 micrograms of *Neisseria meningitidis* group B factor H binding proteins (fHbp) subfamily A and 60 micrograms of *Neisseria meningitidis* group B fHbp subfamily B adsorbed on aluminium phosphate.

Other ingredients are Sodium Chloride, Histidine, Polysorbate 80 and Water for Injections.

The product is available in a pre-filled syringe (Type I glass) with plastic Luer Lok adapter, chlorobutyl rubber plunger stopper and a synthetic isoprene bromobutyl rubber tip cap with a plastic rigid tip cap cover with or without a needle.

2.2.2. Active Substance

General information

The finished product contains two active substances (ASs), both of which are recombinant *Neisseria meningitidis* group B fHbp from subfamily A and subfamily B, expressed in and purified from *Escherichia coli*.

Based on their primary amino acid sequence, fHBP variants can be segregated into two subfamilies, designated subfamily A and B. To ensure that the vaccine elicits a broad functional immune response, one component of bivalent recombinant lipidated *Neisseria meningitidis* group B factor H binding proteins (MnB rLP2086 proteins) corresponds to an fHBP variant from subfamily A (variant A05) and the second one from subfamily B (variant B01).

The MnB rLP2086 proteins (subfamily A and B) are individually expressed in *Escherichia coli* and the fermentation and recovery processes are identical. However, different purification processes were developed for subfamily A and subfamily B lipoprotein.

The MnB rLP2086 subfamily A protein and subfamily B protein are composed of 258 and 261 amino acids, respectively. The subfamily A and B protein is covalently lipidated at the N-terminus.

Manufacture, characterisation and process controls

Description of manufacturing process

The commercial active substance manufacturing takes place at Boehringer Ingelheim RCB GmbH & Co KG, Vienna, Austria (BI RCV).

The MnB rLP2086 antigens (subfamily A and B) are individually expressed in *E. coli* and the fermentation and recovery processes are identical. The upstream fermentation process consists of 3 stages: shake flask, seed fermentor and production fermentation. Vials of working cell bank (WCB) are expanded in a series of steps and then grown to a defined cell density in the production fermentor, where expression of the rLP2086 protein is induced. The cells are harvested by centrifugation and lysed by homogenization. The cellular fragments are recovered by a second centrifugation step and the protein is extracted from the cellular fragments. The extract is centrifuged to remove cellular debris and clarified using depth filtration followed by membrane filtration. The clarified protein extract is then transferred to purification.

The purification processes for MnB rLP2086 subfamily A and subfamily B differ. Both purification processes consist of a chromatographic purification, followed by acid precipitation and depth filtration. These steps are then followed by higher resolution purification steps. Then the AS pool is concentrated, diafiltred into AS buffer, filled and stored frozen.

The solutions and buffers to prepare the columns for use and the buffers used for elution are described in sufficient detail. Holding times and temperatures for the elution pools or filtrates are validated. Cleaning and sanitization steps of the columns are described.

The same in-process tests apply to both purification processes of MnB rLP2086 subfamily A and subfamily B. The final ultrafiltration/diafilitration (UFDF) pool is filtered and stored in sample bags (as required).

Control of materials

Expression plasmid and cell banking system

rLP2086 Subfamily A and B are produced in *E. coli*.

MCBs as well as the WCBs are enrolled in a stability program and tested according to a pre-approved stability protocol.

Other materials

A list of materials used in the manufacture of the cell banks and AS is provided. The materials are purchased from approved suppliers and whenever possible compendial grade material is selected. Purified water or water for injection (WFI) manufactured at the facilities is used and meets USP/Ph. Eur. requirements. The materials used in the manufacture are tested and released upon receipt in accordance with internal raw material specifications. The composition of media for MCB, WCB preparation and fermentation process is provided, as well as the solutions used in the cell separation and recovery process, solutions/buffers used in the purification process.

The acceptance criteria for non-compendial raw materials are provided.

Information has been provided to demonstrate absence of adventitious agents (see section on adventitious agents under Finished Product).

Control of critical steps and intermediates

A comprehensive overview of critical in-process controls and critical in process tests performed throughout the MnB rLP2086 subfamily A and subfamily B manufacturing process is given. Acceptable information has been provided on the control system in place to monitor and control the active substance manufacturing process with regards to critical as well as non-critical operational parameters and in-process tests.

All critical process parameters (CPPs) are described as well as relevant non-CPPs that have an impact on quality attributes.

Characterisation of MnB rLP2086 (subfamily A and B)

Characterisation was performed on one lipoprotein batch subfamily A and one batch subfamily B derived from the full scale commercial process. The difference between the two lipoproteins is determined by the protein part, while the tri-acylated N terminal (determining the lipid isoforms) is essentially the same for both subfamilies.

The lipoprotein has an N-terminal cysteine residue which is linked to fatty acids. There are no other cysteines and therefore no disulphide bridges. The presence of high sequence homology, and highly conserved residues in the hydrophobic cores and the interdomain contacts, suggests that the structural features are common across both MnB rLP2086 subfamilies. Nevertheless there are some charge differences between the two subfamilies.

MnB rLP2086 subfamily A and B lipoproteins have been highly characterized. These approaches enabled detailed characterization of the primary structure of MnB rLP2086 subfamily A and B including the sequence of the amino acid polypeptide and the composition and the structure of the N-terminal lipids, which are the critical determinants 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 including far and near UV circular dichroism and size-exclusion high performance liquid chromatography (SEC-HPLC).

Process validation

Validation studies of both active substance manufacturing processes have been successfully completed from each of three independent, consecutive thaws of the WCB at the commercial scale.

Process validation protocols were approved prior to the start of validation. The acceptance criteria included all CPPs. The removal of process-related impurities as well as product-related impurities is sufficiently validated. The impurities characterised have been studied in clinical trials.

The validation of the production processes demonstrated that the manufacturing process, when operating within defined process controls, would consistently produce AS meeting pre-determined acceptance criteria and demonstrate expected, reproducible, and consistent process performance.

Specification

Active substance release tests and acceptance criteria are provided. The specifications for MnB rLP2086 subfamily A and subfamily B AS are identical.

Analytical methods

Compendial methods are used for bioburden, pH and endotoxin. Non-compendial or adapted methods comprise appearance*, in vitro* Relative Antigenicity Method (IVRA), purity, protein concentration

determination, Polysorbate 80 (to calculate PS80 to protein molar ratio), residual DNA and residual host cell protein (HCP). The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with ICH guidelines. A summary of all the analytical procedures and associated validation reports is provided.

Batch analysis

Batch analysis data of the active substance were provided. The results are within the specifications and confirm consistency of the manufacturing process.

Stability

The shelf life for the active substance is based on 60 months of real time stability data from the process validation/primary stability batches generated at the long term condition of –55 ± 8 ^{o}C. The 60 months of accumulated data available for the primary stability batches demonstrate that the quality attributes remain in conformance with the proposed commercial stability acceptance criteria throughout the duration of the study.

2.2.3. Finished Medicinal Product

Description of the product and pharmaceutical development

The two recombinant lipidated Neisseria meningitidis group B factor H binding proteins (fHbp) (also referred to as MnB rLP2086) are adsorbed onto Aluminium Phosphate (AlPO4).

The finished product contains the following excipients: Sodium Chloride (for osmolality), Histidine (pH control), Polysorbate 80 (surfactant) and Water for Injections (diluent). There are no overages in the formulation of the vaccine. The vaccine is formulated to the target concentrations of 120 mcg/mL/subfamily.

The intended commercial formulation is the same as that used during clinical studies.

The container closure system is a 1 mL pre-filled syringe (made of Type I glass) with plastic Luer Lok adapter, chlorobutyl rubber plunger stopper, and a synthetic isoprene bromobutyl rubber tip cap with a plastic rigid tip cap cover with or without needle.

Manufacture of the product and process controls

The formulated finished product is filled into syringes to deliver a nominal dose of 0.5 mL and stoppered. The filled syringes are stored at 2- 8°C until ready to be shipped.

In-process controls (process parameters and in process tests) are used to ensure control of the individual process steps, process consistency and product quality.

Process validation

Process validation was performed successfully on three consecutive full scale process performance qualification runs. The obtained results demonstrate that the commercial manufacturing process performs as expected. Hold times were challenged during validation, whereas other process conditions were set on target. Results of process parameter monitoring, routine in process testing, extended in-process testing and batch release testing indicate a consistent finished medicinal product manufacturing process. Filter qualification data and shipping qualification data are also considered to be satisfactory.

The compendial excipients used for MnB bivalent rLP2086 finished product (sodium chloride, histidine and water for injection) comply with the monographs of the European Pharmacopoeia. The aluminium

phosphate suspension is also manufactured by Pfizer. Adequate data are presented on the development, manufacture, control and stability of the aluminium phosphate suspension.

Manufacturing process development

Changes to the manufacturing process throughout clinical development to commercial manufacture were justified.

The product produced throughout clinical development and process validation was demonstrated though comprehensive comparability studies as representative of the product planned for commercial distribution.

Comparability data are focused on the product's critical quality attributes (CQAs), namely total protein, bound protein, purity and in vitro relative antigenicity. Comparability study results are considered to be satisfactory.

Product specification

Trumenba finished product specifications are provided. The specifications are defined and established to ensure the quality, purity, potency and safety of the commercial finished product at the recommend storage temperature of 2-8 °C.

The analytical test methods and the proposed acceptance criteria were derived through (1) evaluation of the development experience with MnB bivalent rLP2086 finished product, (2) characterization and process validation data, (3) the manufacturing history at scale, (4) the release and ongoing stability data, and (5) the toxicological and clinical evaluation of Trumenba. In addition, compendial requirements for protein based products were considered in the evaluation.

Analytical methods

Endotoxin testing using the LAL method (Ph.Eur. 2.6.14), pyrogenicity (Ph.Eur. 2.6.8), osmolality (Ph.Eur. 2.2.35), pH (Ph.Eur. 2.2.3), sterility (Ph.Eur. 2.6.1) and extractable volume (Ph.Eur. 2.9.17) are performed according to the indicated Ph. Eur. Monographs. The use of a modified rabbit pyrogenicity test has been justified.

Non-compendial methods are described in sufficient detail and validated in conformance with ICH guidelines.

The in vivo potency assay (IVPA) is used to determine the immunogenicity of bivalent rLP2086 finished product.

Batch analysis

The batch analyses data for MnB bivalent rLP2086 finished product lots manufactured at full commercial scale have been provided. All data meet the specifications in place at the time of release.

Stability of the product

The proposed shelf life of the product is 3 years at 2-8 °C. Syringes should be stored in the refrigerator horizontally to minimize the re-dispersion time. The product should not be frozen.

Long term stability studies in line with ICH gudielines were performed and presented. These studies support the 3 years stability of the product under the proposed storage conditions.

Adventitious agents

MnB bivalent rLP2086 vaccine is composed of components derived from bacterial fermentation.

Animal derived ingredients used in MnB bivalent rLP2086 vaccine production are casamino acids (or acid hydrolysate of casein) used in the media for the production of the working cell banks and animal tallow derivatives in materials of construction of equipment (stoppers, filters, manifold and/or containers) that come into contact with active substance and finished product during their manufacture as well as packaging components.

Casamino acids used were derived from bovine milk. The milk derivatives used in the manufacture of casamino acid were sourced from healthy animals in the same conditions as animal sourced for milk deemed fit for human consumption. This material is considered compliant with the requirements to minimise TSE risks as laid out in the Note for Guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products (EMEA/410/01 Rev.3).

Materials of construction of equipment used in the final packaging process may contain trace levels of animal tallow derivatives. As tallow is processed under rigorous conditions, it is considered compliant with the TSE note for guidance.

The information provided does not give rise to any concerns on adventitious agents. The absence of adventitious agents has been sufficiently demonstrated.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

The quality documentation submitted in support of Trumenba was considered of good quality. Nevertheless several concerns and one major objection have been raised during the procedure.

Active Substance

Several questions were raised in relation to potency testing and associated limits. The Applicant has committed to develop an alternative in vitro antigenicity method.

The Applicant thus proposed: 1) the IVRA test will be used for release and stability testing of active substance and finished product. 2) The in vivo potency (IVP) assay will be used for release and stability testing of finished product. 3) The Applicant proposed a validated slot blot method to test identity of both AS and FP. This proposal was considered acceptable by the CHMP.

Overall the manufacturing process and the process characterisation strategy have been well described. The strategy for defining critical quality attributes and process parameters has been further explained. Upon request, the Applicant has provided experimental data justifying the established acceptable ranges/limits of key process parameters during finished substance manufacture. Further details on the monoclonal antibodies and reference material have been provided.

The HCP test results of the active substances have consistently been below the limit of quantification for the sufficiently sensitive HCP method.

Finished Product

A comprehensive and adequate development programme based on an enhanced approach has been presented, including formulation studies for obtaining a stable formulation for subfamily A and B and process development studies to understand the production process and to define appropriate NORs and PARs. As the product is a suspension that rapidly settles, special attention has been paid to maintaining product homogeneity during formulation and filling. In addition, the impact on product quality parameters under worst case conditions has been studied, where relevant.

Comparability between material used in Phase 3 clinical studies and commercial material has been conducted.

The different steps of the FP manufacturing process have been described in sufficient detail and are considered adequately controlled. Bioburden testing prior to sterile filtration of the MnB rLP2086 Subfamily A active ingredient and MnB rLP2086 Subfamily B active substance is lacking in the current manufacturing process and the Applicant has committed to implement this in-process test post-licensure. This has been considered acceptable as the filtration step has been verified to control endotoxin level sufficiently. The Applicant also committed to verify the bacterial endotoxin content of the aluminium phosphate suspension used as an adsorbant and stabiliser of both MnB rLP 2086 antigens post-marketing. This is also considered acceptable as bacterial endotoxin is already routinely controlled at finished product level.

Three process validation runs were performed at the commercial scale, demonstrating that the manufacturing process produced MnB bivalent rLP2086 vaccine that meets its pre-determined quality attributes. Hold time limits of the different process steps are defined and are adequately supported by results of development studies and additional qualification studies incorporated into the process validation runs.

The choice of the test procedures complies with the Ph. Eur. monograph vaccines for human use (01/2013:0153) and are adequate to verify the identity, protein content, purity, microbial quality and pharmaceutical properties of the product.

The in vitro relative antigenicity (IVRA) assay and in vivo potency assay are proposed for release and stability testing of the finished product. The Applicant committed to develop an alternative in vitro antigenicity method.

A major objection was also raised in relation to the proposed in vivo potency limits, which were considered unacceptable as they were based on process capability only and raised concern that the lower level was not clinically justified. In their responses, the Applicant increased the proposed lower in vivo potency limits for subfamily A and for subfamily B. The Applicant argued that the limits cannot be further tightened in view of the high variation of the in vivo potency assay and provided data to substantiate this. The CHMP agreed that the variation in the assay should be taken into account in defining the specifications. Although the in vivo assay is highly relevant, its intrinsic variation limits its usefulness.

Other elements in the control of the vaccine potency have also been taken into account. The vaccine is a reasonably well-characterized recombinant DNA vaccine and is manufactured according to a well-defined process. Orthogonal analytical test methods in conjunction with the in vivo assay are used to ensure consistency of potency, such as the purity, total protein, percentage adsorption, and the in vitro antigen (IVRA) potency assay. This overall strategy can be considered adequate to control the potency and the Applicant has further committed to improve the precision of both potency assays as indicated hereafter:

The data provided for validation of the in vivo potency assay shows the high variation in the in vivo potency assay. Therefore, the company committed to file a variation to improve the method performance.

The Applicant has further committed to adapt the current IVRA assay to a format that allows a statistical evaluation of the assay in line with chapter 5.3. of the Ph. Eur. as a short-term solution.

With reference to Directive 2010/63/EU and to secure an undisrupted supply of medicinal products to the European Market, the Applicant is advised to further explore the development of the monocyte activation test (MAT) as additional experimental conditions could be tested to address the limitations listed.

The proposed shelf life of Trumenba of 3 years at 2-8 °C has been satisfactory supported by the provided stability data.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The CHMP has identified the following measures necessary to address the identified quality developments issues that may have a potential impact on the safe and effective use of the medicinal product: None.

2.2.6. Recommendation(s) for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

- For batch release testing the company should do further work to improve the method performance.
- The Applicant should adapt the current *in vitro* relative antigenicity (IVRA) assay to allow statistical evaluation of the assay in line with chapter 5.3. of the Ph. Eur.
- The Applicant should introduce bioburden sampling prior to sterile filtration of the MnB rLP2086 Subfamily A and MnB rLP2086 Subfamily B bulks
- The Applicant should introduce testing of the aluminium phosphate suspension for endotoxin content
- The Applicant should continue to further investigate and develop an alternative *in vitro* antigenicity method
- The Applicant should re-evaluate the active substance and finished product acceptance criteria after 30 additional commercial scale batches are available or 3 years whichever comes first.

2.3. Non-clinical aspects

2.3.1. Introduction

The bivalent rLP2086 drug product is a sterile liquid suspension without preservative composed of rLP2086 subfamily A and B proteins, tri-lipidated at the respective N-terminus. Trumenba is formulated at 120 µg/mL/antigen in 10 mM histidine buffer, pH 6.0, 150 mM sodium chloride (NaCl) with 0.5 mg/mL aluminum as aluminum phosphate (AlPO4) as a stabilizer. Polysorbate 80 (PS80) is added to the drug substance and is present in the final drug product.

Protein LP2086 is recognized as a bacterial virulence factor, is found on the surface of meningococcal bacteria and is essential for bacteria to avoid host immune defences. It binds to human complement factor H (fH), resulting in its designation as factor H binding protein (fHBP). Factor H is a negative regulator of complement activation. Binding of fH to the bacterial surface was found to increase resistance of the N. meningitidis to complement-mediated bacterial killing and enhanced the ability of the organism to circumvent innate host defences (Granoff et al, 2009).

LP2086 or factor H binding protein (fHBP) was identified as a vaccine candidate in an extensive program which also included immunisation of mice, rabbits and non-human primates with protein fractions from MnB strains and identification of the bactericidal serum response in a hSBA assay. A combination of rLP2086 subfamily A and rLP2086 subfamily B antigens provided a broad response in hSBA assay with ten MnB strains after immunisation in rabbits.

2.3.2. Pharmacology

Primary pharmacodynamic studies

The lipoprotein LP2086 was immunogenic in mice, rabbits and rhesus macaques. The non-lipidated protein P2086 was far less immunogenic than LP2086. A bivalent vaccine containing fHBP variants from

subfamilies A and B (A05 and B01) provided broader coverage in rabbits than vaccines containing only a single variant.

The epidemiology of fHBP was studied using a collection of invasive disease isolates of Neisseria meningitidis collected from meningococcal reference laboratories from UK, Norway, Czech Republic, France, USA, Germany and Spain, between 2000 and 2006, defined as the "Extended MnB SBA strain pool". All strains in the Extended MnB SBA strain pool had the complete gene for fHBP except one. The majority of isolates in the strain pool (77%) express one of the fHBP variants B24, B16, A22, B03, B44, B09, A19, A12, A05 and A07. In general, the frequency of fHBP subfamily A expressing MnB strains was lower than the frequency of subfamily B expressing strains, but in young infants < 1 year and older individuals ≥ 65 years, expression of subfamily A was higher than in other age groups.

The level of fHBP surface expression was measured with the Meningococcal Antigen Surface Expression (MEASURE) assay. fHbp expression above the limit of detection was detected in >95% of the investigated strains, but showed large variation. fHbp expression level was an important factor determining susceptibility of MnB strains to serum bactericidal antibodies induced by rLP2086. At fHBP expression levels below 1100 MFI the risk that a strain is not susceptible increases. The human serum bactericidal assay (hSBA) with human complement was used to measure the amount of vaccine-elicited antibody in serum capable of initiating complement-dependent bactericidal activity.

In a collection of contemporary, recently collected MnB strains from the UK, the Netherlands, Canada and the US (collected 2011 – 2014), the most prevalent fHBP variants (11 variants representing 79% of strains) were similar to the most prevalent variants in the Extended MnB SBA strain pool. Strains from recent outbreaks in France and the US also had for the major part similar fHBP variants and clonal complexes as the most prevalent variants in the Extended MnB SBA strain pool, except for two novel variants (B153 and B228).

Carriage rates of MnB differed 14 – 27% among adolescents and young adult subjects in UK, Spain, the Netherlands and Canada. The subfamily distribution of fHBP among carriage isolates differed from invasive isolates: among carriage isolates, the major part was type A, while among invasive isolates, the major part belongs to type B. The most prevalent fHBP variants among the carriage isolates, A22 and A05, are also among the most prevalent clinical isolates in the Extended MnB SBA strain pool.

In hSBA assays on 27 MnB test strains using serum from adolescent or young adult subjects from several clinical studies, the percentage of subjects with hSBA titre ≥1:4 after 3 vaccinations ranged approximately 55 - 100%, with most values between 70% and 100%. These strains included the primary test strains (tested in the Phase 2/3 clinical studies) and several of the secondary test strains. Against strains from outbreaks in France and the US, among which the primary test strains A22, B24 and B44 and the secondary test strain B03, the percentage of subjects with hSBA titre ≥1:4 among sera from adolescents and young adults from several clinical studies ranged 47 - 93% after 2 vaccinations and 55 - 100% after 3 vaccinations. The data show that the immune response is increased with subsequent doses to all included outbreak strains.

The four primary test strains, expressing A22, A56, B24 and B44 were selected in a step-wise selection process based on random selection taking into account subfamily distribution and fHBP expression level. Seroprotection rates using sera from adolescent or young adult subjects from several clinical studies against the four primary test strains were 3 – 35% at baseline and 81 – 100% after 3 vaccinations. For the secondary test strains, ten strains expressing A06, A07, A12, A15, A19, A29, B03, B09, B15, and B16 were selected.

Secondary pharmacodynamic studies

Secondary pharmacodynamics studies were not performed because they are generally not considered necessary to support the development and licensure of preventative vaccines.

Safety pharmacology programme

Safety pharmacology studies are not generally needed for vaccine candidates unless there is a specific cause for concern based on either non-clinical or clinical data. Because there were no clinical signs of toxicity or treatment-related effects on the cardiovascular, respiratory, or central nervous systems, in the repeat-dose toxicity study in rabbits, safety pharmacology studies were not conducted.

No sequence homologs of N meningitidis fHBP variants A05 and B01 were found in the human genome using BLASTP (Protein Basic Local Alignment Search Tool).

Pharmacodynamic drug interactions

Nonclinical studies evaluating pharmacodynamic drug interactions were not conducted and are generally not needed for preventative vaccines.

2.3.3. Pharmacokinetics

Pharmacokinetic studies (absorption, distribution, metabolism, and excretion) have not been conducted for bivalent rLP2086. Pharmacokinetic studies are normally not needed for vaccines as specified in the WHO guideline on nonclinical evaluation of vaccines (2005), and the CHMP considered this acceptable.

2.3.4. Toxicology

The toxicology studies were performed in compliance with GLP in rabbits. Rabbits are considered a relevant animal species because rLP2086 was shown to be immunogenic in rabbits. Two repeated-dose studies and two reproductive toxicology studies were performed in rabbits. Single dose toxicity investigations were included in the repeat-dose studies. Local effects were also investigated in these studies. The final formulation was tested in the second repeated-dose study and the second reproductive study.

Single dose toxicity and Repeat dose toxicity

Five doses (1 dose/2 week cycle) were given in the first study i.e. 100 and 400 µg bivalent rLP2086 i.m./animal. No major toxicological effects were observed that were attributed to the vaccine formulation. Five doses of 400 µg bivalent rLP2086 i.m /animal (1 dose/2 week cycle) were given in a second repeat-dose study. In this study there were also no major toxicological effects observed that were attributed to the vaccine formulation.

After one dose of rLP2086, very slight to slight oedema and erythema were observed at the injection site and increases in fibrinogen and total globulins which are considered associated with an acute phase response and/or antibody formation which are part of the immune response. Also a slight increase in body temperature was observed.

In repeated dose toxicity studies in which 5 doses were administered IM to rabbits with 2 weeks between doses, at maximum dose of 400 µg/dose, observations were mostly similar to the observations after one dose administration, i.e. slight oedema and erythema at the injection site, slightly increased body temperature and increased fibrinogen and total globulins. Histopathologically, slight to moderate inflammatory changes were observed at the injection site. No target organ toxicity was observed.

Genotoxicity and Carcinogenicity

Genotoxicity and carcinogenicity studies were not performed. These studies are not needed in accordance with the Note for guidance on preclinical pharmacological and toxicological testing of vaccines, CPMP/SWP/465/95, 1997 and the WHO guidelines on nonclinical evaluation of vaccines, 2005.

Reproduction Toxicity

In the 2 reproductive toxicity studies in rabbits, with administration of 200 µg rLP2086/dose to female rabbits at 17 and 4 days prior to mating and on gestation days 10 and 24, no effects on fertility and embryo-foetal development were observed. One subgroup was subjected to caesarean section on GD 29 and one group was allowed to deliver and the F1 pups were studied until PPD (post-partum day) 21. The fertility index in the females with confirmed matings were similar in the vaccine group compared to the saline control. Among animals which delivered naturally, there was a slight increase in the number of stillborn pups in groups given adjuvant (3 pups from 3 different does) or vaccine (5 pups from 4 different does) compared to saline controls (0 pups) as well as a slight increase in pup mortality on post-partum days 1-4 in the vaccine-treated group (13/137 from 5 different does) compared to the adjuvant- or saline-treated groups (6/138 from 4 different does and 4/132 from 3 different does). The incidences of stillborn pups and post-partum mortality were however within historical control range. No vaccine related deaths occurred and no fertility, body weight, food consumption, clinical or necroscopy observations in either dams or offspring were attributed to adjuvant or vaccine.

Local Tolerance and other toxicity studies

Local tolerance was investigated in the repeat-dose toxicity studies and no additional toxicology studies were performed which is acceptable.

2.3.5. Ecotoxicity / environmental risk assessment

No environmental risk assessment studies were performed. According to the Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use (EMEA/CHMP/SWP/4447/00), vaccines are exempt from performing environmental risk studies because due to the nature of their constituents no significant risk to the environment is expected.

2.3.6. Discussion on non-clinical aspects

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. A survey of over 2,150 different invasive meningococcal serogroup B isolates collected from 2000-2014 in 7 European countries, the US and Canada demonstrated that over 91% of all meningococcal serogroup B isolates expressed sufficient levels of fHbp to be susceptible to bactericidal killing by vaccine-induced antibodies.

Due to the fact that aluminium phosphate is essential for the stability, it appeared not possible to manufacture a stable formulation of the rLP2086 vaccine without the addition of aluminium phosphate, and therefore the potential impact of aluminium phosphate as an immunological adjuvant could not be evaluated experimentally. Considering its properties, it is however likely that it will have adjuvant activity. The SmPC states that the antigens are adsorbed on aluminium phosphate which is in line with other aluminium-adsorbed vaccines.

Pharmacokinetic studies have not been conducted for bivalent rLP2086, which is in line with current guidelines and in this case there are no specific circumstances for which specific studies should be

considered. Genotoxicity and cancer studies were not performed which is in line with current guidelines for this type of medicinal product (i.e. vaccine).

Injection site findings in repeated dose toxicity studies were of slight severity and not unexpected after administration of adjuvanted vaccine. No target organ toxicity was observed.

In the reproductive toxicity study with rabbits delivering naturally, there seemed to be a slight increase in the number of stillborn pups in groups given adjuvant (3 pups from 3 different does) or vaccine (5 pups from 4 different does) compared to saline controls (0 pups). Also there seemed to be an increase in pup mortality on post-partum days 1-4 in the vaccine-treated group (13/137 from 5 different does) compared to the adjuvant- or saline-treated groups (6/138 from 4 different does and 4/132 from 3 different does). However these findings appeared to be within historical control range.

2.3.7. Conclusion on the non-clinical aspects

There are no objections from a non-clinical point of view. The non-clinical program adequately supports the marketing authorisation application for Trumenba.

2.4. Clinical aspects

2.4.1. Introduction

Brief description of the clinical studies in the MAA supporting the immunogenicity:

- Three early studies, B1971003, B1971004 and B1971005-Stage 1 and Stage 2 were conducted to test safety and immunogenicity. B1971005-Stage 2 tested 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.
- One Phase 2 study, B1971012, examined various 2 and 3 dose schedules and supports the 2 dose (0, 6-month) posology for routine vaccination (discussed under dose response studies).
- Further, three Phase 2 studies investigated concomitant vaccinations, B1971010 (Repevax), B1971011 (Gardasil), and B1971015 (Menactra and Adacel).
- One Phase 2 study, B1971042, was performed in laboratory workers aged 18-65 years.
- After the safety and immunogenicity of bivalent rLP2086 was established, three Phase 3 studies were conducted: i) B1971009, a lot to lot consistency and immunogenicity and safety study in adolescents 10 to 18 years old; ii) B1971016, an immunogenicity and safety study in young adults 18 to 25 years old; and iii) B1971014, a large scale safety study in adolescents and young adults 10 to 25 years old in which immunogenicity was not evaluated. The two pivotal Phase 3 studies (B1971009 and B1971016) tested the immunogenicity using 4 primary and 10 secondary MnB test strains.

B1971012, B1971004 and B1971005 are discussed under the section on dose response studies. B1971009 and B1971016 are discussed under main clinical studies and B1971014 is discussed in the safety section. B1971003, B1971010, B1971011, B1971015 and B1971042 are discussed under supportive studies.

Persistence of the immune response was investigated in study B1971005 and B1971033 (an extension study whose preliminary results were submitted during the evaluation and which is still ongoing).

Considering B1971012 is the only study providing support for the 2-dose regimen proposed by the Applicant, and the only study including the 0, 1, 6 m schedule, the study results are presented in more detail.

GCP

The Clinical trials were performed in accordance with GCP as claimed by the Applicant.

The Applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Study ID	Study centres /location	Study Posology	Study Objective	Subjs by arm entered/ compl.	Gender M/F Median Age	Primary Endpoint
B1971003	3 sites in Australia	120 µg (0,1,6 m)	Assay development, safety and tolerability assessment & immunogenicity of bivalent rLP2086	N=60	26.7/73.3 26.0 years	hSBA titres for MnB test strains expressing fHbp variants A05 and B02.
B1971004	1 site in USA	60 µg, 120 µg, 200 µg (0,2,6 m)	Safety & immunogenicity of bivalent rLP2086	Group 1 : 12 Group 2: 12 Group 3: 12 Group 4: 12	29.6 / 60.4 30.0 years	rLP2086-specific IgG results
B1971005	25 sites in Australia, Spain, and Poland	60 µg, 120 µg, 200 µg (0,2,6 m)	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	Group 1 : 22 Group 2: 198 Group 3: 198 Group 4: 121 (Control)	46.6 / 53.4 14.0 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).
B1971042	1 site in the USA	120 µg (0,2,6 m)	Safety, tolerability, & immunogenicity of bivalent rLP2086 in laboratory workers	N=13	30.8 / 69.2 50.0 years	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.
B1971015	80 sites in the USA	120 µg (0,2,6 m)	Safety, tolerability & immunogenicity of bivalent rLP2086 when used concomitantly with MCV4 and Tdap vaccines	Group 1 (rLP2086 /MCV4/Tdap): 888 Group 2 (MCV4/Tdap /Saline): 878 Group 3 (rLP2086/ Saline followed by MCV4/Tdap: 882	51.0 / 49.0 10.0 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.
B1971011	63 sites in the USA	120 µg (0,2,6 m)	Immunogenicity of Gardasil® (HPV) when given concomitantly with bivalent rLP2086. To assess the safety, tolerability & immunogenicity of bivalent rLP2086.	Group 1 (rLP2086/ HPV): 999 Group 2 (rLP2086/ saline): 998 Group 3 (HPV/ saline): 502	66.5 / 33.5 13.0 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 response in subjects receiving HPV + rLP2086.
B1971010	34 sites in Finland,	120 µg (0,2,6 m)	Safety & immunogenicity of bivalent rLP2086 when used	Group 1 (rLP2086/dTaP-IPV):	51.1 / 48.9	% subjects achieving the prespecified level of antibody to Repevax antigens 1-month after Dose 1

	Germany and Poland.		concomitantly with Repevax (dTaP/IPV)	373 Group 2 (dTaP/IPV): 376	13.0 years	(Visit 2) was computed along with the difference in proportions (Group 1- Group 2) and 2-sided 95% exact CI for the difference.
B1971012	60 sites in Czech Republic, Denmark, Finland, Germany, Poland, Spain, and Sweden	120 µg	Safety & immunogenicity of bivalent rLP2086	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 Group 5 (0,4 m): 143	49.2/50.8 14.4 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.
B1971009	82 sites in Canada, USA, Czech Republic, Finland, Germany, Italy, Poland, and UK	120 µg (0,2,6 m)	Lot consistency, safety, tolerability, & immunogenicity of bivalent rLP2086 vaccine in healthy subjects aged ≥10 to <19 years	Lot 1: 1509/ Lot 2: 600/ Lot 3: 589/ HAV-saline: 898/	51.5/48.5 13.9 years	% 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 (lot consistency objective: hSBA GMTs for each of the 2 primary test strains PMB80 (A22) and PMB2948 (B24) measured 1 month after Dose 3 in Group 1, Group 2, & Group 3.
B1971016	53 sites in Canada, Denmark, Finland, Poland, Spain, and the USA	120 µg (0,2,6 m)	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	Group 1 (rLP2086): 2480 Group 2 (saline): 824	41.3/58.7 21.5 years	% 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
B1971014	78 sites in Australia, Chile, Czech Republic, Denmark, Estonia, Finland, Germany, Lithuania, Poland, Spain, Sweden, and the USA	120 µg (0,2,6 m)	To evaluate the safety of bivalent rLP2086 compared to a control (HAV vaccine/saline), as assessed by serious adverse events (SAEs) and medically attended adverse events (AEs).	Group 1 (rLP2086): 3804 Group 2 (HAV/ saline): 1908	48.2 / 51.8 17.0 years	Adverse events and serious adverse events.

2.4.2. Pharmacokinetics

Pharmacokinetic studies are not usually required with vaccines in accordance with current guidelines. Measurement of the plasma concentration of the vaccine over time is not feasible.

2.4.3. Pharmacodynamics

The major pharmacodynamic effect of a vaccine is to elicit an immune response to the antigens included in the vaccine. In brief, there is no specific vaccine antigen blood level required to elicit the immune response. Thus, bioavailability and bioequivalence assessments are not relevant to vaccine antigenicity and have not been measured, in accordance with current guidelines.

Mechanism of action

Trumenba is a bivalent lipoprotein 2086 vaccine that consists of two purified recombinant lipoprotein 2086 (rLP2086) antigens, from each of the factor H binding protein (fHBP) subfamilies (A05 from subfamily A and B01 from subfamily B). LP2086 is an outer membrane lipoprotein which was identified through a combined biochemical and immunological screening approach. It is a complement fHBP that enables bacteria to bind human complement factor H, which is a key negative regulator of the alternative complement pathway. Complement factor H, in concert with several other proteins, protects healthy human cells by preventing inappropriate activation of the complement system. However, when factor H is bound to fHBP on the bacterial surface, it enables the bacteria to avoid attack by the complement system.

Anti-LP2086 antibodies elicited through a vaccine may provide protection by direct complement mediated bactericidal killing and potentially by preventing bacteria binding to factor H to thereby limiting bacterial survival in vivo. The Meningococcal Antigen Surface Expression (MEASURE) assay was developed to relate the level of fHbp surface expression to killing of meningococcal serogroup B strains in serum bactericidal assays with human complement (hSBA). A survey of over 2,150 different invasive meningococcal serogroup B isolates collected from 2000-2014 in 7 European countries, the US and Canada demonstrated that over 91% of all meningococcal serogroup B isolates expressed sufficient levels of fHbp to be susceptible to bactericidal killing by vaccine-induced antibodies.

fHbp/LP2086 Sequence Analysis and Conservation

To assess the breadth of coverage by a LP2086-containing vaccine against MnB invasive disease strains, extensive epidemiological evaluations on thousands of MnB invasive disease isolates of N meningitidis collected between 2000 and 2006 from meningococcal reference laboratories from UK, Norway, Czech Republic, France, USA, Germany and Spain were conducted. This helped to understand the distribution and sequence diversity of fHBP. Initially, 1263 invasive MnB disease isolates were collected to establish a representative pool of invasive MnB disease strains. This representative MnB strain pool was termed the “MnB serum bactericidal antibody (SBA) strain pool”. This pool was later supplemented with 551 strains from Spain and Germany reported by Hoiseth et al.

A total of 198 unique fHBP amino acid sequences (designated as variants) were identified in the extended MnB SBA strain pool, and approximately 80% of the invasive disease isolates in this collection expressed 1 of the 10 most prevalent fHBP variants. The fHBP amino acid sequences were used to construct phylogenetic trees that describe the sequence relatedness of individual variants to each other. fHBP variants segregated into 2 distinct subfamilies, designated A and B. Thirty percent (30%) of invasive disease MnB strains expressed fHBP variants belonging to subfamily A and 70% of strains expressed fHBP variants of subfamily B. fHBP sequence identity within each subfamily is substantial (>83%) but is only ~60% to 75% between subfamilies, which constituted an important observation for the design of the bivalent rLP2086 vaccine. Phylogenetic analysis also revealed that the fHBP variants could be further

divided into up to 9 subgroups, with the majority of strains (>99%) having sequences that fall into 6 major subgroups. The majority of isolates in the strain pool (77%) express one of the fHBP variants B24, B16, A22, B03, B44, B09, A19, A12, A05 and A07.

The justification of the composition of bivalent rLP2086 is further discussed under the non-clinical section. The preclinical immunological observations together with the extensive epidemiological data supported that a bivalent vaccine composition (bivalent rLP2086) containing lipidated fHBP variants from each of the two subfamilies was required to provide broad serum bactericidal activity against MnB.

Immunogenicity measurements

Serum bactericidal antibody assays measure functional antibody activity in human sera that results in the complement-dependent killing of the target meningococcal strains. The inverse relationship between hSBA activity and meningococcal disease was suggested in the early 1900s and established by Goldschneider and colleagues in 1969 (Goldschneider et al, *J Exp Med*. 1969). Additional studies conducted since then established the value of the hSBA as a surrogate marker for protection. An hSBA titre is defined as the reciprocal of the highest test serum dilution that kills at least 50% of the target MnB bacteria in the assay. Since a serum dilution of 1:4 is usually the lowest dilution that is tested in hSBA, a hSBA titre equal to 1:4 is the limit of detection (LOD) of hSBA.

Serum bactericidal antibodies titres of ≥1:4 measured by hSBA are considered a marker for a possible protective immune response, although not regarded as a definitive surrogate or an established immunological correlate of protection for MnB or for this vaccine.

As bivalent rLP2086 is not genetically linked to the serogroup-defining capsular polysaccharide, and as it is designed to afford broad protection against MnB disease rather than to protect against an epidemic MnB strain that can be considered clonal, an unbiased approach was essential for selecting appropriate MnB test strains for the hSBAs to support Phase 2/3 clinical evaluation of bivalent rLP2086 and provide data representative of the breadth of vaccine responses against diverse MnB strains causing clinical disease.

Selection of test strains

From the MnB SBA strain pool (N=1263; Subfamily A, n=368; Subfamily B, n= 895), four primary test strains were randomly selected: two from fHBP subfamily A and two from subfamily B: A22, A56, B24, B44. Strains were selected using a random approach taking into account the in vitro fHBP surface expression level known to influence hSBA susceptibility. To address relative differences in fHBP *in vitro* surface expression levels, strains with low to medium (above a threshold level) rather than high surface expression levels were selected in a random process. Furthermore, hSBAs using these test strains were required to show low baseline hSBA positivity (i.e. low baseline responses in subjects' serum samples obtained prior to immunization) as populations at risk for meningococcal disease are characterized by low baseline bactericidal activity. In addition, the MnB test strains had to express fHBP sequence variants that differed from the vaccine antigen variants (i.e. heterologous) to demonstrate that vaccine induced responses provide broad coverage against diverse MnB strains. Finally, in collaboration with regulatory agencies, agreement on the final strains also depended on inclusion of strains expressing fHBP variants identified frequently in MnB invasive disease isolates in Europe and the US (i.e. fHBP variants A22 and B24).

Based on these considerations, the 4 primary MnB test strains (fHBP variant) selected were PMB80 (A22), PMB2001 (A56), PMB2948 (B24), and PMB2707 (B44). The primary MnB test strains represent Invasive Meningococcal Disease (IMD) isolates expressing fHBP variants from 4 of the 6 major fHBP subgroups.

A hSBA using these four primary test strains was used in two Phase 3 studies, B1971009 and B1971016, and in the following Phase 2 Studies: B1971005-Stage 2, B1971010 (50% of subjects tested with A22 and

B24 and 50% with A56 and B44), B1971011, B1971012 and B1971042. In Study B1971015 subjects were evaluated for only 2 of 4 primary MnB test strains in hSBAs (A22 and B24).

In addition, a hSBA with 10 secondary strains was used in the two phase 3 studies measuring immunogenicity (B1971009 and B1971016). Similar to the strategy used to select the primary MnB test strains, fHBP surface expression was taken into consideration, as well as prevalence of the fHBP variant and other epidemiologic markers. In addition, the secondary MnB test strains had to be amenable to robust assay development, and low baseline hSBA positivity had to be observed before accepting a secondary strain for hSBA. The fHBP variants expressed by the ten secondary MnB SBA test strains include A06, A07, A12, A15, A19, A29, B03, B09, B15 and B16. These were selected from the MnB SBA strain pool, except for the A07 expressing strain which was obtained from the extended MnB SBA strain pool (N=1814 strains).

Finally, two studies used hSBAs with additional MnB Test Strains. In Study B1971005 (Stage 1), functional antibodies were analysed in qualified hSBAs with the MnB test strains PMB2001 (A56) and PMB2707 (B44), as well as in qualified hSBAs with additional MnB test strains PMB3302 (A04), PMB1745 (A05), PMB17 (B02), and PMB1256 (B03). In Study B1971003, MnB test strains PMB1745 (A05) and PMB17 (B02) were tested in qualified hSBAs.

During scientific advice procedures, the CHMP endorsed that the pool that was used to select test strains for the assessment of vaccine immunogenicity in Phase 3 studies was of an appropriate constitution and that the selection method for strains was appropriate. The selected strains were endorsed.

Primary and Secondary pharmacology

N/A

Pharmacodynamic interactions with other medicinal products

The effect of concomitant administration of Repevax (diphtheria, tetanus, pertussis (acellular, component) and poliomyelitis (inactivated) vaccine), Gardasil (human papillomavirus quadrivalent (Types 6, 11, 16, and 18) vaccine, recombinant), Adacel (tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccine) and Menactra (Meningococcal groups A, C, Y and W- 135, polysaccharide, diphtheria toxoid conjugated vaccine, not licensed in EU) with bivalent rLP2086 was assessed in several phase II studies. Please refer to the section on clinical studies, supportive studies.

2.4.4. Discussion on clinical pharmacology

Analytical methods for immunogenicity measurement

Measuring bactericidal activity is highly relevant as it reflects the presence of functional serum meningococcal antibodies. A hSBA titre of at least 1:4 can be considered as a marker for a possible protective immune response; however it is not regarded as a definitive surrogate or an established immunological correlate of protection for the present application.

The Applicant selected four primary strains (PMB80 (A22), PMB2001 (A56), PMB2948 (B24), and PMB2707 (B44)) and ten secondary strains (PMB3175 (A29), PMB3010 (A06), PMB3040 (A07), PMB824 (A12), PMB1672 (A15), PMB1989 (A19), PMB1256 (B03), PMB866 (B09), PMB431 (B15) and PMB648 (B16)) from a pool of clinical MnB isolates to use in the hSBA assay for the pivotal immunogenicity studies in support of the current application. These strains were selected using a random approach that took into account the in vitro fHBP surface expression level, by selecting strains with low to medium surface expression levels. Furthermore strains were required to show low baseline hSBA positivity and to be heterologous to vaccine antigen variants. Finally, in collaboration with regulatory agencies, agreement on

the final strains also depended on inclusion of strains expressing fHBP variants identified frequently in MnB invasive disease isolates in Europe and the US (i.e. fHBP variants A22 and B24).

The process of the test strain selection has been endorsed by CHMP within the context of scientific advice procedure. Further, in scientific advice the CHMP has agreed to the use of the 4 primary MnB strains. The selected 4 primary MnB test strains belong to the 4 most prevalent ST clonal complexes in Europe and represent 4 of 6 LP2086 variant subgroups.

The Applicant applied a qualified hSBA in earlier studies. This hSBA was modified and validated in collaboration with CBER and FDA and has been used throughout most of the clinical studies submitted in context of this application.

The justification of the formulation of rLP2086, i.e. the choice of antigens, is discussed in detail in the non-clinical section.

2.4.5. Conclusions on clinical pharmacology

The selection of reference strains and SBA as correlate for protection has been discussed in this section. Both aspects have been adequately justified by the Applicant and are in line with previous CHMP scientific advice. The overall strategy was considered satisfactory by the CHMP and endorsed.

2.5. Clinical efficacy

2.5.1. Dose response studies

The safety, tolerability and immunogenicity of three different dose levels: 60, 120, and 200 µg in a 0, 2, 6-month schedule was evaluated in two phase I/II studies, B1971004 and B1971005. Whilst B1971004 focused on whether the vaccine was safe and could elicit an immune response, B1971005 assessed the safety and immunogenicity of bivalent rLP2086 and provided the basis for the dose level selection in healthy adolescents 11 to ≤18 years old. Furthermore, Study B1971012 evaluated different dosing schedules.

Study B1971004 was a Phase 1, single-centre, randomized, open-label, active- and placebo-controlled, parallel-group study in healthy adults. A total of 48 subjects (18 to ≥40 years of age) were enrolled (staggered) in parallel in a 1:1:1:1 ratio to receive 3 intramuscular (IM) injections of 60, 120, or 200 µg of bivalent rLP2086 vaccine or the control regimen (Tdap/saline) in a 0-, 2-, 6-month schedule. The primary objective of this study was to assess the safety and tolerability of 60-, 120-, and 200-µg doses of rLP2086 vaccine in healthy adults aged 18 to 40 years. The secondary objective of this study was to assess the immunogenicity of 60-, 120-, and 200-µg doses of rLP2086 vaccine as determined by quantitation of immunoglobulin G (IgG) titres that were elicited by the rLP2086 vaccine subfamily A and B proteins in healthy adults aged 18 to 40 years.

The primary immunologic endpoints were the rLP2086-specific IgG results assessed using a Luminex assay and calculated as GMTs. The data from this study supported further assessment of the immune response to the rLP2086 vaccine. Increases in IgG GMTs were detected for both subfamily A and B proteins after administration of the rLP2086 vaccine at the 60-, 120-, or 200-µg dose level. The study was too small to conclude on a dose response relationship (12 persons per group). The safety was acceptable, and a higher rate of reactions was seen with the 200 µg dose.

Study B1971005 was a randomized, single-blind, placebo-controlled, Phase 2 trial of the safety, immunogenicity, and tolerability of bivalent rLP2086 at doses of 60 µg (n=22), 120 µg (n=198), and 200 µg (n=198) using a 0, 2, 6-month schedule. The study was conducted in 2 stages. Stage 1 was designed to evaluate the immunogenicity and tolerability/safety of the different dose levels. Stage 2 of the study

was exploratory and was designed to evaluate the duration of the MnB-specific immune responses for up to 4 years after the third vaccination. The results of stage 2 are discussed under the section Supportive studies - Persistence of immunity.

For Stage 1 of the study the primary objective was to assess the immunogenicity of 60 µg, 120 µg, and 200 µg bivalent rLP2086 as measured by hSBA performed with MnB strains expressing LP2086 subfamily A and B proteins in healthy adolescents aged 11 to 18 years. The secondary objective of this study was to assess the immunogenicity of 60 µg, 120 µg, and 200 µg bivalent rLP2086 as determined by quantitation of immunoglobulin binding to rLP2086 vaccine subfamily A and B proteins in healthy adolescents aged 11 to 18 years. Immunogenicity endpoints were evaluated for 60 µg, 120 µg, and 200 µg of bivalent rLP2086 on hSBA titres obtained with 2 of the 4 primary MnB test strains, PMB2001 (A56) and PMB2707 (B44), and additional MnB test strains PMB3302 (A04), PMB1745 (A05), PMB17 (B02), and PMB1256 (B03). Strains PMB80 (A22) and PMB2948 (B24) of the 4 primary test strains used in phase 3 studies were not used during Stage 1 because the final selection of the 4 primary test strains had not occurred when Stage 1 was conducted. The IgG assay measures levels of antibodies specific for subfamily A and subfamily B rLP2086 antigens (vaccine antigens) in the serum of the vaccinated individuals.

The primary endpoint was the proportion of subjects achieving ≥4-fold rise in hSBA titre from baseline to 1 month after Dose 2 and Dose 3 for the MnB test strains, PMB1745 (A05) and PMB17 (B02), for the mITT Population. The 4-fold rise was defined as a 4-fold rise in rLP2086 specific hSBA titres from pre-dose 1 (baseline). The mITT population was the primary analysis population: control (n=119); 60 µg (n=22); 120 µg (n=195); and 200 µg (n=192).

The results of Stage 1 indicate that post–dose 3 the hSBA response rates at the 60µg, 120µg, and 200µg dose levels were as follows: 91.7%, 93.6%, and 93.5% for PMB3302 (A04 variant), respectively; 89.5%, 92.8%, and 94.0% for PMB1745 (A05 variant), respectively; 90.0%, 95.4%, and 92.7% for PMB2001 (A56 variant), respectively; 81.0%, 86.6%, and 84.8% for PMB17 (B02 variant), respectively; 53.3%, 74.7%, and 66.3% for PMB1256 (B03 variant), respectively; and 76.2%, 86.4%, and 84.4% for PMB2707 (B44 variant), respectively. hSBA results from Stage 1 of this study generally demonstrated better responses at the higher vaccine dose levels (120 µg and 200 µg compared to 60 µg). There was no dose-proportional increase in the magnitude of the immune response between the 120 µg and 200 µg doses. The IgG data showed an increase in Ig GMTs with every active dose but did not show a dose response relationship. Concerning the safety findings, most local and systemic events reported were of mild or moderate severity. Overall, there was a trend for slightly more severe and more frequent reports of reactions at the 200-µg dose level compared to lower doses.

Overall, from Stage 1 of study B1971005, available immunogenicity data and available reactogenicity data for the three dose levels that were tested clearly supported the selection of the 120 µg dose for the final formulation: there was no increase in functional immunogenicity with the 200 µg dose but there was an increase in reactogenicity. Data concerning the 60 µg dose, albeit limited, pointed towards a reduced response compared to the 120 µg dose, in particular for the B03 and B44 strain. Compared to the 60 µg group, an improvement in the immune response was observed with the 120 µg group.

In study B1971005, although the point estimates at baseline or after dose 3 are comparable to those of phase 2 and 3 studies, some variability could be noted because due to the small sample size there is less precision around the point estimates in this study.

Study B1971012 investigated different dosing schedules. This was a phase 2 randomised single-blind trial intended to assess the safety, tolerability and immunogenicity of bivalent rLP2086 vaccine when administered according to regimens of either 0, 1, and 6-months (group 1); 0, 2, and 6-months (group 2); 0 and 6-months (group 3); 0 and 2-months (group 4); or 0 and 4-months (group 5; same as 2 and 6-month schedule) in healthy subjects aged 11 to 18 years inclusive.

The co-primary objectives were to assess the immune response (hSBA) 1 month after the third vaccination among subjects who received the 0,1,6 month vaccine schedule and the 0,2,6 month vaccine schedule. The secondary objectives included the assessment of the immune response following the 0,6 month vaccine schedule, and the description of the immune response, measured by hSBA performed with MnB strains expressing LP2086 subfamily A and B proteins, for all dosing regimens throughout the study. The safety profile was also assessed (primary objective safety). Furthermore, the study included an exploratory objective to describe the immune response (measured by 4-fold response and composite response on serum bactericidal assay using hSBA performed with 4 primary MnB test strains, 2 expressing an LP2086 subfamily A protein and 2 expressing an LP2086 subfamily B protein) measured at each post-vaccination blood draw visit with bivalent rLP2086. This exploratory objective was added in a protocol amendment after start study. Approximately 1716 subjects (20 subjects per site) were planned to be enrolled in this study at approximately 86 sites. Subjects were stratified into 2 age groups: ≥11 to <14 and ≥14 to <19 years of age at the time of enrolment.

An overview of visits, vaccinations and blood draws per group is given in Table 1:

Table 1. Study Design B1971012

	Vaccination 1 Visit	Vaccination 2 Visit	Vaccination 3 Visit and Post–Vaccination 2 Visit Blood Draw	Post–Vaccination 3 Visit Blood Draw	Vaccination 4 Visit	Post–Vaccination 4 Visit Blood Draw	Final Telephone Contact
Visit number	1	2	3	4	5	6	7
Month (approx.)	0	1	2	3	6	7	12
Group 1	rLP2086	rLP2086	Saline		rLP2086		Final Telephone Contact
Group 2	rLP2086	Saline	rLP2086		rLP2086		Final Telephone Contact
Group 3	rLP2086	Saline	Saline		rLP2086		Final Telephone Contact
Group 4	rLP2086	Saline	rLP2086		Saline		Final Telephone Contact
Group 5	Saline	Saline	rLP2086		rLP2086		Final Telephone Contact
Blood draw	20 ml		20 ml	20 ml		20 ml	

For assessment of the immune response to bivalent rLP2086, functional antibodies were analysed in hSBAs with the 4 primary MnB test strains: PMB80 [A22], PMB2001 [A56], PMB2707 [B44], and PMB2948 [B24]. The primary endpoint for the co-primary objectives was the proportion of subjects achieving an hSBA titre ≥ LLOQ for each of the 4 primary MnB test strains measured 1 month after the third vaccination of bivalent rLP2086 for subjects in Groups 1 and 2. The LLOQ for each of the 4 hSBA test strains in the primary endpoint analysis was an hSBA titre equal to 1:8. The limit of detection (LOD) for each primary test strain was a titre equal to 1:4 (viewed as a presumptive correlate of protection against meningococcal disease).

Study subjects were blinded to their allocated vaccine group. Investigators and the sponsor knew the allocated vaccine group of all subjects throughout the study. The primary analysis was done on those subjects who were eligible, randomized and received all allocated doses, had pre-vaccination samples and post-last dose samples (in the right window) available and had valid and determinate assay results available.

Results

A total of 1714 subjects were enrolled in this study, 1713 were randomised: 427 in group 1 (0,1,6-Schedule), 430 in group 2 (0,2,6-Schedule), 427 in group 3 (0,6-Schedule), 286 in group 4 (0,2-Schedule) and 143 in group 5 (2,6-Schedule). 1552 subjects completed the vaccination phase; 385 in group 1, 395 in group 2, 386 in group 3, 262 in group 4 and 125 in group 5. Of the 1713 subjects randomized in the study, 1450 subjects (84.6%) were included in the evaluable immunogenicity population. Of the 263 subjects (15.4%) excluded from the evaluable immunogenicity population, 62 (14.5%) were in Group 1, 70 (16.3%) in Group 2, 56 (13.1%) in Group 3, 45 (15.7%) in Group 4, and 30 (21.0%) in Group 5. Subjects could have been excluded from the evaluable immunogenicity population (EIP) for more than 1 reason.

In total, 50.8% of the subjects were female. The proportion of subjects in the 11- to <14-year-old cohort (36.6%) was lower than the proportion of subjects in the 14- to <19-year-old cohort (63.4%). The mean age at enrolment was 14.4 years (range of 11 to 18 years). The demographic characteristics were similar across all 5 groups.

The study was not designed nor powered to compare the dose regimens. As this is the only study evaluating the 2-dose schedule (0,6m), the results of the 3-dose (0,1,6; 0,2,6) and 2-dose (0,6m) schedules are particularly relevant, although any comparison can only be descriptive in nature. There was no placebo control group. At baseline, varying proportions of subjects across the 5 groups had different hSBA titres ≥LLOQ based on strain (A22: 22-28%, A56: 18-21%; B24: 11-16%, B44: 4-8%). The primary endpoints do not incorporate baseline immunity; however analysis were performed also by baseline hSBA titres and similar observations were made.

The primary endpoint in this study was the proportion of subjects who achieved an hSBA titre greater than the lower limit of quantitation (≥ LLOQ) after the second or third dose of vaccine. The endpoint was met if the lower limit of the 97.5% CI around the proportion of subjects with hSBA ≥ LLOQ against each primary strains was over 50%, which would indicate that there is a relevant immune response. This was achieved for all strains and for all vaccine groups.

The first secondary immunogenicity objective was also met since the proportion of subjects in Group 3 (0,6m) achieving an hSBA titre ≥1:8 after 2 doses of bivalent rLP2086 was 93.5%, 98.4%, 81.1%, and 77.5% for the 4 primary MnB test strains with the lower limit of the 97.5% CI being >50% for all strains (it ranged from 72.2 to 90.0 based on strain). One month following the third dose in group 1 (0,1,6m) and 2 (0,2,6m) there was a strong immune response to the A-strains (>91-99.5%) and to the B-strains (>85%-90%). The response to the B strains is somewhat lower than the response to the A-strains.

After the study was completed and analyses of immune responses performed as such, regulatory agency feedback was received which recommended that a LLOQ of 1:16 be used for the hSBA with test strain PMB80 (A22). Thus, the Applicant performed post hoc immunogenicity analyses applying an LLOQ of 1:16 for the hSBA with test strain PMB80 (A22). In general, the immunogenicity results for the hSBA with test strain PMB80 (A22) are similar, irrespective of the LLOQ used in the analyses (1:8 or 1:16) and therefore did not alter the study conclusion. In the phase III studies, the LLOQ was 1:16 for PMB80 (A22), and 1:8 for PMB2001 (A56), PMB2907 (B44) and PMB2948 (B24). The table below summarises the results of the study after 2 and 3 doses for the first 3 groups, with the 1:16 LLOQ for A22, including the percentages ≥ LLOQ, the percentages with ≥ 4-Fold rise in hSBA titre and the composite response. See description further below.

Table 2. Immune Responses Among Individuals 11 to 18 Years of Age Administered Trumenba After Various 2- and 3-Dose Schedules (Study B1971012)

		Group 1 (0, 1, and 6 Months)		Group 2 (0, 2, and 6 Months)		Group 3 (0 and 6 Months)	
		N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
hSBA Strain (fHbp Variant)	**Dose**						
PMB80 (A22)	**% hSBA ≥ 1:16**						
	Dose 2	351	73.5 (68.6, 78.0)	344	88.1 (84.2, 91.3)	369	93.2 (90.2, 95.6)
	Dose 3	360	91.4 (88.0, 94.1)	357	95.0 (92.1, 97.0)	--	--
	≥ 4-Fold rise in hSBA titre (%)						
	Dose 2	343	55.7 (50.3, 61.0)	336	73.8 (68.8, 78.4)	362	80.7 (76.2, 84.6)
	Dose 3	351	78.1 (73.4, 82.3)	349	84.0 (79.7, 87.6)	--	--
PMB2001 (A56)	**% hSBA ≥ 1:8**						
	Dose 2	353	96.6 (94.1, 98.2)	339	97.9 (95.8, 99.2)	370	98.4 (96.5, 99.4)
	Dose 3	362	99.4 (98.0, 99.9)	359	98.9 (97.2, 99.7)	--	--
	≥ 4-Fold rise in hSBA titre (%)						
	Dose 2	338	86.1 (81.9, 89.6)	327	90.5 (86.8, 93.5)	354	90.4 (86.8, 93.3)
	Dose 3	347	93.4 (90.2, 95.8)	347	94.2 (91.2, 96.4)	--	--
PMB2948 (B24)	**% hSBA ≥ 1:8**						
	Dose 2	344	62.2 (56.9, 67.4)	337	70.3 (65.1, 75.2)	359	81.1 (76.6, 85.0)
	Dose 3	354	89.0 (85.2, 92.0)	354	88.4 (84.6, 91.6)	--	--
	≥ 4-Fold rise in hSBA titre (%)						
	Dose 2	341	47.2 (41.8, 52.7)	333	54.1 (48.5, 59.5)	357	65.5 (60.4, 70.5)
	Dose 3	351	74.6 (69.8, 79.1)	350	75.4 (70.6, 79.8)	--	--
PMB2707 (B44)	**% hSBA ≥ 1:8**						
	Dose 2	341	54.0 (48.5, 59.3)	331	61.9 (56.5, 67.2)	356	77.5 (72.8, 81.8)
	Dose 3	356	88.5 (84.7, 91.6)	352	86.1 (82.0, 89.5)	--	--
	≥ 4-Fold rise in hSBA titre (%)						
	Dose 2	339	43.4 (38.0, 48.8)	328	55.2 (49.6, 60.6)	355	66.8 (61.6, 71.6)
	Dose 3	354	82.2 (77.8, 86.0)	349	81.7 (77.2, 85.6)	--	--
Composite response (A response for all 4 hSBA strains combined)							
	Before Dose 1	339	3.5 (1.8, 6.1)	333	2.4 (1.0, 4.7)	345	3.2 (1.6, 5.6)
	Dose 2	308	45.1 (39.5, 50.9)	311	54.3 (48.6, 60.0)	343	73.5 (68.5, 78.1)
	Dose 3	337	83.1 (78.6, 86.9)	345	81.7 (77.3, 85.7)	--	--

Abbreviations: hSBA = serum bactericidal assay using human complement; fHbp = factor H binding protein.
Note: The lower limit of quantitation is an hSBA titre = 1:16 for PMB80 (A22) and 1:8 for PMB2001 (A56), PMB2948 (B24), and PMB2707 (B44).

The % of subjects achieving defined hSBA titres against the primary test strains one month after the last dose for groups 1, 2 and 3 is presented in Table 3 below.

Table 3. Subjects Achieving Defined hSBA Titres One month after last dose – EIP (Group 1,2,3) (B1971012)

		Vaccine Group (as Randomized)											
		Group 1				Group 2				Group 3			
		0,1,6-Schedule				0,2,6-Schedule				0,6-Schedule			
Strain	titre ≥	N	n	%	(95% CI)	N	n	%	(95% CI)	N	n	%	(95% CI)
[A22]													
	4	360	331	91.9	(88.6, 94.5)	357	339	95.0	(92.1, 97.0)	369	347	94.0	(91.1, 96.2)
	8	360	330	91.7	(88.3, 94.3)	357	339	95.0	(92.1, 97.0)	369	345	93.5	(90.5, 95.8)
	16	360	329	91.4	(88.0, 94.1)	357	339	95.0	(92.1, 97.0)	369	344	93.2	(90.2, 95.6)
	32	360	303	84.2	(80.0, 87.8)	357	309	86.6	(82.6, 89.9)	369	302	81.8	(77.5, 85.6)
	64	360	223	61.9	(56.7, 67.0	357	228	63.9	(58.6, 68.9)	369	199	53.9	(48.7, 59.1)
	128	360	114	31.7	(26.9, 36.7)	357	116	32.5	(27.7, 37.6)	369	95	25.7	(21.4, 30.5)
[A56]													
	4	362	361	99.7	(98.5, 100.0)	359	356	99.2	(97.6, 99.8)	370	366	98.9	(97.3, 99.7)
	8	362	360	99.4	(98.0, 99.9)	359	355	98.9	(97.2, 99.7)	370	364	98.4	(96.5, 99.4)
	16	362	359	99.2	(97.6, 99.8)	359	355	98.9	(97.2, 99.7)	370	364	98.4	(96.5, 99.4)
	32	362	345	95.3	(92.6, 97.2)	359	345	96.1	(93.5, 97.9)	370	350	94.6	(91.8, 96.7)
	64	362	318	87.8	(84.0, 91.0)	359	327	91.1	(87.6, 93.8)	370	310	83.8	(79.6, 87.4)
	128	362	262	72.4	(67.5, 76.9)	359	264	73.5	(68.7, 78.0)	370	244	65.9	(60.9, 70.8)
[B24]													
	4	354	319	90.1	(86.5, 93.0)	354	319	90.1	(86.5, 93.0)	359	298	83.0	(78.7, 86.7)
	8	354	315	89.0	(85.2, 92.0)	354	313	88.4	(84.6, 91.6)	359	291	81.1	(76.6, 85.0)
	16	354	293	82.8	(78.4, 86.6)	354	296	83.6	(79.3, 87.3)	359	265	73.8	(68.9, 78.3)
	32	354	215	60.7	(55.4, 65.9)	354	199	56.2	(50.9, 61.5)	359	169	47.1	(41.8, 52.4)
	64	354	118	33.3	(28.4, 38.5)	354	94	26.6	(22.0, 31.5)	359	81	22.6	(18.3, 27.2)
	128	354	46	13.0	(9.7, 16.9)	354	37	10.5	(7.5, 14.1)	359	26	7.2	(4.8, 10.4)

[B44]													
	4	356	318	89.3	(85.6, 92.3)	352	309	87.8	(83.9, 91.0)	356	281	78.9	(74.3, 83.1)
	8	356	315	88.5	(84.7, 91.6)	352	303	86.1	(82.0, 89.5)	356	276	77.5	(72.8, 81.8)
	16	356	302	84.8	(80.7, 88.4)	352	295	83.8	(79.5, 87.5)	356	252	70.8	(65.8, 75.5)
	32	356	244	68.5	(63.4, 73.3)	352	230	65.3	(60.1, 70.3)	356	175	49.2	(43.8, 54.5)
	64	356	166	46.6	(41.4, 52.0)	352	149	42.3	(37.1, 47.7)	356	99	27.8	(23.2, 32.8)
	128	356	98	27.5	(23.0, 32.5)	352	80	22.7	(18.5, 27.5)	356	49	13.8	(10.4, 17.8)

When considering the different endpoints, an additional dose may provide an increased immune response for the B-strains in particular. The difference is also seen for the A-strains when considering the proportion of subjects with hSBA titres ≥1:32, ≥1:64, ≥1:128, suggesting an overall less strong response to two doses compared to three doses. This is also supported by the exploratory outcomes and composite response i.e. the overall response is increased by an additional dose at 1 or 2 months following the first dose.

In between the first and second dose for Group 3 (0,6 m) a decline in hSBA antibodies was noted, in particular against the B44 strain. A decay was also seen for the 0,1,6m group between the second and third dose, although this appears less strong and the timing of samples is such that no conclusions can be drawn (data not shown). These observations could indicate that the 0,6 m schedule might not be ideal in providing fast robust protection, which would be needed in outbreak scenario's for example - as the response to the first dose is moderate and declines substantially before the second dose.

The response one month after the second dose in the 0,1,6 m schedule is numerically lower than the response one month after the second dose in the 0,2,6 m schedule – although CIs overlap and the caveat of the different timings in sampling without a proper control group should be taken into account. However, it would not be unexpected that a longer period between the first and second dose could result in a more robust immune response to the second dose.

Immune responses measured as GMTs one month after the second or third dose are presented in Table 4 below for groups 1, 2, 3. The results are in line with the other endpoints in the study.

Table 4. Immune Responses Among Individuals 11 to 18 Years of Age Administered Trumenba After Various 2- and 3-Dose Schedules (Study B1971012)

		Group 1 (0, 1, and 6 Months)		Group 2 (0, 2, and 6 Months)		Group 3 (0 and 6 Months)	
		N	GMT (95% CI)	N	GMT (95% CI)	N	GMT (95% CI)
hSBA Strain (fHbp Variant)	**Dose**						
PMB80 (A22)	**hSBA GMT**						
	Dose 2	351	29.0 (26.0, 32.5)	344	35.6 (32.2, 39.4)	369	50.6 (45.9, 55.8)
	Dose 3	360	58.4 (52.4, 64.9)	357	58.3 (53.2, 63.9)		--
PMB2001 (A56)	**hSBA GMT**						
	Dose 2	353	77.3 (68.5, 87.1)	339	94.6 (84.6, 105.7)	370	125.6 (112.6, 140.2)
	Dose 3	362	152.9 (137.2, 170.5)	359	155.6 (140.4, 172.4)	--	--
PMB2948 (B24)	**hSBA GMT**						
	Dose 2	344	13.8 (12.2, 15.6)	337	14.9 (13.2, 16.7)	359	20.6 (18.4, 23.2)
	Dose 3	354	29.1 (25.9, 32.7)	354	25.6 (23.0, 28.5)	--	--
PMB2707 (B44)	**hSBA GMT**						
	Dose 2	341	13.1 (11.3, 15.1)	331	15.5 (13.5, 17.9)	356	22.5 (19.6, 25.7)
	Dose 3	356	40.3 (35.2, 46.1)	352	35.0 (30.6, 39.9)	--	--

Abbreviations: GMT=geometric mean titre; hSBA=serum bactericidal assay using human complement; fHBP=factor H binding protein.

GMTs increased from baseline (before Injection 1) and continued to increase with each subsequent dose of bivalent rLP2086. For the 4 primary MnB test strains, the GMTs were greater after 3 doses of bivalent rLP2086 (Groups 1 and 2) than after 2 doses (Groups 3, 4, and 5). The GMTs were similar between the two 3-dose groups, and they were similar among the three 2-dose groups. For Groups 1 and 2, the observed GMTs after 2 doses for subfamily A strains, as well as after 3 doses for subfamily B strains, are indicative of a robust immune response.

For Group 3, small increases in GMTs were noted after 1 dose of bivalent rLP2086 as follows: 12.0, 18.5, 9.2, and 5.7 for PMB80 (A22), PMB2001 (A56), PMB2948 (B24), and PMB2707 (B44), respectively. After 2 doses GMTs increased to 48.4 for PMB80 (A22), 125.6 for PMB2001 (A56), 20.6 for PMB2948 (B24), and 22.5 for PMB2707 (B44). Taken together, for Groups 3, 4, and 5, the observed GMTs are indicative of an immune response for subfamily A and B strains after 2 doses of bivalent rLP2086.

Exploratory analyses were performed for the evaluable immunogenicity population of Study B1971012 using prospectively the same 5 co-primary immunogenicity endpoints as used in Phase 3 study B1971009. The response was compared between the 0, 6-Month schedule (group 3) with the 3-dose and other 2-dose schedules, showing that the percentage of subjects achieving a composite hSBA response were lower for the 0, 1-month and 0, 2-month regimens, 51% (95% CI: 43.8, 58.3) and 56.8% (95% CI: 52.5, 61.0), respectively, compared with the response rate of 73.5% (95% CI: 68.5, 78.1) achieved by those receiving bivalent rLP2086 at 0 and 6 months (see Table 5 below, and also Table 2 above).

The responses after the 3-dose schedules were slightly higher than the response following a 2-dose schedule given at 0 and 6 months for the composite endpoint and for the B-strains (Tables 5 below and 2 above). For example, the composite responses after a 0, 1, 6-month schedule and a 0, 2, 6-month schedule were, respectively, 83.1% (95% CI: 78.6, 86.9) and 81.7% (95% CI: 77.3, 85.7), compared with the composite response of 73.5% (95% CI: 68.5, 78.1) achieved with the 0 and 6-month schedule in the evaluable population. However considering also the very low pre-vaccination composite response across groups, the responder rate for the composite response demonstrates that a substantial proportion of individuals (~ 74%) receiving the vaccine at 0 and 6 months achieved protective hSBA antibody levels against 4 diverse strains considered to be representative of disease-causing serogroup B strains. Little difference was seen for the A strains among groups 1, 2, 3.

Table 5. Proportion of Subjects With ≥4-Fold Rise in hSBA Titre and Composite Response 1 Month After the Final Dose in Study B1971012 – Evaluable Immunogenicity Population

	0, 2, 6-Month	0, 1, 6-Month	0, 6-Month	0, 4-month	0, 2-month	0, 1-month
fHBP Variant	**% (95% CI)[a]**	**% (95% CI)[a]**	**% (95% CI)[a]**	**% (95% CI)[a]**	**% (95% CI)[a]**	**% (95% CI)[a]**
4-Fold Response (Primary Strains)						
A22	84.0 (79.7, 87.6)	78.1 (73.4, 82.3)	80.7 (76.2, 84.6)	78.4 (69.6, 85.6)	73.8 (70.0, 77.3)	59.0 (52.0, 65.7)
A56	94.2 (91.2, 96.4)	93.4 (90.2, 95.8)	90.4 (86.8, 93.3)	89.3 (82.0, 94.3)	91.8 (89.2, 93.9)	89.4 (84.4, 93.2)
B24	75.4 (70.6, 79.8)	74.6 (69.8, 79.1)	65.5 (60.4, 70.5)	54.5 (44.8, 64.1)	56.1 (52.0, 60.2)	53.1 (46.1, 60.0)
B44	81.7 (77.2, 85.6)	82.2 (77.8, 86.0)	66.8 (61.6, 71.6)	63.1 (53.4, 72.0)	57.0 (52.8, 61.1)	50.5 (43.5, 57.5)
Composite response (hSBA titre ≥ LLOQ for all 4 primary strains)						
Before Vaccination 1	2.4 (1.0, 4.7)	3.5 (1.8, 6.1)	3.2 (1.6, 5.6)	2.7 (0.6, 7.6)	3.6 (2.2, 5.5)	4.0 (1.7, 7.7)
After Final Dose	81.7 (77.3, 85.7)	83.1 (78.6, 86.9)	73.5 (68.5, 78.1)	58.9 (49.0, 68.3)	56.8 (52.5, 61.0)	51.0 (43.8, 58.3)

Abbreviations: fHBP = factor H binding protein; hSBA = serum bactericidal assay using human complement; LLOQ = lower limit of quantitation; LOD = limit of detection.
Note: LLOQ = 16 for A22; 8 for A56, B24, and B44.
Note: Injection = administration of investigational product (rLP2086 vaccine or saline). Baseline is defined as Visit 1.
Note: The 4-fold increase is defined as follows: (1) For subjects with a baseline hSBA titre below the limit of detection (LOD, or an hSBA titre <1:4), a response is defined as an hSBA titre ≥1:16. (2) For subjects with a baseline hSBA titre ≥ LOD (i.e., hSBA titre ≥1:4) and < lower limit of quantitation (LLOQ), a response is defined as an hSBA titre ≥4 times the LLOQ. (3) For subjects with a baseline hSBA titre ≥ LLOQ, a 4-fold response is defined as an hSBA titre ≥4 times the baseline titre.
a. Exact 2-sided confidence interval (Clopper and Pearson) based upon the observed proportion of subjects.

Persistence of Antibodies following the 0,6 month schedule (extension study B1971033)

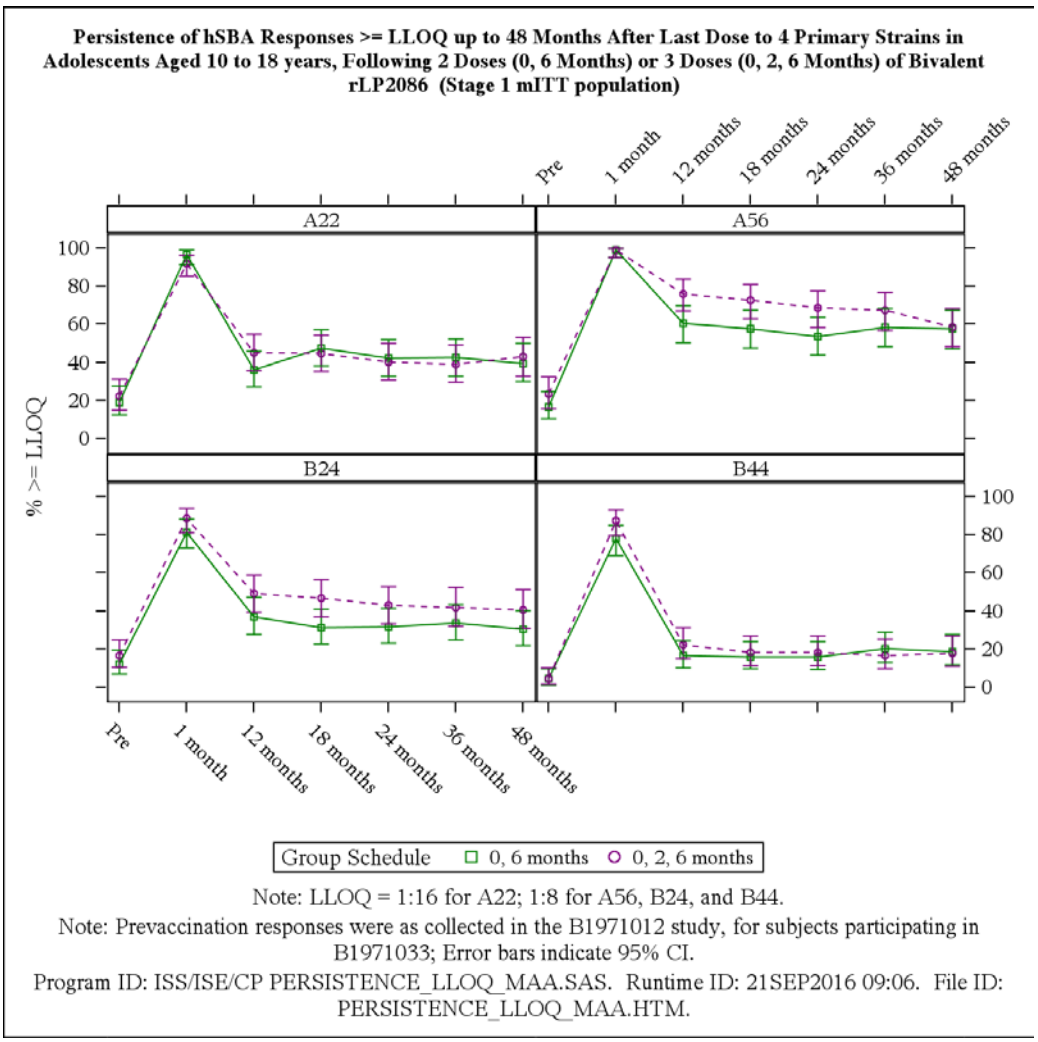
During the procedure the Applicant submitted persistence and booster data for recipients of bivalent rLP2086 at 0, 6 months months in an interim analysis from **Study B1971033**, in which a subset of subjects from Study B1971012 were enrolled to evaluate bactericidal antibody persistence (annually, for 4 years after the primary series) and the response to a single booster dose of bivalent rLP2086 given 4 years after the last dose of the primary series in Study B1971012.

An outline of the study is given in the section covering the supportive studies. In summary, Study B1971033 is an open-label, follow-up study of subjects previously enrolled in a primary study, including Study B1971012. Subjects attended visits over 4 years for collection of blood samples and received a single booster dose of Trumenba approximately 4 years after receipt of a primary series of 2 or 3 doses of Trumenba. The hSBA responses for subjects enrolled from primary Study B1971012 Group 1 (0-, 1-, 6-Month Schedule), Group 2 (0-, 2-, 6-Month) and Group 3 (0-, 6-Month) are presented in Tables 30 and 31. A booster response in hSBA responses at 1 month following a dose of Trumenba approximately 4

years after a primary series of 2 doses (Group 3) or 3 doses (Groups 1 and 2) was observed (see following paragraph).

The antibodies persistence data from study B1971033 indicate that the 2 dose schedule is sufficient to elicit immune responses that are similar to the 3 dose schedule in terms of persistence of antibodies (see Figure 3 below). Similar to the 3-dose schedule, the biggest decline following the 2-dose schedule occurs in the first 12 months after which the serum Ab levels appear to stabilise, at least for strains A22, B24 and B44. For strain A56 the initial decline is less marked and continues for the period measured, i.e. the 48 months after the last dose. Also see the section on persistence of immunity in the supportive studies section.

Figure 3. Long-term Immunogenicity: Persistence of hSBA Responses (% hSBA ≥LLOQ) up to 48 Months to 4 Primary MnB Test Strains Representative of Prevalent Strains in the US, in Adolescents Aged 10 to 18 years, Following 2 Doses (0, 6 Months) or 3 Doses (0, 2, 6 Months) of Bivalent rLP2086 – B1971012



For strains A22 and B44 there was no clear difference between the two dosing schedules in the persistence of Abs; for strain B24 levels remained higher following the 0,2,6 month schedule compared to the 0,6 month schedule although CIs overlap, and the decline was similar. For strain A56 the decline in Abs appeared less pronounced with the 0,2,6 months schedule compared to the 0,6 m schedule although here too CIs overlapped and at 48 months after the last dose Abs levels were similar.

Although there was some loss to follow up, this was limited (all groups and strains around 10%) and considered unlikely to have had an impact on the results and conclusions.

In conclusion, the persistence data did not point towards a clear advantage of the three dose schedule compared to the two dose schedule. Where there was already an improved response one month after primary vaccination this difference remains (B24) or diminishes over time (B44). As circulating serum antibodies are considered important to maintain protection against invasive meningococcal disease, the persistence data suggests that booster doses would be required to maintain protection.

Response to booster (extension study B1971033)

As mentioned above, a subset of subjects included in study B1971012 was given a booster dose 4 years after the last dose in the primary series of 2 or 3 doses. This subset was part of an extension study (B1971033), which is described in detail in the section covering the supportive studies. The preliminary results (hSBA GMTs and % subjects with hSBA ≥ LLOQ) are presented in Tables 30 and 31 and are summarised below.

One month after a booster dose of bivalent rLP2086, the proportions of subjects with hSBA titres ≥LLOQ were similar in the 0, 6-month schedule group and the 3 dose groups receiving bivalent rLP2086. The proportions of responders for the 4 primary test strains ranged from 91.9% to 98.4% in the 0, 6-month schedule group and from 98.2% to 100% in the 0, 2, 6-month schedule group.

The observed hSBA response in terms of GMTs following the booster dose was similar for the 0, 2, 6-month and 0, 6-month schedule groups and was greater than that observed after the final dose of the primary series.

These results show that a primary series with bivalent rLP2086 administered on a 0, 6-month schedule, or on other 2-dose or 3-dose schedules evaluated in B1971012, induces immunologic memory, as demonstrated by substantial increases in bactericidal activity to a single booster dose given 4 years after a primary series. Furthermore, there was no notable difference in the booster responses after a primary vaccine series given at 0, 6 months or 0, 2, 6 months.

Conclusions from dose finding studies

All in all, the available data supported the selection of the 120 µg formulation of bivalent rLP2086 over the 60 and 200 µg formulations. The results from study B1971012 supported further evaluation of the 0,2,6m dose and/or the 0,1,6m dose in phase 3 studies.

Regarding the two dose schedule at 0,6 m, available data showed that the overall response is increased by an additional dose at 1 or 2 months for the B strains. Regarding the A-strains, the difference in response between the 0,6 m schedule and the 0,1,6 or 0,2,6 month schedule is less and for relevant endpoints 95% CIs overlapped. When considering the % subjects with hSBA titre ≥ LLOQ, the responses were in the same magnitude for the two A strains, but increased with the three dose schedule compared to the two dose schedule for the 2 B strains: ~89% (3 doses) vs ~81% (2 doses) for B24 and ~86-88% (3 doses) vs ~78% (2 doses) for B44. This difference is small, and despite the lesser response to the B-strains the response following the two dose schedule could still be considered acceptable. In addition, the persistence data submitted during the procedure do not point towards a clear advantage of the three dose schedule compared to the two dose schedule. The decline in antibodies follows a similar pattern with the 0,6 month schedule as the three dose schedules (i.e. the decline is not faster or more severe). Where there was already an improved response one month after primary vaccination this difference remains (B24) or diminishes over time (B44). As circulating serum antibodies are considered necessary to maintain protection against invasive meningococcal disease, the persistence data suggests that booster-doses would be required to maintain protection. Finally the immune response to the booster dose

-given 4 years after the primary series- show that both schedules (2 and 3 doses) are able to elicit an immunological memory. There was no notable difference in the booster responses after a primary vaccine series given at 0, 6 months or 0, 2, 6 months.

Considering all the data available, there is some benefit of three doses (0,1-2,6m) over two doses (0,6m) regarding the response against the B strains one month after the primary vaccination. There is no discernible difference for the A strains. Data on the proportion of subjects with hSBA titre ≥LLOQ for each of the 4 primary strains at each blood sampling time point (not shown) demonstrated that an (assumed protective) immune response in a large proportion of vaccinees may be achieved quicker with a 0,1-2,6 months schedule compared to a 0,6 month schedule. The 3-dose schedule therefore remains important to address the need for more rapid immunity, e.g. in outbreak situations.

The Applicant committed to confirm these data post-approval in a Phase 3 study (B1971057) planned to start in 2017 in Europe and the US. The study is powered to evaluate the immunogenicity of bivalent rLP2086 on a 0, 6-month schedule, using pre-specified lower confidence interval criteria derived from the 0, 6-month arm in the B1971012 study and the same methodology for statistical evaluation used in the Phase 3 trials of the 3-dose schedule submitted in this application.

2.5.2. Main studies

Two Phase 3 studies, in which bivalent rLP2086 was administered on a 0, 2, 6-month schedule, provide immunogenicity data to support the efficacy of bivalent rLP2086.

B1971009 was a 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.

B1971016 was a phase 3, randomized, placebo-controlled, observer-blinded, trial that assessed the safety, tolerability, and immunogenicity of bivalent rLP2086 vaccine when given as a 3-dose regimen in healthy young adults aged ≥18 to <26 Years.

The main objective in both studies was to assess 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. Five co-primary endpoints were defined for the primary immunogenicity objective in both studies based upon results for hSBAs performed with each of the following 4 primary test strains: PMB80 (A22), PMB2001 (A56), PMB2948 (B24), and PMB2707 (B44). The LLOQ was 1:16 for PMB80 (A22), and 1:8 for PMB2001 (A56), PMB2907 (B44) and PMB2948 (B24). The LOD is 1:4.

- One of the 5 co-primary endpoints was the composite endpoint defined as the proportion of subjects achieving an hSBA titre ≥ LLOQ for all 4 primary MnB test strains combined, 1 month after the third vaccination with bivalent rLP2086.
- Four of the co-primary endpoints were 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.

Additionally, the lot to lot consistency was determined in study B1971009.

Methods

Study Participants

B1971009

The study included healthy male or female subjects aged ≥10 and <19 years at the time of enrolment who had not been vaccinated previously with a meningococcal serogroup B vaccine or a HAV vaccine. Subjects with a history of anaphylactic reactions to vaccines / vaccine related components, microbiologically proven disease caused by N meningitidis or N gonorrhoeae, receipt of any blood products including immunoglobulin within 6 months before the first study vaccination, receiving any allergen immunotherapy, neuro-inflammatory or autoimmune condition, current chronic use of systemic antibiotics or other severe acute or chronic medical or psychiatric conditions were excluded from participation. Subjects were excluded if they were pregnant or breastfeeding and should use adequate contraception.

B1971016

The study included healthy male or female subjects aged ≥18 and <26 years at the time of enrolment who had not been vaccinated previously with a meningococcal serogroup B vaccine. Subjects scheduled to receive HPV vaccine during the period up to 28 days after Visit 2 were excluded. Subjects with a history of anaphylactic reactions to vaccines / vaccine related components, microbiologically proven disease caused by N meningitidis or N gonorrhoeae, receipt of any blood products including immunoglobulin within 6 months before the first study vaccination, receiving any allergen immunotherapy, neuroinflammatory or autoimmune condition, current chronic use of systemic antibiotics or other severe acute or chronic medical or psychiatric conditions were excluded from participation. Subjects were excluded if they were pregnant or breastfeeding and should use adequate contraception.

The inclusion/exclusion criteria ensured the inclusion of a health, young population in both studies.

Treatments

B1971009

Subjects in Groups 1, 2, and 3 received 1 dose (0.5 mL) of bivalent rLP2086 (Lot 1, 2, or 3, respectively, Lot numbers 11-003091; 11-003046; 11-006372; 12-005669) at each of the 3 vaccination visits (Visits 1, 2, and 4); subjects in Group 4 received 1 dose (0.5 mL or 1.0 mL, depending on country-specific guidelines) of HAV vaccine at Visit 1, 1 dose (0.5 mL) of saline at Visit 2, and 1 dose (0.5 mL or 1.0 mL, depending on country-specific guidelines) of HAV vaccine (Havrix, 0.5-mL dose or 1.0-mL dose) at Visit 4.

B1971016

Group 1 received bivalent rLP2086 (Lot number 12-005668) at Month 0 (Day 1) followed by subsequent vaccinations at Months 2 and 6. Group 2 received a saline injection at Month 0, Month 2, and Month 6.

Objectives

B1971009

Primary Immunogenicity Objectives

- To assess 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.
- 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 expressing an LP2086 subfamily A protein and 1 expressing an LP2086 subfamily B protein, 1 month after the third vaccination with bivalent rLP2086.

Primary Safety Objective

- To evaluate the safety profile of bivalent rLP2086 compared to a control (HAV vaccine/saline), as measured by local reactions, systemic events, AEs, serious adverse events (SAEs), newly diagnosed chronic medical conditions (NDCMCs), medically attended AEs (MAEs), and immediate AEs.

Secondary Objectives

- To describe the immune response as measured by hSBA performed with 10 secondary MnB test strains expressing LP2086 subfamily A or B proteins, measured 1 month after the third vaccination with bivalent rLP2086.
- To describe the immune response 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, measured 1 month after the second vaccination with bivalent rLP2086.

Exploratory Objectives

- To describe the immune response to a 2-dose series of bivalent rLP2086, 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, measured 1 month after the 2-dose series.
- To describe the immune response to a booster dose of bivalent rLP2086, 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, measured 1 month after the booster vaccination.
- To evaluate the safety profile of a 2-dose series of bivalent rLP2086, as measured by AEs, SAEs, NDCMCs, MAEs, and immediate AEs.
- To evaluate the safety profile of a booster dose of bivalent rLP2086, as measured by AEs, SAEs, NDCMCs, MAEs, and immediate AEs.

B1971016

Primary Immunogenicity Objective

To assess 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.

Primary Safety Objective

To evaluate the safety profile of bivalent rLP2086 compared to a control (saline), as measured by local reactions, systemic events, AEs, serious adverse events (SAEs), newly diagnosed chronic medical conditions (NDCMCs), medically attended adverse events (MAEs), and immediate AEs.

Secondary Objectives

- To describe the immune response as measured by hSBA performed with 10 secondary MnB test strains expressing LP2086 subfamily A or B proteins measured 1 month after the third vaccination with bivalent rLP2086.
- 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 second vaccination with bivalent rLP2086.

Exploratory Objectives

- To describe the immune response to a 2-dose series of bivalent rLP2086, 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 2-dose series.

- To describe the immune response to a booster dose of bivalent rLP2086, 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 booster vaccination.
- To evaluate the safety profile of a 2-dose series of bivalent rLP2086, as measured by AEs, SAEs, NDCMCs, MAEs, and immediate AEs.
- To evaluate the safety profile of a booster dose of bivalent rLP2086, as measured by AEs, SAEs, NDCMCs, MAEs, and immediate AEs.

The objectives in the two pivotal studies are quite similar, aside from the assessment of the lot to lot consistency in study B1971009 and the age groups included. The exploratory objectives in both studies refer to a two-dose series and a booster dose, whilst in the primary and secondary objectives the suggestion is that the primary dosing schedule consists of three doses. Initially these exploratory analysis were performed to support the use of a 2-dose/booster schedule, however this approach is no longer pursued. Therefore these exploratory analyses will not be discussed as they do not provide evidence to the recommended indication. The data will be discussed for the three dose schedule.

Outcomes/endpoints

B1971009 - Immunogenicity

Test strains

For a full description of the primary and secondary MnB test strains, please see section on clinical pharmacology.

Sera from all subjects were tested in hSBAs with 2 of the primary MnB test strains, PMB80 (A22) and PMB2948 (B24). In addition, sera from all subjects in Group 1 and 50% of subjects from Group 4 were tested in hSBAs with the other 2 primary MnB test strains, PMB2001 (A56) and PMB2707 (B44).

The secondary MnB test strain immunogenicity analysis was based on hSBA results from subjects in Group 1 using 10 MnB test strains expressing the following fHBP variants: A06, A07, A12, A15, A19, A29, B03, B09, B15, and B16. Nine hundred (900) subjects from Group 1 were to be tested using hSBAs for the 10 secondary MnB test strains, divided over 3 subsets. Each subset was used to assess the response to 3 or 4 of the 10 secondary MnB test strains, in addition to the 4 primary MnB test strains. Once all subjects completed enrolment (Visit 1), the independent statistical centre randomly allocated 600 subjects at US sites and 300 subjects from other investigative sites from Group 1 across the 3 subsets (i.e., 300 subjects per subset). Among Group 1 subjects, a maximum of 8 MnB test strains (up to 4 secondary MnB test strains and 4 primary MnB test strains) were tested. Sera obtained prior to the first vaccination with bivalent rLP2086, and 1 month after the second vaccination (Visit 3) and third vaccination (Visit 5) with bivalent rLP2086, were assessed in qualified hSBAs using the 10 secondary MnB test strains. The independent statistical centre randomly selected 100 subjects per subject list (with the same US to ex-US ratio as in subjects) for which hSBA testing at 1 month after the second vaccination (Visit 3) was done. hSBA testing could not be performed after the second vaccination for all subjects in the 3 subsets due to a limited supply of qualified assay reagents.

Primary endpoints

Five (5) co-primary endpoints were defined for the primary immunogenicity objective based upon results for hSBAs performed with each of the following 4 primary test strains for Group 1 subjects: PMB80 (A22), PMB2001 (A56), PMB2948 (B24), and PMB2707 (B44).

The LLOQ was 1:16 for PMB80 (A22), 1:8 for PMB2001 (A56), 1:8 for PMB2907 (B44) and 1:8 for PMB2948 (B24). The LOD is 1:4.

- One of the 5 co-primary endpoints was the composite endpoint defined as the proportion of subjects achieving an hSBA titre ≥ LLOQ for all 4 primary MnB test strains combined, 1 month after the third vaccination with bivalent rLP2086.

- Four of the co-primary endpoints were 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.

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 titre 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.

The primary endpoints for the lot consistency objective were hSBA geometric mean titres (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.

Secondary endpoints

The descriptive secondary endpoints for the 10 secondary MnB test strains included:

- Proportions of subjects with hSBA titres ≥ LLOQ for each of the 10 secondary MnB strains, at baseline and 1 month after the third vaccination with bivalent rLP2086.

- Proportions of subjects with hSBA titres ≥1:4, ≥1:8, ≥1:16, ≥1:32, ≥1:64, and ≥1:128 for each of the 10 secondary MnB strains, at baseline and 1 month after the third vaccination with bivalent rLP2086.

- hSBA GMTs for each of the 10 secondary MnB strains at baseline and 1 month after the third vaccination with bivalent rLP2086.

For Group 1 subjects, additional secondary immunogenicity endpoints included:

- Proportion of subjects with a composite hSBA response, defined as subjects with an hSBA titre of ≥ LLOQ for all 4 primary MnB test strains combined, at baseline.

- Proportion of subjects achieving a composite hSBA response, defined as subjects achieving an hSBA titre of ≥ LLOQ for all 4 primary test MnB strains combined, at 1 month after the second vaccination with bivalent rLP2086.

For subjects in Groups 1, 2, and 3, additional secondary immunogenicity endpoints included:

- Proportion of subjects achieving at least a 4-fold increase in hSBA titre from baseline to 1 month after the second vaccination with bivalent rLP2086 for each of the 4 primary MnB test strains (Group 1) and from baseline to 1 month after the second and third vaccinations with bivalent rLP2086 for PMB80 (A22) and PMB2948 (B24) (Group 2 and Group 3), using the same definition of 4-fold increase as for the co-primary endpoints.

- hSBA GMTs for each of the applicable 4 primary MnB test strains (group 1) and for PMB80 (A22) and PMB2948 (B24) (group 2 and group 3), at baseline and 1 month after the second vaccination with bivalent rLP2086 vaccine.

- Proportions of subjects achieving hSBA titres of ≥ LLOQ, ≥1:4, ≥1:8, ≥1:16, ≥1:32, ≥1:64, and ≥1:128 for each of the 4 primary MnB test strains (Group 1) and for PMB80 (A22) and PMB2948 (B24) (Groups 2 and 3), at baseline, 1 month after the second, and 1 month after the third vaccination with bivalent rLP2086.
- Proportion of subjects achieving at least a 2-fold increase from baseline to 1 month after the third vaccination with bivalent rLP2086 for each of the 4 primary MnB test strains (Group 1) and for PMB80 (A22) and PMB2948 (B24) (Groups 2 and 3), using the following definition:
  - For subjects with a baseline hSBA titre below the LOD (or an hSBA titre of <1:4), a response was defined as an hSBA titre of ≥1:16 or the LLOQ (whichever titre was higher).
  - For subjects with a baseline hSBA titre of ≥ LOD (i.e., hSBA titre of ≥1:4) and < LLOQ, a 2-fold response was defined as an hSBA titre of ≥2 times LLOQ.
  - For subjects with a baseline hSBA titre of ≥ LLOQ, a 2-fold response was defined as an hSBA titre of ≥2 times baseline hSBA titre.

Exploratory immunogenicity and safety endpoints referred to the 2-dose and booster schedule (see objectives), which is no longer pursued. Immunogenicity was measured (similar endpoints as above) one month after the 2-dose series and to 1 month after the booster dose for each of the 4 primary test strains and each of the 10 secondary tests strains.

B1971009 - Safety Measurements

Any subject who received at least 1 dose of investigational product was included in the evaluation for safety. The following safety parameters were assessed:

1. Physical examination.
2. Reactogenicity: solicited local reactions and systemic events, including fever.
3. Use of antipyretic medication.
4. Unsolicited AEs and SAEs.

An AE was any untoward medical occurrence in a clinical investigation subject administered a product or medical device; the event did not necessarily need to have a causal relationship with the investigational product or usage.

The safety parameters included reactogenicity, i.e., both local reactions and systemic events that occurred in the 7 days (Days 1 to 7) after investigational product administration. These prospectively collected reactogenicity were considered solicited AEs and included:

- Local reactions at the site of investigational product administration (redness, swelling and pain).
- Systemic events (fever, vomiting, diarrhoea, headache, fatigue, chills, muscle pain [other than muscle pain at the injection site], and joint pain

Grading of events is fully described in the protocol and CSR.

B1971016 - Immunogenicity

Test strains

As in study B1971009, 4 primary test strains, PMB80 (A22 variant), PMB2001 (A56 variant), PMB2948 (B24 variant), and PMB2707 (B44 variant), were used in the hSBAs for determination of primary and other immunogenicity endpoints in this study. Sera obtained from all subjects prior to the first vaccination

with bivalent rLP2086 or saline, 1 month after Vaccination 2 with bivalent rLP2086 or saline (Visit 3), and 1 month after Vaccination 3 with bivalent rLP2086 or saline (Visit 5) were used in these assays.

The secondary strain immunogenicity objective was based on hSBA results from subjects in Group 1 using 10 MnB test strains expressing the following fHBP variants: A29, A06, A12, A07, A15, A19, B16, B09, B03, and B15. Three subsets were selected for this analysis. Each subset was used to assess the response to 3 or 4 of the 10 secondary test strains in addition to the 4 primary test strains. Once all subjects completed enrolment (Visit 1), the independent statistical centre randomly allocated the 900 subjects from Group 1 across the 3 subsets (i.e. 300 subjects per subset).

At least 150 (100 from US sites and 50 from other investigative sites) hSBA results from the EIP 1 month after Vaccination 3 were available for each secondary test strain. Nine hundred (900) subjects (600 subjects from US sites and 300 subjects from non-US sites) from Group 1 were to be tested using hSBAs for the 10 secondary MnB test strains.

hSBA testing could not be performed after the second vaccination for all subjects in the 3 subsets due to a limited supply of qualified assay reagents.

Primary endpoints

As in study B1971009, 5 co-primary endpoints were defined for the primary immunogenicity objective based upon results for hSBAs performed with each of the following 4 primary test strains for Group 1 subjects: PMB80 (A22), PMB2001 (A56), PMB2948 (B24), and PMB2707 (B44). Please see above for a full description of the co-primary endpoints.

Secondary endpoints

For Group 1 subjects, the descriptive secondary immunogenicity endpoints for the 4 primary test strains included:

- Proportion of subjects with a composite hSBA response, defined as subjects with an hSBA titre of ≥ LLOQ for all 4 primary strains at baseline.
- Proportion of subjects achieving a composite hSBA response defined as subjects achieving an hSBA titre of ≥ LLOQ for all 4 primary test strains at 1 month after the second vaccination with bivalent rLP2086.
- Proportion of subjects achieving at least a 4-fold increase from baseline to 1 month after the second vaccination with bivalent rLP2086 for each of the 4 primary test strains using the following definition:
    - For subjects with a baseline hSBA titre below the LOD or an hSBA titre of <1:4, a 4-fold response was defined as hSBA titre of ≥1:16 or the LLOQ (whichever titre is 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.
- Proportions of subjects with hSBA titres ≥1:4, ≥1:8, ≥1:16, ≥1:32, ≥1:64, and ≥1:128 for each of the 4 primary test strains, at baseline and 1 month after the third vaccination with bivalent rLP2086.
- hSBA geometric mean titres (GMTs) for each of the 4 primary test strains at baseline and 1 month after the second and the third vaccination with bivalent rLP2086.

- Proportion of subjects achieving at least a 2-fold increase from baseline to 1-month after the second and the third vaccination with bivalent rLP2086 for each of the 4 primary test strains using the following definition:
    - For subjects with a baseline hSBA titre below the LOD or an hSBA titre if <1:4, a response was defined as hSBA titre of ≥1:16 or the LLOQ (whichever titre is higher).
    - For subjects with a baseline hSBA titre of ≥ LOD (i.e., hSBA titre of ≥1:4) and < LLOQ, a 2-fold response was defined as hSBA titre of ≥2 times the LLOQ.
    - For subjects with a baseline hSBA titre of ≥ LLOQ, a 2-fold response was defined as hSBA titre of ≥2 times the baseline hSBA titre.

The descriptive secondary endpoints for the 10 secondary MnB test strains were:

- Proportions of subjects with hSBA titres ≥ LLOQ for each of the test strains at baseline and 1 month after the third vaccination with bivalent rLP2086.
- Proportions of subjects with hSBA titres ≥1:4, ≥1:8, ≥1:16, ≥1:32, ≥1:64, and ≥1:128 for each of the test strains at baseline and 1 month after the third vaccination with bivalent rLP2086.
- hSBA GMTs for each of the test strains at baseline and 1 month after the third vaccination with bivalent rLP2086

Exploratory immunogenicity and safety endpoints referred to the 2-dose and booster schedule (see objectives), which is no longer pursued. Immunogenicity was measured (similar endpoints as above) one month after the 2-dose series and to 1 month after the booster dose for each of the 4 primary test strains and each of the 10 secondary tests strains.

Sample size

B1971009

The overall Type I error for this study was 5%. Assuming a total of 880 evaluable subjects globally and 440 evaluable subjects from the US, the sample size in Group 1 provided approximately 100% power on the primary immunogenicity objective for the global population and the US population.

Table 6. Sample Size and Power for the Primary Immunogenicity Objective

			Global evaluable population (all evaluable subjects from Group 1)
Endpoints			(N=880)
4-Fold Response	Point Estimate	LCI	Power
PMB80 (A22)	88.4%	75 %	100%
PMB2001 (A56)	96.1%	85 %	100%
PMB2948 (B24)	77.3%	65 %	100%
PMB2707 (B44)	73.5%	60 %	100%
Composite Response (LLOQ)	87.1%	75 %	100%
Overall Power			100%

Sample size for the lot-lot consistency objective used the A22 and B24 MnB test strains variants for hypothesis testing.

The criterion for equivalence was a 2-fold difference. Assuming the difference of hSBA titre in logarithm scale was 0.2 between any 2 lots, and the common standard deviations of the log titres (natural logarithm) were 1.53 and 1.33 for the 2 MnB test strains, sample sizes of 350 evaluable subjects per lot provided 98.9% and 99.8% power to declare equivalence between 2 lots for the 2 MnB test strains, respectively.

Overall, there were 6 comparisons between any 2 lots among the 3 lots for the 2 primary MnB test strains (PMB80 [A22] and PMB2948 [B24]). Over these 6 comparisons, 350 subjects per lot could provide 96% power to declare lot-to-lot equivalence, using 2-fold equivalence criterion with Type I error of 5% (2-sided).

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).

B1971016

The study Type I error is 5%, which was controlled for the primary objective. The sample size estimation was based on power 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% confidence interval [CI]) based on exploratory Phase 2 data.

Table 7. Sample Size and Power for the Primary Immunogenicity Objective

			Global evaluable population (all evaluable subjects from Group 1)
Endpoints			(N=1700)
4-Fold Response	Point Estimate	LCI	Power
PMB80 (A22)	72.1%	55%	100%
PMB2001 (A56)	93.8%	85%	100%
PMB2948 (B24)	63.2%	50%	100%
PMB2707 (B44)	73.9%	60%	100%
Composite Response (LLOQ)	76.7%	60%	100%
Overall Power			100%

Overall, assuming 880 evaluable subjects from US sites and a total of 1700 evaluable subjects globally, the sample size in Group 1 provided >99% power for both the subjects from US sites and from global sites. With a randomization ratio of 3:1, assuming approximately a 30% non-evaluable rate (insufficient sera, protocol violation, subject dropouts, indeterminate assay results), 3300 subjects were enrolled.

The approach and methodology was deemed acceptable by the CHMP.

Randomisation

For both studies, allocation of subjects to vaccine groups proceeded 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.

B1971009

Approximately 3600 subjects were to participate in this study at approximately 120 sites (approximately 30 subjects at each site). 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). Randomization was 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.

B1971016

Approximately 3300 subjects were to be randomly assigned to 1 of 2 groups in a 3:1 ratio (Group 1:Group 2). Subject randomization was stratified according to geographic region.

Blinding (masking)

B1971009 and B1971016

The study staff dispensing and administering the vaccine were unblinded, 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.

Steps were undertaken to ensure the blinding was maintained. In case the blind was broken, this would be recorded (including date and reason) and reported. This was acceptable.

Statistical methods

B1971009 - Analysis populations

For the immunogenicity analyses, 2 analysis populations were defined to address the primary and secondary immunogenicity objectives: the evaluable immunogenicity population (EIP) and the modified intent-to-treat (mITT) immunogenicity population. In addition, separate populations were defined to address the exploratory immunogenicity objective: 2-dose series per-protocol (evaluable immunogenicity) population, booster dose per-protocol (evaluable immunogenicity) population, 2-dose series mITT population, and booster dose mITT population. The EIP was the primary analysis population for immunogenicity data.

Intent-to-Treat Population: all subjects who were randomized.

Evaluable Immunogenicity Population: all eligible randomized subjects who had received investigational products at visit 1, 2 and 4 as randomized and had baseline and post vaccination 3 (within 28 to 42 days) blood draws available. Subjects were to have valid and determinate assay results for the proposed analysis, received no prohibited vaccines or treatment, and have no other major protocol violations as determined by the sponsor's global medical monitor.

2-Dose Series Per-Protocol (Evaluable Immunogenicity) Population: all eligible randomized subjects who had received investigational products at visit 1 and 2 as randomized and had baseline and post vaccination 2 (within 28 to 42 days) blood draws available. Subjects were to have valid and determinate assay results for the proposed analysis, received no prohibited vaccines or treatment through 1 month after Dose 2, and have no other major protocol violations through 1 month after Dose 2 as determined by the sponsor's global medical monitor.

Booster Dose Per-Protocol (Evaluable Immunogenicity) Population: all eligible randomized subjects who had received investigational products at visit 1, 2 and Visit 4 as randomized and had baseline and have post-booster blood draw (within 28 to 42 days) available. Subjects were to have valid and determinate assay results for the proposed post–booster dose analysis, received no prohibited vaccines or treatment through 1 month after booster dose, and have no other major protocol violations through 1 month after booster dose as determined by the sponsor's global medical monitor.

mITT Population: All randomized subjects who had at least 1 valid and determinate assay result related to a proposed analysis were included in the mITT population.

2-Dose Series mITT Population: Included all subjects who were randomized and who had at least 1 valid and determinate assay result for the 2-dose series analysis.

Booster Dose mITT Population: Included all subjects who were randomized, who received the first 2 doses of the investigational product, and who have at least 1 valid and determinate assay result for the booster dose analysis.

B1971009 - Analysis plan

No interim analysis was planned for this study. Study alpha (type I error) is allocated to analysis on the primary objectives. Type I error (5%) is controlled with a hierarchical order by testing the primary immunogenicity objective first, followed by the lot consistency objective once the immunogenicity objective is achieved. All secondary objectives are for descriptive purpose without controlling on type I error. Safety data will be descriptively summarized and no type I error will be controlled.

Primary analysis

There were 2 primary immunogenicity objectives in this study: efficacy and lot consistency.

- The study was considered successful for proof of efficacy in the US, if the null hypothesis was rejected for all of the 5 co-primary endpoints for subjects enrolled from US investigative sites only.
- The study was considered successful for proof of efficacy in all other regions if the null hypothesis was rejected for all of the 5 co-primary endpoints for all subjects from all participating countries, including the US.

The study objectives were achieved if the lower bounds of the 95% CIs at Visit 5 were greater than the thresholds specified below (Table 8) for each of the 5 co-primary endpoints among subjects in Group 1. The 5 endpoints (composite hSBA response and 4-fold increase from baseline) at each applicable blood sampling time point will be computed along with 2-sided 95% exact CIs. Statistical inference will be based on the lower confidence intervals of the response rates on the 5 co-primary endpoints in Group 1.

Table 8. Co-primary Endpoint Significance Criteria B1971009

Endpoints	**Lower Bound Confidence Interval Threshold**
4-Fold response	
PMB80 (A22)	75%
PMB2001 (A56)	85%
PMB2948 (B24)	65%
PMB2707 (B44)	60%
Composite response (LLOQ)	75%

Abbreviation: LLOQ = lower limit of quantitation.

The primary analysis for the lot consistency objective was based on the EIP for the 6 geometric mean ratios (GMRs) (comparisons on GMT between any 2 lots for each of the 2 primary MnB test strains) at Visit 5. The 95% CIs were presented along with the GMT ratios. The CIs will be constructed by back transformation of the confidence limits computed for the mean of the logarithmically transformed assay data based on Student t distribution.

The lot consistency objective was achieved if the 2-sided 95% CIs on the hSBA GMTs ratios between any 2 of the 3 lots for both PMB80 (A22) and PMB2948 (B24) were within the interval (0.5, 2) at Visit 5, after the primary immunogenicity objective was achieved. The CIs will be constructed by back transformation of the confidence limits computed for the mean of the logarithmically transformed assay data based on Student t distribution.

For the purpose of geometric mean (GMT and GMRs) calculations, titres below the LLOQ were generally set as half the LLOQ and this method was used as the primary approach of data handling on titres below the LLOQ.

A mixed-effect model with repeated measures (MMRM) was utilized to assess the effect of race, centre, and sex, in which both baseline and the post vaccination titres (in logarithmic scale) were modelled as dependent variables for each primary strain.

B1971009 - Missing data

Missing data sensitivity assessments were conducted if the percentage of missing data for any primary endpoint exceeded 10%. Proportion of subjects with missing data was summarized for visits, by strain, by applicable group. Descriptive summaries were provided to describe the relationship between the missing data indicator and other design variables, covariates, (age, race, gender, centre, etc.) and observed hSBA data.

For the 4-fold response on each primary strain, only subjects with determinate hSBA results for that strain at both time points (baseline and post vaccination) were included in the analysis. For the composite hSBA response, only subjects with determinate hSBA results for all 4 primary MnB test strains at that blood sampling visit were included in the analysis.

Sensitivity analysis (based on Missing At Random (MAR), using mixed effects model with repeated measurement (MMRM)) were applied to the primary endpoints (5 co-primary endpoints on response and GMT) and to the titres below LLOQ to calculate GMT for the primary strains.

B1971016 - Analysis populations

As for study B1971009.

B1971016 - Analysis plan

No interim analysis was planned for this study. Study alpha (type I error) is allocated to analysis on the primary objectives. Type I error was controlled for the primary objective at the 5% level (2-sided). The statistical tests were 1-sided at the 2.5% level. All other immunogenicity analyses were descriptively summarized and no Type I error was spent.

Primary analysis

The primary objective was achieved if the lower bounds of the 95% CIs for the response rates at Month 7 (Visit 5) were greater than the threshold specified in Table 9 for each of the 5 co-primary endpoints.

Table 9. Co-primary Endpoint Significance Criteria B1971016

Endpoints	Lower Bound Confidence Interval Threshold
4-Fold response	
PMB80 (A22)	55%
PMB2001 (A56)	85%
PMB2948 (B24)	50%
PMB2707 (B44)	60%
Composite response (LLOQ)	60%

Abbreviation: LLOQ = lower limit of quantitation.

B1971016 - Missing data

See B1971009. In addition, if a subject had missing data at any blood sampling visit for any primary MnB test strain, the subject was categorized as "missing (1)"; if the subject had hSBA titres for all blood sampling visits for all test strains, then the subject was categorized as "non-missing (0)."

Considering the number of subjects allocated in each subset for the secondary MnB test strains assay (N=300) and the descriptive objective on the secondary MnB test strains, no comprehensive sensitivity analysis on missing data was performed for the secondary MnB test strains data.

A MMRM was utilized to assess the effect of race, centre, and sex, in which both baseline and the post vaccination titres (in logarithmic scale) were modelled as dependent variables for each primary test strain. This also served as a sensitivity analyses for missing data for the GMT. In addition covariates matrixes were used to account for the intra-subject correlation among the repeated measures. These analyses were only applied to the mITT population for the primary test strains only.

B1971016 - Exploratory analyses

Exploratory analyses were performed to explore the relationship between vaccine-induced immune responses for the primary MnB test strains and for the secondary MnB test strains. Collectively, the primary and secondary strains expressed fHBP variants from each of the 6 major fHBP subgroups: 4 subgroups in subfamily A (N1C1, N1C2, N2C1, and N2C2) and 2 subgroups in subfamily B (N4N5 and N6). Relationships were studied with Pearson's correlation coefficients, Kappa statistics, Graphical presentations, RCDC of the proportion of subjects exhibiting an hSBA response (hSBA titre ≥LLOQ) by number of MnB test strains, and discordance rates.

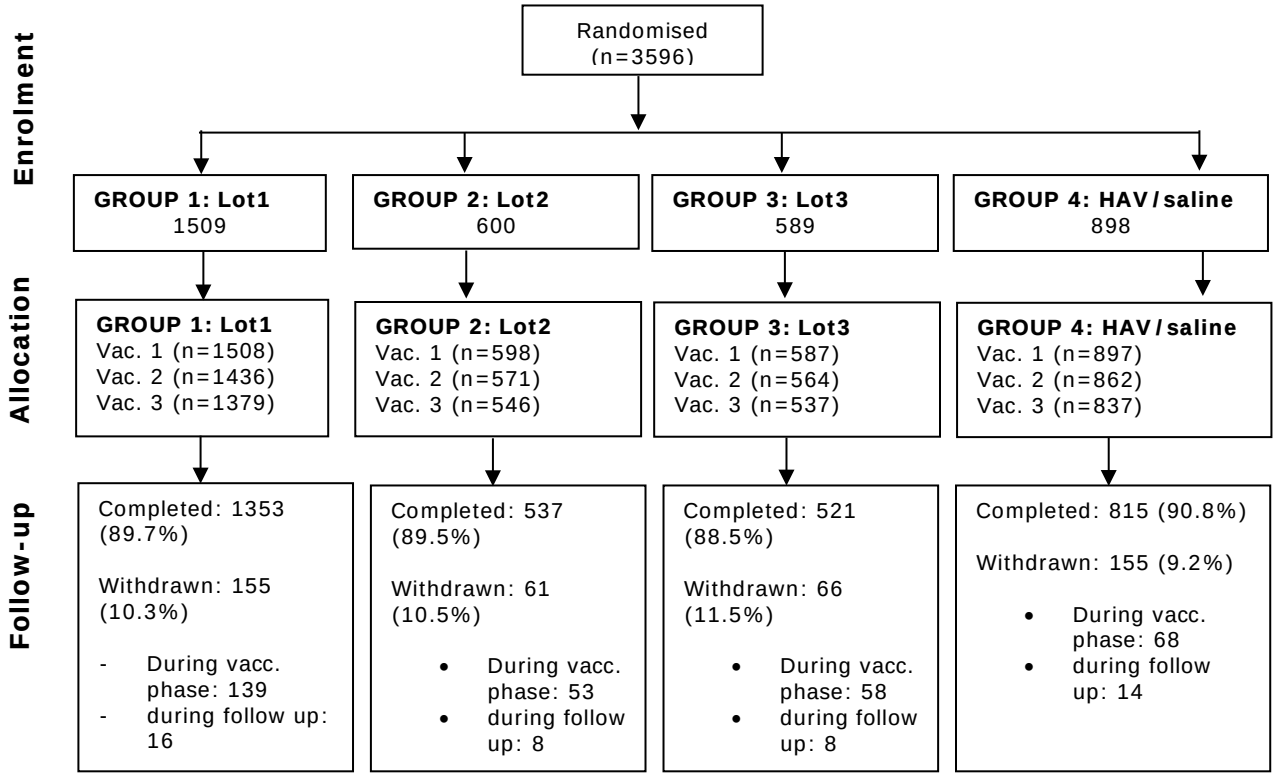
Overall, the analysis plan and methods proposed to deal with missing data was considered appropriate. The results for the US only primary immunogenicity analysis are not presented as these were consistent with the global outcomes.

Results Study B1971009

Results are presented first for study B1971009 and then for study B1971016.

B1971009

Participant flow



Reasons for withdrawal during the vaccination phase included lost to follow up (2.2%, n=78), no longer willing to participate (2.1%, n=74), withdrawal of consent (1.9%, n=69), protocol deviation (0.8%, n=27) and adverse event (0.7%, n=25). In addition, 7 subjects withdrew due to pregnancy, 6 in the rLP2086 arms and 1 in the control group. Reasons for withdrawal were well balanced across groups with the exception of adverse event (0.3% of the control group withdrew for this reason, 0.7-1.0% of active arms withdrew for this reason). A total of 46 (1.3%) subjects were withdrawn during the follow-up (Visit 6) for the following reasons: 45 (1.3%) subjects were lost to follow-up and 1 subject was withdrawn because of "other" reason (unblinded by the investigator because subject needed to know what vaccines were given).

Recruitment

First Subject First Visit: 18 April 2013; Last Subject Last Visit: 14 April 2015; Final Serology Date: 17 June 2015

Conduct of the study

There were two minor protocol amendments (clarifications / administrative) after start study (May/June 2013). Two amendments were made prior to start study (dd 24-09-2012 and 24-01-2013), including the revision of study success criteria, objectives and endpoints amongst others. These protocol amendments were made prior to study start and are not expected to influence the conduct of the study.

Baseline data

Overall, 51.5% of subjects were male and 48.5% were female. The majority of the subjects were white (87.3%) and non-Hispanic/non-Latino (94.2%). The mean age (SD) at first vaccination was 13.9 (2.6) years (range of 10 to 19 years). One (1) subject was randomized at 18 years of age in accordance with

the protocol; however, the subject's vaccination was delayed because of concurrent antibiotic use. The subject was 19 years of age on the day of vaccination. Demographic characteristics were similar between groups.

For the EIP (i.e. primary analysis population) the demographic characteristics were similar as to the safety population. 51.8% of subjects were male and 48.2% were female. The majority of the subjects were white (88.7%) and non-Hispanic/non-Latino (94.7%). The mean age (± SD) at first vaccination was 13.9 (±2.6) years (range of 10 to 18 years). Here too, the demographic characteristics were similar between the groups.

Overall, demographic characteristics were balanced between groups.

Numbers analysed

A total of 3059 (85.1%) were included in the (evaluable immunogenicity population) EIP, 537 (14.9%) subjects were excluded from the EIP. Reasons for exclusion were: No pre-Vaccination 1 or post-Vaccination 3 blood draw: 496 (13.8%); No valid & determinate assay result at pre-vaccination/post-Vaccination 3 draw visit: 354 (9.8%); did not receive all vaccines as randomized at all vaccination visits: 299 (8.3%); Were not eligible, became ineligible: 63 (1.8%); Received prohibited vaccines/treatment: 28 (0.8%); Important protocol deviation: 1 (0.0%).

Overall, the 4 study groups were comparable with respect to the percentages of subjects who were excluded from the evaluable immunogenicity population.

A total of 3590 (99.8% of 3596 subjects randomized) subjects were included in the mITT population. There were 6 (0.2%) subjects excluded from the mITT population.

Outcomes and estimation

Primary outcomes

The 5 co-primary endpoints for this objective were the proportion of subjects in Group 1 achieving at least a 4-fold increase in hSBA titre for each of the 4 primary MnB test strains and the proportion of subjects achieving a composite response at 1 month after the third vaccination with bivalent rLP2086. These results are presented in the table below. The lower limit of the 2-sided 95% CIs was greater than the corresponding pre-specified lower bound threshold for each of the 4 primary MnB strains and for the composite response; therefore, the first primary objective (immunogenicity) was met using subjects from all sites globally.

Table 10. Primary Immunogenicity Analysis – Subjects Achieving ≥4-Fold Rise in hSBA Titre and Composite Response at 1 Month After Vaccination 3 for Primary Strains – EIP (B1971009)

	Vaccine Group (as Randomized) Group 1 rLP2086 Lot 1			
Endpoint Strain (Variant)	**N**	**n (%)**	**(95% CI)**	**Lower Bound Threshold**
hSBA titre fold rise ≥4 from baseline				
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 ≥ LLOQ for all 4 primary strains)	1170	977 (83.5)	(81.3, 85.6)	75%

Similar results were seen for the US sites only (not presented).

The second primary objective (lot consistency) of this study was to demonstrate that the immune responses induced by 3 lots of bivalent rLP2086 were equivalent as measured by hSBA performed with 2 primary MnB test strains, 1 expressing a LP2086 subfamily A protein and 1 expressing a LP2086 subfamily B protein, 1 month after the third vaccination with bivalent rLP2086. Results are presented in Table 11 below. The 95% CI for all pairwise GMRs between lots were well within the interval (0.5, 2.0), for both test strains PMB80 (A22) and PMB2948 (B24). Therefore, the lot consistency objective was met.

Table 11. Primary Lot Consistency Analysis – Comparison of hSBA GMTs 1 Month After Vaccination 3 for Primary Strains – EIP (B1971009)

	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)

Secondary outcomes (primary strains)

The results for hSBA Titre ≥4-Fold Rise and Composite Response are presented in Table 23 (Summary of Efficacy for Study B1971009).

The proportion of subjects achieving an hSBA titre fold rise ≥4 from baseline to 1 month after Vaccination 2 was 73.8% for PMB80 (A22), 84.8% for PMB2001 (A56), 56.2% for PMB2948 (B24), and 55.9% for PMB2707 (B44) in Group 1. The proportion of subjects achieving an hSBA titre fold rise ≥4 from baseline to 1 month after Vaccination 3 was 83.2% for PMB80 (A22), 90.2% for PMB2001 (A56), 79.8% for PMB2948 (B24), and 85.9% for PMB2707 (B44) in Group 1 (Table 11 above).

The proportion of subjects with a composite response at baseline for Group 1 was 1.1%, which was similar to the control group (2.0%; Group 4). In Group 1, the proportion of subjects achieving a composite response 1 month after the second and third vaccination was 54.1% and 83.5%, respectively. The proportion of subjects in the control group (Group 4) who achieved a composite response 1 month after the second and third vaccination was 2.9% and 2.8%, respectively.

Proportions of subjects achieving hSBA titres at different defined levels (≥1:4, ≥ 1:8, ≥1:16, ≥1:32, ≥1:64, and ≥1:128) were determined for each of the 4 primary MnB test strains in Groups 1 and 4 and for A22 and B24 in Groups 2 and 3. A hSBA titre of ≥1:4 is assumed to be protective against IMD. In addition, a more conservative hSBA titre of ≥1:16 was used.

One month after vaccination 2, the proportions of subjects in Group 1 with an hSBA titre ≥1:4 were 94.9% for A22, 99.1 for A56, 69.2% for B24, and 66.7% for B44. One month after vaccination 3, the proportions of responders in Group 1 with an hSBA titre ≥1:4 were 97.9% for A22, 99.5 for A56, 88.9% for B24, and 90.4% for B44. Results for A22 and B24 in Groups 2 and 3 were numerically similar to those of Group 1. The responses in Group 4 (HAV/Saline) did not change (from baseline) over time for each primary test strain.

One month after vaccination 2, the proportions of subjects in Group 1 with an hSBA titre ≥1:16 were 94.3% for A22, 99.1 for A56, 60.0% for B24, and 57.7% for B44. One month after vaccination 3, the proportions of responders in Group 1 with an hSBA titre ≥1:16 were 97.8% for A22, 99.4 for A56, 82.6% for B24, and 86.8% for B44. Results in Groups 2 and 3 were similar to those of Group 1 (for A22 and B24). The responses in Group 4 (HAV/Saline) did not change (from baseline) over time for each primary test strain.

The proportion of subjects with a hSBA titre ≥ LLOQ (Table 23 (Summary of Efficacy for Study B1971009)) increased substantially from baseline to 1 month after vaccination 2 with an additional increase 1 month after vaccination 3 for all primary test strains. After vaccination 2 the proportion of responders in Group 1 with titres at ≥ LLOQ was as follows: 94.3% for PMB80 (A22), 99.1% for PMB2001 (A56), 66.4% for PMB2948 (B24), and 64.0% for PMB2707 (B44) in Group 1. Results for PMB80 (A22) and PMB2948 (B24) in Groups 2 and 3 were numerically similar to those of Group 1. In Group 1, the proportion of responders after 1 month after vaccination 3 was: 97.8% for PMB80 (A22), 99.5% for PMB2001 (A56), 87.1% for PMB2948 (B24), and 89.3% for PMB2707 (B44). Results for PMB80 (A22) and PMB2948 (B24) in Groups 2 and 3 were numerically similar to those of Group 1. These results indicate a strong response against all primary strains.

Prior to vaccination a significant proportion of subjects had hSBA titres ≥LLOQ. Dependent on vaccination group and strain, 27.5-34.9% had hSBA titres ≥ LLOQ against the two A-strains and 3.6-8.4% had hSBA titres ≥ LLOQ against the two B-strains. The responses in Group 4 (HAV/saline) did not change (from baseline) over time.

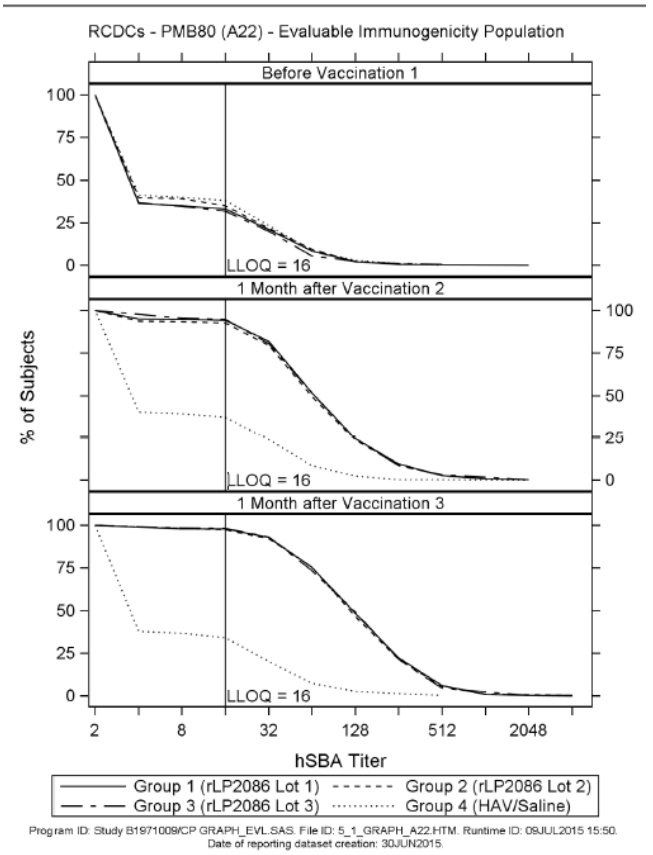
The hSBA Geometric Mean Titres are presented below.

Table 12. hSBA GMTs for Primary Strains – EIP (B1971009)

Endpoint Strain (Variant) Sampling Time Point	**Vaccine Group (as Randomized)**											
	Group 1 rLP2086 Lot 1			**Group 2 rLP2086 Lot 2**			**Group 3 rLP2086 Lot 3**			**Group4 HAV/saline**		
	N	GMT	(95% CI)	N	GMT	(95% CI)	N	GMT	(95% CI)	N	GMT	(95% CI)
PMB80 (A22)												
Before Vaccination 1	1238	12.6	(12.08, 13.14)	502	12.9	(12.06, 13.79)	479	12.2	(11.43, 13.04)	748	13.4	(12.63, 14.12)
Post Vaccination 2	1263	50.4	(47.76, 53.09)	510	47.7	(43.82, 51.97)	487	49.6	(45.58, 53.99)	743	13.2	(12.52, 14.00)
Post Vaccination 3	1266	86.8	(82.29, 91.50)	518	84.3	(77.54, 91.68)	492	85.1	(78.26, 92.47)	749	12.6	(11.96, 13.35)
PMB2001 (A56)												
Before Vaccination 1	1135	8.4	(7.80, 9.05)	N/A	N/A	N/A	N/A	N/A	N/A	362	8.3	(7.22, 9.46)
Post Vaccination 2	1222	131.2	(124.03, 138.70)	N/A	N/A	N/A	N/A	N/A	N/A	358	8.9	(7.77, 10.24)
Post Vaccination 3	1229	222.5	(210.09, 235.56)	N/A	N/A	N/A	N/A	N/A	N/A	363	8.8	(7.63, 10.11)
PMB2948 (B24)												
Before Vaccination 1	1264	4.5	(4.37, 4.60)	510	4.6	(4.43, 4.85)	486	4.6	(4.43, 4.88)	758	4.6	(4.44, 4.78)
Post Vaccination 2	1216	14.3	(13.45, 15.31)	499	14.5	(13.23, 15.98)	470	15.2	(13.75, 16.85)	758	4.5	(4.40, 4.70)
Post Vaccination 3	1250	24.1	(22.70, 25.48)	516	25.3	(23.08, 27.72)	479	25.2	(23.03, 27.58)	762	4.5	(4.37, 4.68)
PMB2707 (B44)												
Before Vaccination 1	1230	4.3	(4.17, 4.34)	N/A	N/A	N/A	N/A	N/A	N/A	391	4.3	(4.16, 4.54)
Post Vaccination 2	1204	17.1	(15.80, 18.60)	N/A	N/A	N/A	N/A	N/A	N/A	389	4.4	(4.22, 4.58)
Post Vaccination 3	1210	50.9	(47.01, 55.16)	N/A	N/A	N/A	N/A	N/A	N/A	393	4.4	(4.21, 4.63)

The RCDCs (Figure 4 and Figure 5 below) showed that a substantially high proportion of subjects achieved the LLOQ for each of the 4 test strains after vaccination 2 and an even higher proportion of subjects achieved hSBA titres ≥ LLOQ after vaccination 3. The curves were similar for Groups 1, 2, and 3. Titres were below the LLOQ for a large majority of subjects in the control group (Group 4).

Figure 4. Reverse Cumulative Distribution Curves for the Primary MnB Test Strains (A22, A56) (B1971009)



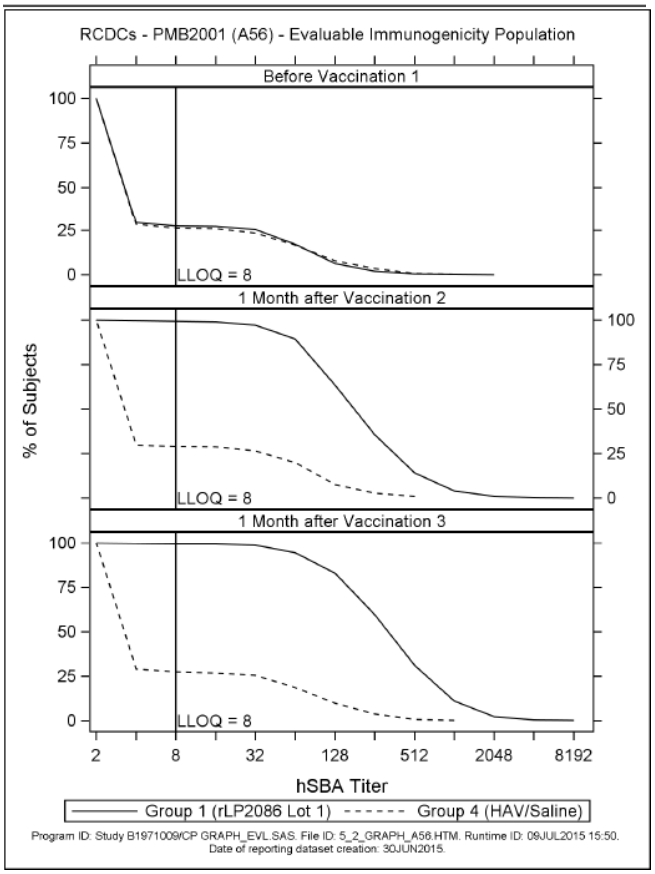
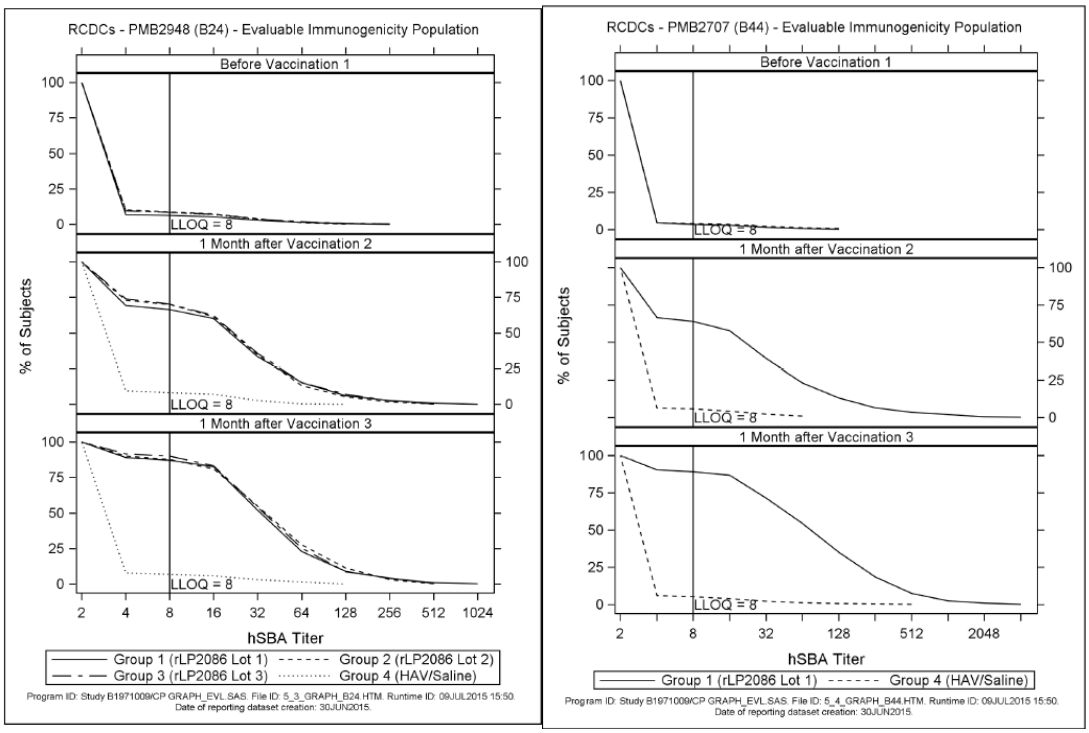


Figure 5. Reverse Cumulative Distribution Curves for the Primary MnB Test Strains (B24, B44) (B1971009)



Secondary outcomes (secondary strains)

hSBA Titres ≥LLOQ for the 10 Secondary MnB Test Strains

The proportion of subjects with an hSBA titre ≥ LLOQ rose substantially from baseline to 1 month after vaccination 3 for both fHBP subfamily A and subfamily B variant-expressing strains.

Table 13. Secondary Immunogenicity Analysis – Immune Responses (hSBA Titre ≥ LLOQ) Among Individuals 10 to 25 Years of Age Against 10 Additional Strains (Secondary Strains) 1 Month Following the Third Dose (0-, 2-, 6-Month Schedule)– EIP (B1971009)

Subfamily/Subgroup Strain (Variant) Sampling Time Point	Vaccine Group (as Randomized) Group 1 rLP2086 Lot 1 N[a]	n[b] (%)	(95% CI)[c]
A/N1C1			
PMB3175 (A29)			
Before Vaccination 1	269	47 (17.5)	(13.1, 22.5)
1 Month after Vaccination 3	278	274 (98.6)	(96.4, 99.6)
A/N1C2			
PMB3010 (A06)			
Before Vaccination 1	277	26 (9.4)	(6.2, 13.5)
1 Month after Vaccination 3	280	268 (95.7)	(92.6, 97.8)
A/N2C1			
PMB3040 (A07)			
Before Vaccination 1	269	116 (43.1)	(37.1, 49.3)
1 Month after Vaccination 3	280	270 (96.4)	(93.5, 98.3)
PMB824 (A12)			
Before Vaccination 1	280	11 (3.9)	(2.0, 6.9)
1 Month after Vaccination 3	277	208 (75.1)	(69.6, 80.1)
PMB1672 (A15)			
Before Vaccination 1	270	56 (20.7)	(16.1, 26.1)
1 Month after Vaccination 3	266	232 (87.2)	(82.6, 91.0)
A/N2C2			
PMB1989 (A19)			
Before Vaccination 1	274	31 (11.3)	(7.8, 15.7)
1 Month after Vaccination 3	275	255 (92.7)	(89.0, 95.5)
B/N6			
PMB1256 (B03)			
Before Vaccination 1	280	12 (4.3)	(2.2, 7.4)
1 Month after Vaccination 3	279	258 (92.5)	(88.7, 95.3)
PMB866 (B09)			
Before Vaccination 1	277	42 (15.2)	(11.2, 19.9)
1 Month after Vaccination 3	276	238 (86.2)	(81.6, 90.1)
PMB431 (B15)			
Before Vaccination 1	275	79 (28.7)	(23.5, 34.5)
1 Month after Vaccination 3	281	276 (98.2)	(95.9, 99.4)
PMB648 (B16)			
Before Vaccination 1	276	21 (7.6)	(4.8, 11.4)
1 Month after Vaccination 3	278	227 (81.7)	(76.6, 86.0)

Abbreviations: hSBA = serum bactericidal assay using human complement; LLOQ = lower limit of quantitation.

Note: LLOQ = 1:16 for A06, A12, and A19; 1:8 for A07, A15, A29, B03, B09, B15, and B16.

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

b. n = Number of subjects with observed hSBA titer ≥ LLOQ for the given strain at the given time point.

c. Exact 2-sided confidence interval (CI) based upon the observed proportion of subjects using the Clopper and Pearson method.

For the 10 secondary strains, pre-vaccination 3.9-43.1% of subjects had an hSBA titre≥LLOQ dependent on the strain.

Among fHBP subfamily A variant-expressing strains, for 4 of these strains, ≥92.7% of subjects achieved hSBA titres ≥ LLOQ: 98.6% for PMB3175 (A29), 95.7% for PMB3010 (A06), 92.7% for PMB1989 (A19), and 96.4% for PMB3040 (A07). For PMB824 (A12) and for PMB1672 (A15), the proportion achieving a titre ≥ LLOQ was 75.1% and 87.2%, respectively.

Among fHBP subfamily B variant-expressing strains the proportion of subjects in Group 1 with an hSBA titre ≥ LLOQ 1 month after vaccination 3 was 92.5 % for PMB1256 (B03), 86.2% for PMB866 (B09), 98.2% for PMB431 (B15), and 81.7% for PMB648 (B16).

These results are suggestive of a strong immune response against all strains tested.

hSBA Titres Achieving Defined Levels for the 10 Secondary MnB Test Strains

Proportions of subjects achieving hSBA titres of ≥1:4, ≥1:16, ≥1:32, ≥1:64, and ≥1:128 for each of the 10 secondary MnB test strains in Group 1 were calculated.

An hSBA titre of ≥1:4 is viewed as a surrogate of protection against IMD. For the purpose of defining the minimal hSBA titre considered as a 4-fold response, a more conservative hSBA titre of ≥1:16 was used.

Among fHBP subfamily A variant-expressing strains, the proportion of subjects with an hSBA titre ≥1:4 at baseline and 1 month after Vaccination 3 for PMB3175 (A29) was 19.0% and 98.6%, respectively, for PMB3010 (A06) it was 9.7% and 96.1%, respectively, and for PMB1989 (A19) it was 20.8% and 93.8%, respectively. The proportion of subjects with an hSBA titre ≥1:4 at baseline and 1 month after Vaccination 3 for PMB3040 (A07) was 43.1% and 96.4%, respectively, for PMB824 (A12) it was 5.4% and 77.6%, respectively, and for PMB1672 (A15) it was 22.6% and 87.2%, respectively.

Among fHBP subfamily B variant-expressing strains, which are all in subfamily N6, the proportion of subjects in Group 1 (bivalent rLP2086 Lot 1) with an hSBA titre ≥1:4 at baseline and 1 month after Vaccination 3 for PMB1256 (B03) was 5.0% and 92.5%, respectively, for PMB866 (B09) it was 15.5% and 86.6%, respectively, for PMB431 (B15) it was 30.5% and 98.2%, respectively, and for PMB648 (B16) it was 8.7% and 82.7%, respectively.

Among fHBP subfamily A variant-expressing strains, the proportion of subjects with an hSBA titre ≥1:16 at baseline and 1 month after Vaccination 3 for PMB3175 (A29) was 16.7% and 98.6%, respectively, for PMB3010 (A06) in subfamily N1C2 it was 9.4% and 95.7%, respectively, and for PMB1989 (A19) it was 11.3% and 92.7%, respectively. The proportion of subjects with an hSBA titre ≥1:16 at baseline and 1 month after Vaccination 3 for PMB3040 (A07) was 42.8% and 96.4%, respectively, for PMB824 (A12) it was 3.9% and 75.1%, respectively, and for PMB1672 (A15) it was 17.0% and 85.0%, respectively.

Among fHBP subfamily B variant-expressing strains, which are all in subfamily N6, the proportion of subjects in Group 1 (bivalent rLP2086 Lot 1) with an hSBA titre ≥1:16 at baseline and 1 month after Vaccination 3 for PMB1256 (B03) was 4.3% and 92.1%, respectively, for PMB866 (B09) it was 13.7% and 83.7%, respectively, for PMB431 (B15) it was 27.6% and 97.5%, respectively, and for PMB648 (B16) it was 7.6% and 79.9%, respectively.

As an example of the results of the other titres, the results for PMB3175 (A29) are presented below.

Table 14. Subjects Achieving Defined hSBA Titres for Secondary Strains – EIP (B1971009)

Strain (Variant)	Sampling Time Point	Titre	N	n	(%)	(95% CI)
A/N1C1						
PMB3175 (A29)						
	Before Vaccination 1	4	269	51	(19.0)	(14.5, 24.2)
		8	269	47	(17.5)	(13.1, 22.5)
		16	269	45	(16.7)	(12.5, 21.7)
		32	269	29	(10.8)	(7.3, 15.1)
		64	269	13	(4.8)	(2.6, 8.1)
		128	269	3	(1.1)	(0.2, 3.2)
	1 Month after Vaccination 3	4	278	274	(98.6)	(96.4, 99.6)
		8	278	274	(98.6)	(96.4, 99.6)
		16	278	274	(98.6)	(96.4, 99.6)
		32	278	271	(97.5)	(94.9, 99.0)
		64	278	239	(86.0)	(81.3, 89.8)
		128	278	145	(52.2)	(46.1, 58.2)

Additional Sensitivity Analyses

The proportions of subjects in Study B1971009 with missing hSBA titres were comparable at each applicable visit across vaccine and control groups for the 4 primary MnB test strains. Additionally, neither the missing hSBA titres nor the demographic factors had an impact on the conclusion that a robust immune response was induced by 3 doses of bivalent rLP2086, when the immune response was analysed by GMTs. Sensitivity analyses using MMRM, ML estimation, and hSBA titre ≥4-fold rise response using GLIMMIX also supported the robust immune responses induced by 2 or 3 doses of bivalent rLP2086.

Correlation, concordance, discordance and PPV between primary and secondary MnB test strains

The correlation coefficients on hSBA titres between primary and secondary MnB test strains within each fHBP subfamily 1 month after vaccination 3 for the EIP were determined. Positive correlations were observed between the primary strain responses and secondary strain responses within the same subfamily. These correlations included pairs in which the secondary test strain and the primary test strain expressed fHBP variants of different phylogenetic subgroups. Between subfamily A strains, correlation coefficients ranged from 0.41 to 0.71. Between subfamily B strains, correlation coefficients ranged from 0.46 to 0.73.

Concordance analysis on response rates for each pair of primary and secondary MnB test strains was performed by using 2 methods: percent agreement (based on hSBA response ≥LLOQ) for and calculation of the Kappa coefficient. The latter was not considered informative due to the Kappa paradox (i.e. high agreement yet a low Kappa coefficient which is sometimes observed). The percent agreement at 1 month after vaccination 3 for A22 ranged from 74.5% to 95.6%; for A56, 75.3% to 98.1%; for B24, 78.1% to 90.0%; and for B44, 77.3% to 89.7%. One month after the second dose it ranged from 67.0% to 94.7% for A22; for A56, 64.4% to 100.0%; for B24, 54.8% to 68.1%; and for B44, 54.9% to 70.6%.

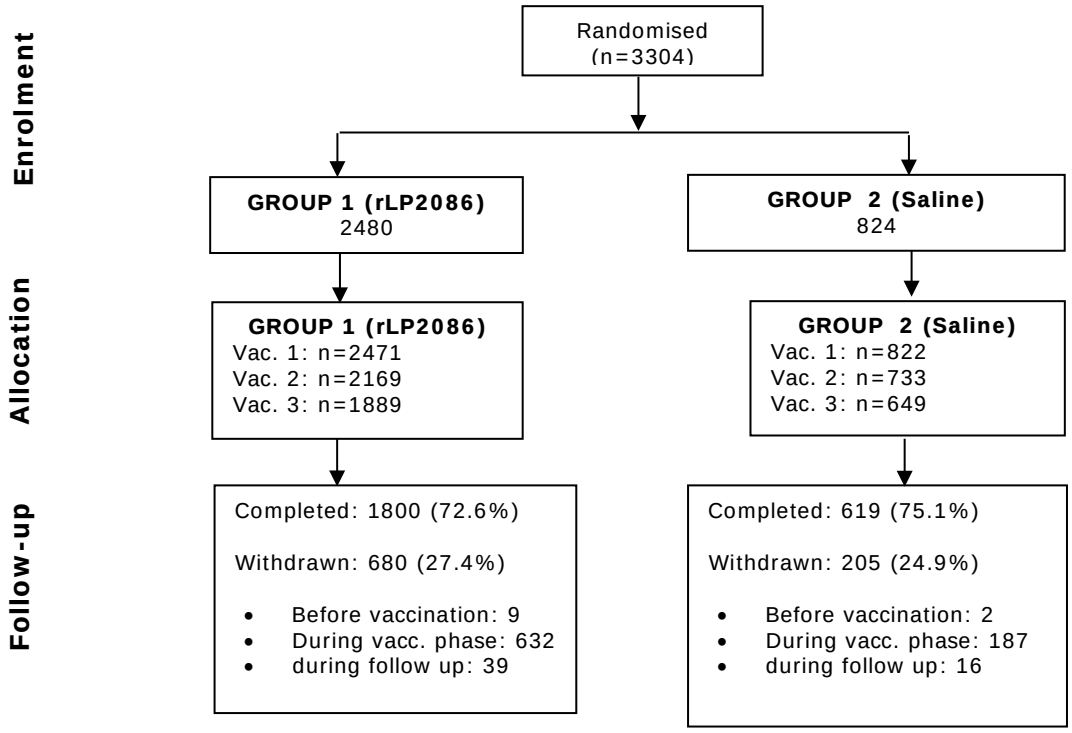
The proportion of subjects who had hSBA titres that were ≥LLOQ for the primary strain and < LLOQ for the secondary strain 1 month after the third vaccination was generally low: for A22, the discordance ranged from 0.4% to 24.1%; for A56, 1.1% to 24.4%; for B24, 0.4% to 13.6%; for B44, 0.8% to 14.5%. The proportion of subjects who had hSBA titres that were ≥LLOQ for the primary strain and < LLOQ for the secondary strain 1 month after the second vaccination was generally low: for A22, the discordance ranged from 0.0% to 29.1%; for A56, 0.0% to 35.6%; for B24, 0.0% to 19.7%; and for B44, 0.0% to 21.1%.

The positive predictive value (PPV) analysis was performed post hoc and is discussed under ancillary analyses.

Overall concordance between the response against primary and secondary test strains is lower following the second dose compared to the third dose, which is not unexpected as it is more likely to see concordance with a higher overall response. Overall the concordance observed between primary and secondary strain pairs is acceptable and suggest a sustained hSBA response across different strains.

Results Study B1971016

Participant flow



Of the 3304 randomized subjects, 2474 (74.88%) subjects completed the vaccination phase of the study: 3293 (99.67%) subjects received Vaccination 1; 2902 (87.83%) subjects received Vaccination 2; and 2538 (76.82%) subjects received Vaccination 3. A total of 819 (24.79%) subjects withdrew during the vaccination phase. Twenty-eight (28; 0.85%) subjects withdrew from the vaccination phase due to an AE. Subjects who withdrew from the vaccination phase were followed for safety purposes and 6-month (after the last vaccination) follow-up telephone contacts were attempted, unless the subjects withdrew consent or were lost to follow-up during the vaccination phase. A total of 2770 (83.84%) subjects completed the 6-month follow-up telephone contact, and 2419 (73.21%) subjects completed the study.

Recruitment

First Subject First Visit: 03 May 2013

Last Subject Last Visit: 13 February 2015

Final Serology Date: 09 July 2015

Conduct of the study

There were no major protocol amendments.

There were 3 amendments to the original protocol dated 14 March 2011. Subject enrolment began 03 May 2013, after Amendment 2 had taken effect. Amendment after start of study (amendment 3, 07-11-2013) encompassed adjustment of blood volume to be collected at visit 5 for assay development, update of EDMC charter, clarification of solicited vs unsolicited AE terminology and updates to template/editorial.

A number of subjects (n=65) did not satisfy all eligibility criteria at baseline but received Vaccination 1. The majority, 32 subjects did not use a highly effective method of contraception. Eight subjects did not meet eligibility criteria after baseline but continued to receive vaccination. For 21 subjects there was noncompliance with the temporary delay of blood draw criteria. For 36 subjects there was noncompliance with the temporary delay criteria for vaccination.

No protocol deviations were recorded which were deemed to have impacted the assessment of safety.

Baseline data

Overall the demographic characteristics were balanced between the study groups.

Table 15. Demographic Characteristics – Safety Population (B1971016)

	Vaccine Group (as Administered)		
	Group 1	**Group 2**	
	rLP2086	**Saline**	**Total**
	(N=1723)	**(N=582)**	**(N=2305)**
	n (%)	**n (%)**	**n (%)**
Sex			
Male	671 (38.94)	233 (40.03)	904 (39.22)
Female	1052 (61.06)	349 (59.97)	1401 (60.78)
Race			
White	1441 (83.63)	480 (82.47)	1921 (83.34)
Black	239 (13.87)	87 (14.95)	326 (14.14)
Other	23 (1.33)	8 (1.37)	31 (1.34)
Asian	20 (1.16)	7 (1.20)	27 (1.17)
Ethnicity			
Non-Hispanic/non-Latino	1451 (84.21)	486 (83.51)	1937 (84.03)
Hispanic/Latino	272 (15.79)	96 (16.49)	368 (15.97)
Age at 1st vaccination (years)			
Mean Age (SD)	21.50 (2.15)	21.49 (2.20)	21.49 (2.16)
Median Age	21.0	22.0	21.0

Numbers analysed

Of the 3304 subjects randomized in the study (2480 in Group 1 and 824 in Group 2), 2305 (69.8%) subjects (69.5% in Group 1 and 70.6% in Group 2) were included in the evaluable immunogenicity population. Of the 999 (30.2%) subjects excluded from the EIP, 757 (30.5%) subjects were in Group 1 and 242 (29.4%) subjects were in Group 2. Subjects could have been excluded from the immunogenicity populations for more than 1 reason. Reasons for exclusion were:

- subjects were not eligible or they became ineligible for the study before or at the post-Vaccination 3 blood draw visit (96 (2.9%))
- did not receive all vaccines as randomized at all vaccination visits (766 (23.2%))
- did not have the scheduled prevaccination or post-Vaccination 3 blood draws (970 (29.4%))
- did not have a valid and determinate assay result at the prevaccination or post-Vaccination 3 blood draw visits (838 (25.4%))

Overall, the 2 study groups were comparable with respect to the percentages of subjects who were excluded from the EIP for the various reasons.

Outcomes and estimation

Primary outcomes

The primary objective of this study was to assess the immune response as measured by hSBA performed with 4 primary MnB test strains, 2 expressing a LP2086 subfamily A protein (PMB80 [A22] and PMB2001 [A56]) and 2 expressing a LP2086 subfamily B protein (PMB2948 [B24] and PMB2707 [B44]), measured 1 month after the third vaccination with bivalent rLP2086.

The 5 co-primary endpoints for this objective were the proportion of subjects in Group 1 achieving at least a 4-fold increase in hSBA titre compared to baseline for each of the 4 primary test strains, and the composite hSBA response (defined as hSBA titre ≥ LLOQ for all 4 primary strains combined) measured 1 month after Vaccination 3 in the evaluable immunogenicity population. The study objectives would be achieved if the lower bounds of the 95% CIs at 1 month after the third vaccination were greater than the threshold specified for each of the 5 co-primary endpoints among subjects in Group 1.

The results of these analyses are presented in Table 16 below. The percentages of subjects with ≥4 fold increase in hSBA titre ranged from 79.3 to 90.0 % depending on the strain. The lower limit of the 2-sided 95% CIs was greater than the corresponding prespecified lower bound threshold for each of the 4 primary strains and the composite hSBA response, therefore the primary immunogenicity objective was met using subjects from all sites globally.

Table 16. Primary Immunogenicity Analysis – Subjects Achieving ≥4-Fold Rise in hSBA Titre and Composite Response at 1 Month After Vaccination 3 for Primary Strains – EIP (B1971016)

	Vaccine Group (as Randomized) Group 1 rLP2086			
Endpoint Strain (Variant)	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%

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

The results in the mITT were similar to those observed for the EIP and also met the criteria for the primary immunogenicity objective. Results for subjects at US sites for the mITT population were also similar to the results of the evaluable immunogenicity population.

Secondary outcomes (primary strains)

hSBA ≥ 4-Fold Response and Composite Response at various time-points

The proportion of subjects achieving at least a 4-fold rise in hSBA titre from baseline to 1 month after Vaccination 2 was 66.9% for PMB80 (A22), 85.9% for PMB2001 (A56), 67.9% for PMB2948 (B24), and 55.5% for PMB2707 (B44) in Group 1. The proportion of subjects achieving at least a 4-fold rise in hSBA titre from baseline to 1 month after Vaccination 3 for the primary MnB test strains for Group 1 was 80.5% for PMB80 (A22), 90.0% for PMB2001 (A56), 79.3% for PMB2948 (B24), and 79.6% for PMB2707 (B44)

in Group 1. In Group 2, the proportion of subjects achieving at least a 4-fold rise in hSBA titre for the primary MnB test strains ranged from 0.9% to 8.6% after Vaccination 2 and ranged from 1.6% to 10.3% after Vaccination 3. The proportions of subjects achieving at least a 4- fold rise in hSBA titre compared to baseline for each of the 4 primary strains were substantially higher in Group 1 than in the control group (Group 2) after both Vaccination 2 and Vaccination 3.

The proportion of subjects with a composite hSBA response at baseline for Group 1 (7.3%) was similar to that in Group 2 (6.1%). In Group 1, the proportion of subjects achieving a composite hSBA response 1 month after the second and third vaccination was 64.5% and 84.9% of subjects, respectively. In Group 2 (control), 7.5% of the subjects achieved a composite response at both 1-month after the second vaccination and 1-month after the third vaccination.

Results were similar for the mITT population. There were no clinically important differences in the subgroup analysis by sex, race, or country.

hSBA GMTs

The hSBA GMTs for each of the 4 primary strains at baseline and 1 month after the second and third vaccination with bivalent rLP2086 are presented in Table 17 for the evaluable immunogenicity population. GMTs increased substantially from baseline to after Vaccination 2 or Vaccination 3 and also increased from Vaccination 2 to after Vaccination 3 for Group 1. Results were similar for the mITT population. There were no clinically important differences in the subgroup analysis by sex, race, or country.

Table 17. hSBA GMTs for Primary Strains – EIP (B1971016)

	Vaccine Group (as Randomized)					
	Group 1 rLP2086			Group 2 Saline		
Strain (Variant) Sampling Time Point	N[a]	GMT[b]	(95% CI)[c]	N[a]	GMT[b]	(95% CI)[c]
PMB80 (A22)						
Before Vaccination 1	1704	12.8	(12.3, 13.3)	573	13.0	(12.2, 13.9)
1 Month after Vaccination 2	1697	49.0	(46.2, 52.1)	570	12.9	(12.1, 13.7)
1 Month after Vaccination 3	1714	74.3	(70.2, 78.6)	577	13.2	(12.4, 14.1)
PMB2001 (A56)						
Before Vaccination 1	1657	8.8	(8.3, 9.3)	563	9.2	(8.3, 10.3)
1 Month after Vaccination 2	1701	114.3	(107.9, 121.0)	552	9.2	(8.2, 10.2)
1 Month after Vaccination 3	1708	176.7	(167.8, 186.1)	552	9.1	(8.2, 10.1)
PMB2948 (B24)						
Before Vaccination 1	1696	7.6	(7.3, 8.0)	570	7.6	(7.0, 8.3)
1 Month after Vaccination 2	1685	35.8	(33.7, 38.2)	570	7.4	(6.8, 8.1)
1 Month after Vaccination 3	1702	49.5	(46.8, 52.4)	573	7.2	(6.6, 7.8)
PMB2707 (B44)						
Before Vaccination 1	1716	4.8	(4.7, 4.9)	578	4.8	(4.6, 5.1)
1 Month after Vaccination 2	1693	22.6	(20.9, 24.4)	577	4.9	(4.6, 5.1)
1 Month after Vaccination 3	1703	47.6	(44.2, 51.3)	577	4.8	(4.6, 5.1)

hSBA Titres ≥ LLOQ at various time point

The proportions of subjects achieving hSBA titres ≥ LLOQ for the 4 primary strains at each blood sampling time point are presented in Table 18 below for the evaluable immunogenicity population.

Table 18. Subjects With hSBA Titre ≥ LLOQ for Primary Strains – Evaluable Immunogenicity Population

	Vaccine Group (as Randomized)					
	Group 1 rLP2086			Group 2 Saline		
Strain (Variant) Sampling Time Point	N[a]	n[b] (%)	(95% CI)[c]	N[a]	n[b] (%)	(95% CI)[c]
PMB80 (A22)						
Before Vaccination 1	1704	572 (33.6)	(31.3, 35.9)	573	192 (33.5)	(29.6, 37.5)
1 Month after Vaccination 2	1697	1437 (84.7)	(82.9, 86.4)	570	198 (34.7)	(30.8, 38.8)
1 Month after Vaccination 3	1714	1602 (93.5)	(92.2, 94.6)	577	211 (36.6)	(32.6, 40.6)
PMB2001 (A56)						
Before Vaccination 1	1657	533 (32.2)	(29.9, 34.5)	563	186 (33.0)	(29.2, 37.1)
1 Month after Vaccination 2	1701	1656 (97.4)	(96.5, 98.1)	552	183 (33.2)	(29.2, 37.3)
1 Month after Vaccination 3	1708	1698 (99.4)	(98.9, 99.7)	552	189 (34.2)	(30.3, 38.4)
PMB2948 (B24)						
Before Vaccination 1	1696	562 (33.1)	(30.9, 35.4)	570	180 (31.6)	(27.8, 35.6)
1 Month after Vaccination 2	1685	1457 (86.5)	(84.7, 88.1)	570	183 (32.1)	(28.3, 36.1)
1 Month after Vaccination 3	1702	1618 (95.1)	(93.9, 96.0)	573	173 (30.2)	(26.5, 34.1)
PMB2707 (B44)						
Before Vaccination 1	1716	189 (11.0)	(9.6, 12.6)	578	64 (11.1)	(8.6, 13.9)
1 Month after Vaccination 2	1693	1157 (68.3)	(66.1, 70.6)	577	72 (12.5)	(9.9, 15.5)
1 Month after Vaccination 3	1703	1489 (87.4)	(85.8, 89.0)	577	66 (11.4)	(9.0, 14.3)

Abbreviations: hSBA = serum bactericidal assay using human complement; LLOQ = lower limit of quantitation. Note: LLOQ = 1:16 for A22; 1:8 for A56, B24, and B44. a. N = number of subjects with valid and determinate hSBA titres for the given strain. b. n = Number of subjects with observed hSBA titre ≥ LLOQ for the given strain at the given time point. c. Exact 2-sided confidence interval (CI) based upon the observed proportion of subjects using the Clopperand Pearson method.

Secondary endpoints for the primary strains are in line with the primary endpoints.

At baseline approximately 30% of subjects had hSBA ≥ LLOQ for strains A22, A56 and B24 – 11% of subjects had hSBA ≥LLOQ for strain B44. One month post dose 2 this increased to 84.7, 97.4, 86.5 and 68.3% for strain A22, A56, B24 and B44 respectively. The response further increased one month post dose 3, bringing the % subjects with hSBA ≥LLOQ to 93.5, 99.4, 95.1 and 87.4% respectively. GMTs clearly increased with every dose for strains A22, A56, and B24, with the largest increase from baseline to one month following dose 2 (thus following the first two doses), and a significant, yet smaller, increase after the third dose for all strains. For strain B44 a significant increase is also seen with the third dose yet here the increase seems larger between dose 2 and three compared to increase between baseline and one month after dose 2.

Results were similar for the mITT population. There were no clinically important differences in the subgroup analysis by sex, race, or country.

Achieving a Defined Level of hSBA Titres

Proportions of subjects achieving hSBA titres at different defined levels (≥1:4, ≥ 1:8, ≥1:16, ≥1:32, ≥1:64, and ≥1:128) were determined and those with an hSBA titre ≥1:4 and ≥1:16 are described below. A hSBA titre of ≥1:4 is assumed to be protective against IMD. In addition, a more conservative hSBA titre of ≥1:16 was used.

The proportion of subjects in Group 1 with an hSBA titre ≥1:4 and ≥1:16 at baseline was 42.1% and 33.6%, respectively, for strain PMB80 (A22); 35.9% and 30.4%, respectively, for PMB2001 (A56), 35.0%

and 29.5%, respectively, for strain PMB2948 (B24), and 14.5% and 7.8%, respectively, for PMB2707 (B44).

The proportion of subjects in Group 1 achieving an hSBA titre ≥1:4 and ≥1:16 at 1 month after Vaccination 2 was 86.2% and 84.7%, respectively, for strain PMB80 (A22); 97.8% and 97.1%, respectively, for PMB2001 (A56), 87.2% and 83.7%, respectively, for strain PMB2948 (B24), and 71.5% and 61.0%, respectively, for PMB2707 (B44).

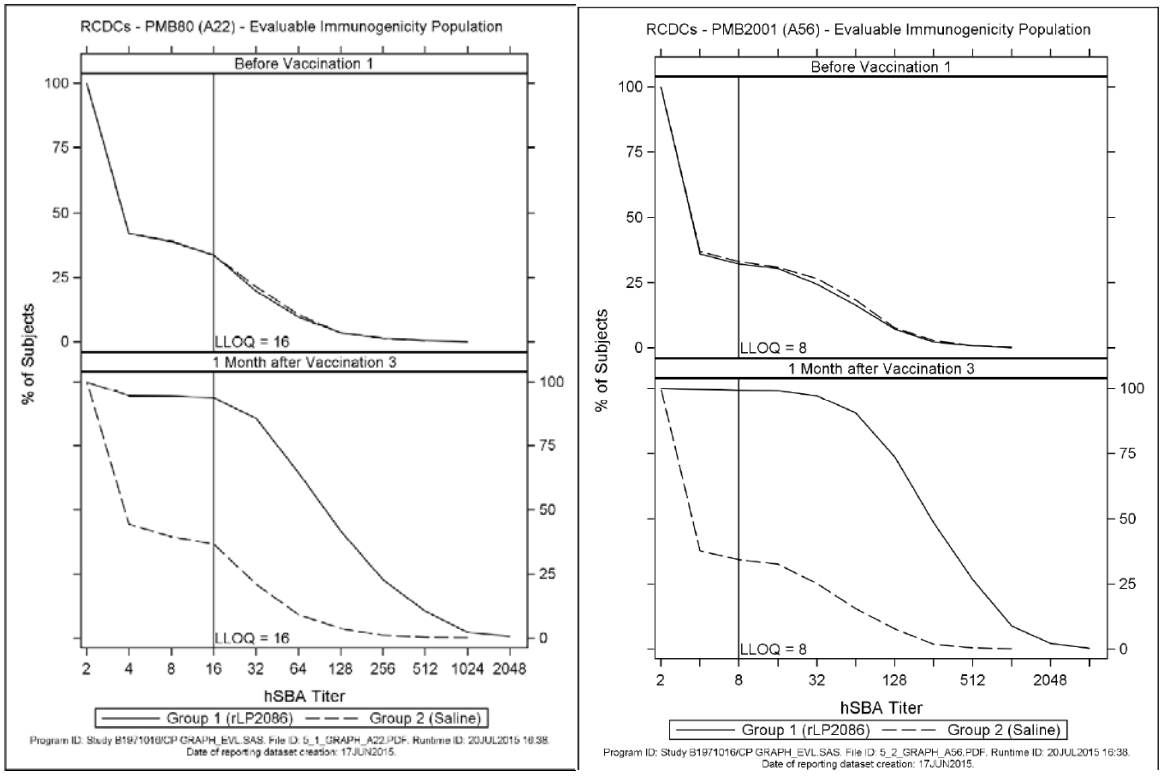
The proportion of subjects in Group 1 achieving an hSBA titre ≥1:4 and ≥1:16 at 1 month after Vaccination 3 was 94.3% and 93.5%, respectively, for strain PMB80 (A22); 99.4% and 99.2%, respectively, for PMB2001 (A56), 95.8% and 93.2%, respectively, for strain PMB2948 (B24), and 89.7% and 83.3%, respectively, for PMB2707 (B44).

The proportions of subjects achieving an hSBA titre ≥1:4 and ≥1:16 for the 4 primary strains were substantially higher in Group 1 than in Group 2 after both Vaccination 2 and Vaccination 3.

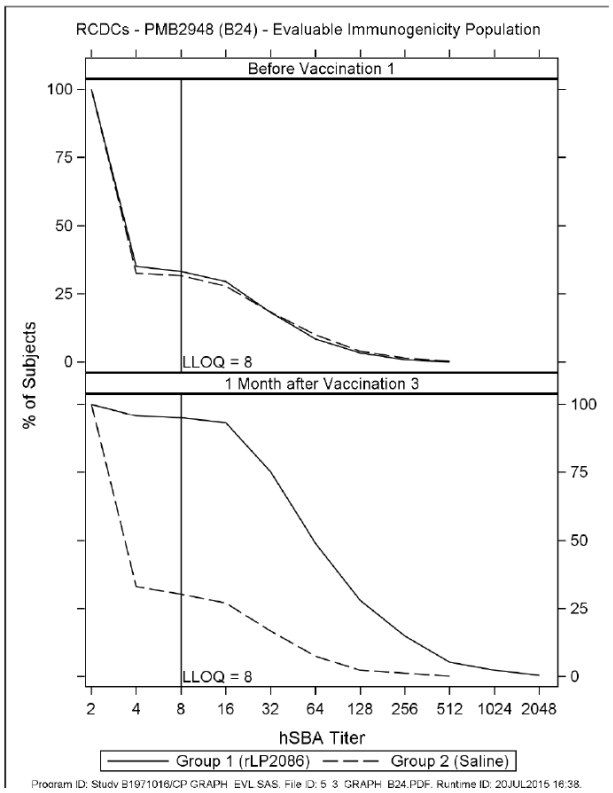
Reverse Cumulative Distribution Curves for the Primary MnB Test Strains

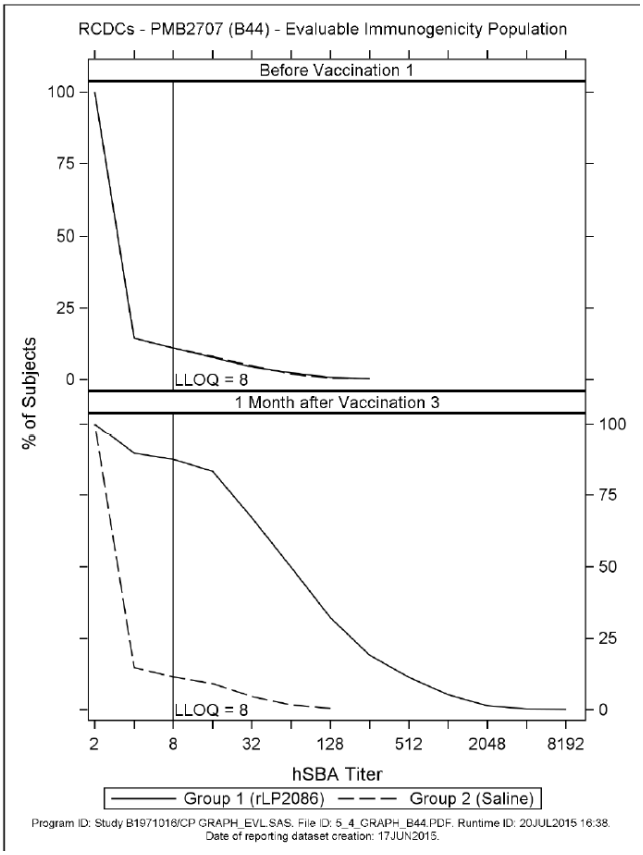
The RCDCs below show that the majority of subjects in Group 1 responded after Vaccination 3 for the 4 primary MnB test strains. Immune responses to the vaccine antigens were substantially higher in Group 1 than in Group 2 after Vaccination 3.

Figure 6. Reverse Cumulative Distribution Curves, Evaluable Immunogenicity Population (B1971016)



The RCDCs also illustrate that the response is potentially the least robust to strain B44 as the curve shows the steepest decline after hSBA titre 1:16 / 1:32, whereas other curves show a stronger plateau.





Secondary outcomes (secondary strains)

Representativeness of Secondary MnB Test Strain Subsets

The demographic characteristics of the subset for secondary MnB strain testing in study B1971016 were similar to those of Group 1 of the evaluable immunogenicity population. There were differences in the distribution of male and female subjects, regional distribution (US subjects versus non US) and degree of missing data in the 3 subsets for secondary strain testing as compared to the overall bivalent rLP2086 group in the B1971016 study. However, these differences did not appear to impact the immune responses elicited by bivalent rLP2086 against the 10 secondary strains, based on responses in subsets that were comparable to the overall group.

hSBA Titres ≥LLOQ for the 10 Secondary MnB Test Strains

The results for subjects with hSBA titres ≥LLOQ for each of the 10 secondary MnB test strains, at baseline and 1 month after the third vaccination with bivalent rLP2086 are summarised as follows (n=270-285 depending on strain).

Among fHBP subfamily A variant-expressing strains, the proportion of subjects with an hSBA titre ≥ LLOQ at baseline and 1 month after Vaccination 3 for strain PMB3175 (A29, subgroup N1C1) was 31.1% (95% CI 25.7, 36.9) and 99.3% (95% CI 97.5, 99.9), respectively; for PMB3010 (A06, subgroup N1C2) it was 16.0% (11.9, 20.9) and 92.0% (88.1, 94.9), respectively; and for PMB1989 (A19, subgroup N2C2) it was 28.8% (23.5, 34.5) and 95.8% (92.7, 97.8), respectively. For the 3 secondary strains in subgroup N2C1 the proportion of subjects with an hSBA titre ≥ LLOQ at baseline and 1 month after Vaccination 3 for PMB3040 (A07) was 55.8% (49.7, 61.8) and 95.7% (92.6, 97.7), respectively; for PMB824 (A12) it was

5.0% (2.8, 8.3) and 71.3% (65.5, 76.5), respectively; and for PMB1672 (A15) it was 37.3% (31.6, 43.2) and 91.8% (87.9, 94.7), respectively.

Among fHBP subfamily B variant-expressing strains (all in subgroup N6) the proportion of subjects with an hSBA titre ≥ LLOQ at baseline and 1 month after Vaccination 3 for PMB1256 (B03) was 11.2% (7.7, 15.5) and 86.4% (81.8, 90.3), respectively; for PMB866 (B09) it was 23.5% (18.6, 28.9) and 77.0% (71.6, 81.9), respectively; for PMB431 (B15) it was 43.8% (37.8, 49.9) and 96.7% (93.9, 98.5), respectively; and for PMB648 (B16) it was 21.9% (17.1, 27.3) and 78.0% (72.6, 82.8) respectively.

Regarding the secondary strains, pre dose one from 5.0% (A12) to 55.8% (A07) had an hSBA titre ≥LLOQ. One month post dose three, the response increased up to 71.3% (A12) and 99.3% (A29) dependent on the strain. There was some variation in the response between strains, but 6/10 strains had an hSBA ≥LLOQ >90%, 7/10 >85% and 9/10 >75%, suggesting an overall strong response.

hSBA Titres Achieving Defined Levels for the 10 Secondary MnB Test Strains

Of the percentages of subjects achieving defined hSBA titres for the 10 secondary strains, subjects who achieved an hSBA titre ≥1:4 and ≥1:16 are described below.

Among fHBP subfamily A variant-expressing strains, the proportion of subjects in Group 1 with hSBA titres of ≥1:4 from baseline to 1 month after Vaccination 3 for strain PMB3175 (A29) was 32.9% and increased to 99.3%, for PMB3010 (A06) in subgroup N1C2 it was 18.9% and increased to 92.4% and for PMB1989 (A19) in subgroup N2C2 it was 39.2% and increased to 96.1%, respectively. The proportion of subjects with hSBA titres of ≥1:4 from baseline to 1 month after Vaccination 3 for PMB3040 (A07) was 55.8% and increased to 95.7%, for PMB824 (A12) it was 10.4% and increased to 73.8%, and for PMB1672 (A15) it was 39.4% and increased to 91.8%, respectively.

In addition, the proportion of subjects in Group 1 with hSBA titres of ≥1:16 from baseline to 1 month after Vaccination 3 for strain PMB3175 (A29) was 27.9% and increased to 98.9%, for PMB3010 (A06) in subgroup N1C2 it was 16.0% and increased to 92.0% and for PMB1989 (A19) in subgroup N2C2 it was 28.8% and increased to 95.8%, respectively. The proportion of subjects with hSBA titres of ≥1:16 from baseline to 1 month after Vaccination 3 for PMB3040 (A07) was 55.5% and increased to 95.7%, for PMB824 (A12) it was 5.0% and increased to 71.3%, and for PMB1672 (A15) it was 33.3% and increased to 91.4%, respectively.

Among fHBP subfamily B variant-expressing strains (all in subgroup N6) the proportion of subjects with an hSBA titre ≥1:4 from baseline to 1 month after Vaccination 3 for PMB1256 (B03) was 13.0% and increased to 86.8%, for PMB866 (B09) it was 24.5% and increased to 78.5%, for PMB431 (B15) it was 44.9% and increased to 97.1%, and for PMB648 (B16) it was 24.4% and increased to 79.1%.

In addition, the proportion of subjects in Group 1 with an hSBA titre ≥1:16 from baseline to 1 month after Vaccination 3 for PMB1256 (B03) was 10.1% and increased to 85.3%, for PMB866 (B09) it was 18.8% and increased to 73.4%, for PMB431 (B15) it was 41.2% and increased to 96.7%, and for PMB648 (B16) it was 18.9% and increased to 76.6%.

Ancillary analyses

Post Hoc analysis of positive predictive values for the phase 3 studies (B1971009 and B1971016)

The positive predictive value (PPV) analyses were performed post hoc. For each primary/secondary strain pair within a given fHBP family, the PPV was defined as proportion of subjects who respond to the secondary strain (hSBA titre ≥ LLOQ for secondary strain) among the total number of primary strain responders (hSBA titre ≥ LLOQ for primary strain).

The PPVs of primary strain responses for secondary strain responses were provided after vaccination 3 in the evaluable immunogenicity population and in the post-vaccination 2 per-protocol (evaluable immunogenicity) population. The PPVs of primary strain responses for secondary strain responses within the same subfamily, given a response ≥ LLOQ for a primary strain, were high. See below for study-specific results.

Study B1971009

For subfamily A strains, the PPVs ranged from 64.4% to 100% at 1 month after the second vaccination and from 75.6% to 99.6% at 1 month after the third vaccination. When the analysis was restricted to those who were negative to primary and secondary strains before vaccination 1, the PPVs ranged from 44.9% to 100% at 1 month after the second vaccination and from 69.6% to 100% at 1 month after the third vaccination.

For subfamily B strains, the PPVs ranged from 78.9% to 100% at 1 month after the second vaccination and from 85.5% to 99.6% at 1 month after the third vaccination. When the analysis was restricted to those who were negative to primary and secondary strains before vaccination 1, the PPVs ranged from 75.0% to 100% at 1 month after the second vaccination and from 84.7% to 99.4% at 1 month after the third vaccination.

Study B1971016

For subfamily A strains, the PPVs ranged from 61.6 to 100% at 1 month after the second vaccination and from 72.2% to 100% at 1 month after the third vaccination. When the analysis was restricted to those who were negative to primary and secondary strains before vaccination 1, the PPVs ranged from 46.9% to 100% at 1 month after the second vaccination and from 64.9% to 100% at 1 month after the third vaccination.

For subfamily B strains, the PPVs ranged from 70.0% to 100% at 1 month after the second vaccination and from 80.5% to 98.8% at 1 month after the third vaccination. When the analysis was restricted to those who were negative to primary and secondary strains before vaccination 1, the PPVs ranged from 44.1% to 100% at 1 month after the second vaccination and from 71.2% to 98.5% at 1 month after the third vaccination.

Overall across studies, the PPV analyses showed that responses to primary strain are predictive of responses to secondary, since subjects who responded to primary strains were very likely to respond to secondary strains at high rates. The PPVs are slightly lower in persons negative to primary and secondary strains prior to vaccination.

Almost consistently, i.e. at different time points in the two phase 3 studies, the worst PPVs of the primary strain response was for the PMB824 (A12) strain and the PMB648 (B16) strain. At few time points the worst PPVs was for PMB1672 (A15) (post vaccination 2 study B1971009) and B09 (post vaccination 2, B1971009). These findings were investigated further. PPVs are related to the individual strain absolute response proportions; thus the fact that PPVs involving A12 and B16 are the lowest of all those examined is not surprising, considering that these 2 secondary strains were generally the strains associated with lower response rates among the 10 secondary strains. It is important to note that even though those response rates were lower in relative terms, the proportions of subjects achieving hSBA titres ≥ LLOQ were high in absolute terms: for A12, 75.1% and 71.3% post-vaccination 3 in Studies B1971009 and B1971016, respectively; and for B16, 81.7% and 78.0% post-vaccination 3 in B1971009 and B1971016, respectively. Thus, these analyses support the finding that bivalent rLP2086 confers broad coverage against MnB strains, as all strains expressing heterologous fHBP variants showed a protective hSBA response greater than the presumptive correlate of protection (hSBA titre ≥1:4) after 2 or 3 doses of vaccine.

Although variation in hSBA response may be due to undefined, strain- and complement-specific differences, the PPVs of primary strains for secondary strain responses were generally high (including secondary strains expressing fHBP variants A12 and B16), and the proportions of subjects achieving hSBA titres ≥ LLOQ were uniformly high for all 14 primary and secondary strains.

Subpopulation analyses

The effect of covariates was evaluated within different studies and across phase II/III studies for those subjects who received the 0,2,6 m schedule against the four primary test strains and were part of the evaluable immunogenicity population. This integrated analysis of efficacy is used to discuss the effect of relevant covariates on the immune response.

Response by age group

The number and percentages of subjects in different age groups who received bivalent rLP2086 (120 µg) administered using a 0, 2, 6-month schedule in two Phase 3 studies and five Phase 2 studies against the four primary test strains in the evaluable immunogenicity population are:

- 10 to 14 years, n=4290, 53.45%;
- 15 to 18 years, n=2184, 27.21%;
- 10 to 18 years, n=6474, 80.66%; and
- 19 to 25 years, n=1552, 19.34%.

The immune responses in the 4 age subgroups (10 to 14, 15 to 18, 10 to 18, and 19 to 25 year age groups) after 3 doses of bivalent rLP2086 showed no substantial differences between age groups in the subgroup analysis for any immunogenicity endpoint analysed, and were consistent with the responses in the overall population.

Table 19. Subjects achieving ≥4-Fold Rise in hSBA Titre and Composite Response, ≥ LLOQ, and hSBA GMTs at 1 Month After Dose 3 by Age Group – AND Subjects achieving hSBA ≥1:16 by Age Group – Subjects Who Received Bivalent rLP2086 Final Formulation (120 µg Dose Level) on a 0-, 2-, and 6-Month Schedule – Evaluable Immunogenicity Population (integrated summary of efficacy)

		Strain (variant)													
Endpoints		PMB80 (A22)			PMB2001 (A56)			PMB2948 (B24)			PMB2707 (B44)			Composite Response	
	Age Group (Years)	N	% or GMT	(95% CI)	N	% or GMT	(95% CI)	N	% or GMT	(95% CI)	N	% or GMT	(95% CI)	%	(95% CI)
≥4-Fold rise & composite response															
	10 to 14	3943	86.8	(85.7, 87.9)	1875	93.7	(92.5, 94.8)	3923	83.3	(82.1, 84.4)	2012	82.3	(80.6, 84.0)	83.5	(81.8, 85.2)
	15 to 18	1961	81.2	(79.4, 82.9)	1406	92.0	(90.5, 93.4)	1939	79.0	(77.1, 80.8)	1473	80.6	(78.5, 82.6)	81.6	(79.5, 83.6)
	19 to 25	1525	80.9	(78.8, 82.8)	1480	90.0	(88.4, 91.5)	1511	79.5	(77.4, 81.5)	1526	79.9	(77.8, 81.9)	85.5	(83.6, 87.3)
≥ LLOQ															
	10 to 14	4031	94.6	(93.9, 95.3)	2038	99.5	(99.1, 99.8)	3971	90.6	(89.7, 91.5)	2024	86.5	(84.9,88.0)	N/A	N/A
	15 to 18	2002	94.8	(93.7, 95.7)	1509	98.9	(98.3, 99.4)	1973	89.0	(87.5, 90.3)	1489	85.4	(83.5,87.2)	N/A	N/A
	19 to 25	1544	93.8	(92.5,95.0)	1537	99.5	(99.0, 99.8)	1534	95.4	(94.2,96.4)	1533	88.0	(86.3,89.6)	N/A	N/A
hSBA GMT															
	10 to 14	4031	62.4	(60.6,64.2)	2038	161.9	(155.4, 168.7)	3971	25.4	(24.6,26.1)	2024	37.3	(35.2,39.5)	N/A	N/A
	15 to 18	2002	68.4	(65.3, 71.5)	1509	155.1	(147.0, 163.6)	1973	28.0	(26.7, 29.3)	1489	36.9	(34.4, 39.5)	N/A	N/A
	19 to 25	1544	75.9	(71.6, 80.5)	1537	178.4	(169.0, 188.3)	1534	50.9	(47.9, 54.0)	1533	49.3	(45.6, 53.3)	N/A	N/A
% subjects achieving a hSBA titre ≥1:16															
Pre dose 1															
	10 to 14	4097	16.4	(15.3, 17.6)	2020	15.7	(14.1, 17.4)	4140	3.4	(2.9, 4.0)	2177	1.8	(1.3, 2.5)	N/A	N/A
	15 to 18	2093	28.1	(26.2, 30.1)	1528	20.1	(18.1, 22.2)	2103	10.5	(9.2, 11.9)	1622	4.6	(3.6, 5.7)	N/A	N/A
	19 to 25	1533	34.4	(32.0, 36.8)	1495	31.2	(28.8, 33.6)	1529	30.3	(28.0, 32.7)	1545	8.1	(6.8, 9.6)	N/A	N/A
1 month after dose 2															
	10 to 14	4050	83.2	(82.0, 84.4)	2126	98.7	(98.1, 99.1)	3927	60.4	(58.8, 61.9)	2079	51.7	(49.5, 53.8)	N/A	N/A
	15 to 18	2041	87.4	(85.8, 88.8)	1578	97.8	(96.9, 98.5)	1997	68.4	(66.3, 70.4)	1563	56.5	(54.0, 59.0)	N/A	N/A
	19 to 25	1531	85.3	(83.4, 87.0)	1532	97.0	(96.0, 97.8)	1519	84.5	(82.5, 86.3)	1525	61.9	(59.4, 64.3)	N/A	N/A
1 Month after Dose 3															
	10 to 14	4031	94.6	(93.9, 95.3)	2038	99.5	(99.1, 99.8)	3971	85.7	(84.6, 86.8)	2024	83.0	(81.2, 84.6)	N/A	N/A
	15 to 18	2002	94.8	(93.7, 95.7)	1509	98.9	(98.2, 99.3)	1973	85.4	(83.7, 86.9)	1489	82.6	(80.6, 84.5)	N/A	N/A
	19 to 25	1544	93.8	(92.5, 95.0)	1537	99.3	(98.7, 99.6)	1534	93.4	(92.1, 94.6)	1533	83.9	(82.0, 85.7)	N/A	N/A

An increase in GMTs noted with increasing age can be seen for strains PMB80 (A22) and PMB2948 (B24) (non-overlapping CIs). It is possible that this is in part caused by differences in baseline immunity between the age groups; a clear age related increase is apparent in those with hSBA titres ≥1:16 pre dose 1. A similar pattern is not seen for the ≥ fourfold rise endpoint and is also not seen for the endpoint ≥ LLOQ / ≥ 1:16 post dose 3. In any case, available data does not point towards a clinically relevant effect of age on the hSBA response for persons aged between 10-26 years.

For older adults, with increasing age, the immune response to vaccines can diminish due to immunosenescence. **Study B1971042** was the only study including subjects >40 years: in total 13 subjects aged 24 to 62 years were included in the study. Five subjects were ≤40 years, eight subjects were >40 years. Only eight subjects were included in the evaluable immunogenicity population of which 4 were aged over 40 years. The number of subjects is too limited for reliable inferences to be made based on this study. It remains uncertain if and how the immune response is affected by age and whether the benefits in older adults are of a similar magnitude as the strong hSBA responses against a range of MnB strains that have been firmly demonstrated in phase II and III studies for adolescents and younger adults. However the limited data available in persons >40 years of age and > 26 years of age suggest that the immunogenicity and safety profile is acceptable, and similar to that seen in younger adults. It is known that the immune response to vaccination can diminish with age due to immunosenescence. However, based also upon experience with other vaccines, the impact of immunosenescence is deemed unlikely to be of such a degree that it would render the benefit/risk balance of rLP2086 negative for the whole population over 65 years.

Most importantly, if for example in an outbreak situation persons over 40 or over 65 would have to be vaccinated this should be possible considering the acceptable safety profile of bivalent rLP2086 and the likelihood of eliciting a protective immune response.

Response by Sex

Across studies the hSBA response was consistently lower in females compared to males. The table below shows the responses per strain stratified by sex for subjects who received bivalent rLP2086 (120 µg) administered using a 0, 2, 6-month schedule in 2 Phase 3 studies and 5 Phase 2 studies. The composite response post dose 3 was 79.7% (95% CI: 77.9, 81.3) for females and 87.3% (95% CI: 85.9, 88.6) for males.

Table 20. Subjects Achieving ≥4-Fold Rise in hSBA Titre, ≥ LLOQ, and hSBA GMTs at 1 Month After Dose 3 by Sex – Subjects Who Received Bivalent rLP2086 Final Formulation (120 µg Dose Level) on a 0-, 2-, and 6-Month Schedule – Evaluable Immunogenicity Population (Integrated Efficacy Analysis)

	Strain (variant)											
	PMB80 (A22)			**PMB2001 (A56)**			**PMB2948 (B24)**			**PMB2707 (B44)**		
	N	% or GMT	(95% CI)	N	% or GMT	(95% CI)	N	% or GMT	(95% CI)	N	% or GMT	(95% CI)
≥4-Fold rise												
Female	3595	82.5	(81.2, 83.7)	2292	89.7	(88.3, 90.9)	3555	79.2	(77.8, 80.5)	2425	76.8	(75.1, 78.5)
Male	3834	85.7	(84.5, 86.7)	2469	94.3	(93.3, 95.2)	3818	83.4	(82.2, 84.6)	2586	85.1	(83.6, 86.4)
≥ LLOQ												
Female	3662	93.8	(93.0, 94.6)	2464	99.3	(98.8, 99.6)	3598	88.9	(87.9, 89.9)	2437	83.2	(81.6, 84.6)
Male	3915	95.1	(94.4, 95.8)	2620	99.4	(99.0, 99.7)	3880	93.2	(92.4, 94.0)	2609	89.9	(88.7, 91.0)
hSBA GMT												
Female	3662	63.0	(60.9, 65.1)	2464	157.3	(151.0, 163.8)	3598	28.0	(27.0, 29.0)	2437	36.1	(34.0, 38.3)
Male	3915	70.0	(67.8, 72.3)	2620	171.8	(165.3, 178.7)	3880	32.0	(31.0, 33.1)	2609	45.0	(42.7, 47.4)

The impact of sex on the response to vaccination has been described previously, however typically it is the females who develop higher antibody responses than males. In this case the difference in response between males and females is small and of unlikely clinical relevance. Therefore no consequences will be attached to this observation.

Response by Race

The effect of race on the immune response after 3 doses of bivalent rLP2086 could not be definitively assessed because the majority of the subjects were white (n=6982, 86.99%). With the limited data available for the additional races represented (black [n=745, 9.28%], other races [n=238, 2.97%], Asian [n=61, 0.76%]), no meaningful differences were detected in the subgroup analysis for any of the immunogenicity endpoints analysed.

Response by baseline immunity

Assessment of immune response to bivalent rLP2086 was conducted using various measures including the proportion of subjects with hSBA titres ≥ the lower limit of quantitation (LLOQ), the proportion with a 4-fold rise in hSBA titres and composite response, and hSBA GMTs for each of the 4 primary MnB test strains. The immunogenicity endpoint for 4-fold increases in hSBA titres addresses variability in baseline MnB titres for each strain and provides a reliable assessment of individual immune responses to bivalent rLP2086 irrespective of pre-existing immunity (serostatus at baseline).

The response (i.e. obtaining an hSBA ≥ LLOQ) in those seronegative at baseline for both pivotal studies B1971009 and B1971016 is presented in the tables below.

Table 21. Subgroup Analysis of Subjects in Group 1 and Group 2 with hSBA Titre ≥ LLOQ for Primary Strains by Baseline hSBA Titre <LLOQ – Evaluable Immunogenicity Population (B1971009)

	Vaccine Group (as Randomized)							
	Group 1 rLP2086 Lot 1				Group 4 HAV/Saline			
Baseline Titre Strain (Variant) Sampling Time Point	N[a]	n[b] %	%	(95% CI)[c]	N[a]	n[b] %	%	(95% CI)[c]
Baseline titre < LLOQ								
PMB80 (A22)								
1 Month after Vaccination 2	817	751	91.9	(89.8, 93.7)	450	73	16.2	(12.9, 20.0)
1 Month after Vaccination 3	816	793	97.2	(95.8, 98.2)	453	68	15.0	(11.8, 18.6)
PMB2001 (A56)								
1 Month after Vaccination 2	812	804	99.0	(98.1, 99.6)	249	34	13.7	(9.6, 18.6)
1 Month after Vaccination 3	818	815	99.6	(98.9, 99.9)	253	31	12.3	(8.5, 16.9)
PMB2948 (B24)								
1 Month after Vaccination 2	1121	716	63.9	(61.0, 66.7)	687	20	2.9	(1.8, 4.5)
1 Month after Vaccination 3	1156	998	86.3	(84.2, 88.3)	691	20	2.9	(1.8, 4.4)
PMB2707 (B44)								
1 Month after Vaccination 2	1153	725	62.9	(60.0, 65.7)	371	8	2.2	(0.9, 4.2)
1 Month after Vaccination 3	1159	1034	89.2	(87.3, 90.9)	375	6	1.6	(0.6, 3.4)

Table 22. Subgroup Analysis of Subjects with hSBA Titre ≥ LLOQ for Primary Strains by Baseline hSBA Titre <LLOQ – Evaluable Immunogenicity Population (B1971016)

	Vaccine Group (as Randomized)							
	Group 1 rLP2086				Group 2 Saline			
Baseline Titre Strain (Variant) Sampling Time Point	N[a]	n[b]	%	(95% CI)[c]	N[a]	n[b]	%	(95% CI)[c]
Baseline titre < LLOQ								
PMB80 (A22)								
1 Month after Vaccination 2	1109	855	77.1	(74.5, 79.5)	371	32	8.6	(6.0, 12.0)
1 Month after Vaccination 3	1124	1014	90.2	(88.3, 91.9)	377	44	11.7	(8.6, 15.3)
PMB2001 (A56)								
1 Month after Vaccination 2	1110	1067	96.1	(94.8, 97.2)	356	36	10.1	(7.2, 13.7)
1 Month after Vaccination 3	1117	1108	99.2	(98.5, 99.6)	362	48	13.3	(9.9, 17.2)
PMB2948 (B24)								
1 Month after Vaccination 2	1102	881	79.9	(77.5, 82.3)	383	33	8.6	(6.0, 11.9)
1 Month after Vaccination 3	1115	1035	92.8	(91.1, 94.3)	387	36	9.3	(6.6, 12.6)
PMB2707 (B44)								
1 Month after Vaccination 2	1498	966	64.5	(62.0, 66.9)	509	17	3.3	(2.0, 5.3)
1 Month after Vaccination 3	1508	1297	86.0	(84.2, 87.7)	510	15	2.9	(1.7, 4.8)

In both studies B1971009 and B1971016 the response, when expressed as percentages of subjects with titres ≥LLOQ, was marginally lower for both B strains compared to the A strains in both the seropositive (as previously shown) and the seronegative subjects at baseline. This suggests that the response to the B-strains, which overall came out as slightly lower than the response to the A-strains, cannot solely be explained by a higher percentages of subjects seronegative at baseline, although it does play part for the response to B44 in B1971016 and both B-strains in study B1971009.

Additionally the Applicant presented all the response (% hSBA ≥LLOQ; ≥4-Fold Rise in hSBA Titre and Composite Response) stratified by serostatus at baseline (hSBA titre ≥LLOQ vs hSBA titre <LLOQ) for the main clinical studies: B1971012, B1971009, B1971016. Overall, vaccination with bivalent rLP2086 substantially increased the responder rate (whether measured as the proportion achieving a 4-fold rise from baseline and composite response or the proportion with hSBA titres ≥LLOQ) after 2 or 3 doses of vaccine, regardless of baseline antibody status. Across the 3 studies for each test strain the majority of

subjects achieved ≥4-fold rise in hSBA titre (as conservatively defined), which was well above the assumed correlate of protection (hSBA ≥1:4). These results suggest that bivalent rLP2086 will benefit individuals without evidence of prior MnB antibodies as well as those pre-exposed to MnB antigens.

Summary of main studies

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 23. Summary of Efficacy for trial B1971009

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	B1971009		
Design	Phase 3, randomized, active-controlled, observer-blinded multicentre trial to assess 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.		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	14 months not applicable not applicable	
Hypothesis	Superiority over set thresholds (efficacy objective) Equivalence (lot-to-lot consistency objective)		
Treatments groups	Group 1		rLP2086 Lot 1, N=1509
	Group 2		rLP2086 Lot 2, N=600
	Group 3		rLP2086 Lot 3, N=589
	Group 4, Control		HAV vaccine/saline, N=898
Endpoints and definitions	Co Primary endpoints: *Response*	*Composite hSBA response*	*1)* The % subjects with hSBA titre ≥ lower limit of quantitation (LLOQ) for all 4 primary MnB test strains combined, 1 month after the 3rd dose with bivalent rLP2086. LLOQ: ≥ 1:8 for strains A56, B24, B44, ≥1:16 for strain A22
		hSBA titre fold rise ≥4 from baseline	*2-4)* % subjects achieving≥ 4-fold increase¥ in hSBA titre from baseline to 1 month after the 3rd vaccination with bivalent rLP2086 for each of the 4 primary MnB test strains.
	Co Primary endpoints: *Lot-to-Lot consistency*	*GMTs*	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.
	Secondary endpoint *(Primary strains)*	composite hSBA response	% subjects with an hSBA titre of ≥ LLOQ for all 4 primary strains at *baseline*.
			% subjects with an hSBA titre of ≥ LLOQ for all 4 primary strains at one month after *2nd vaccination*
		Four fold increase	% subjects ≥4-fold increase from baseline to 1 month after 2nd vaccination
		% hSBA ≥ thresholds	Proportions of subjects with hSBA titres ≥1:4, ≥1:8, ≥1:16, ≥1:32, ≥1:64, and ≥1:128 for each of the 4 primary test strains, at baseline and 1 month after the third vaccination with bivalent rLP2086.

		hSBA GMTs	GMTs for each of the 4 primary test strains at baseline and 1 month after the second and the third vaccination with bivalent rLP2086.
		Two fold increase	% subjects achieving ≥2-fold increase from baseline to 1-month after the second and the third vaccination with bivalent rLP2086 for each of the 4 primary test strains
		RCDCs	Empirical reverse cumulative distribution curves (RCDCs) showing the distribution of hSBA titers were presented graphically for each of the 4 primary MnB test strains, by each group, and at each sampling time point, for the evaluable immunogenicity population, and for secondary MnB strains at baseline and one month post dose 3.
	Secondary endpoint: *(Secondary strains)*	hSBA ≥ LLOQ	% subjects with hSBA titres ≥ LLOQ for each of the test strains at baseline and 1 month after the third vaccination with bivalent rLP2086.
		% hSBA ≥ thresholds	Proportions of subjects with hSBA titres ≥1:4, ≥1:8, ≥1:16, ≥1:32, ≥1:64, and ≥1:128 for each of the test strains, at baseline and 1 month after the third vaccination with bivalent rLP2086.
		hSBA GMTs	GMTs for each of the test strains at baseline and 1 month after the third vaccination with bivalent rLP2086.
Database lock	First Subject First Visit: 18 April 2013 Last Subject Last Visit: 14 April 2015 Final Serology Date: 17 June 2015		

Results and Analysis

Analysis description	**Primary Analysis**
Analysis population and time point description	Evaluable immunogenicity population: all eligible randomized subjects who had received investigational products at visit 1, 2 and 4 as randomized and had baseline and post vaccination 3 (within 28 to 42 days) blood draws available. Subjects were to have valid and determinate assay results for the proposed analysis, received no prohibited vaccines or treatment, and have no other major protocol violations as determined by the sponsor's global medical monitor.

Descriptive statistics and estimate variability	Treatment group		Group 1	Group 2	Group 3	Group 4
	Number of subjects					
	Composite hSBA response; n (%) (95%CI)		N=1170			N=353
			977 (83.5) (81.3-85.6)			10 (2.8) (1.4, 5.1)
	Response by strain					
	hSBA fold rise ≥4 from baseline n (%) (95%CI)	A22	N=1225	N=501	N=478	N=730
			1019 (83.2; 81.0, 85.2)	420 (83.8) (80.3, 86.9)	411 (86.0) (82.5, 89.0)	70 (9.6) (7.6, 12.0)
		A56	N=1128			N=337
			1018 (90.2) (88.4, 91.9)			38 (11.3) (8.1, 15.1)
		B24	N=1235	N=507	N=472	N=752
			985 (79.8) (77.4, 82.0)	388 (76.5) (72.6, 80.2)	370 (78.4) (74.4, 82.0)	20 (2.7) (1.6, 4.1)
		B44	N=1203			N=391
			1033 (85.9) (83.8, 87.8)			4 (1.0) (0.3, 2.6)
	Treatment group		Group 1	Group 2	Group 3	Group 4
	GMTs	A22	N=1266	N=518	N=492	N=749

	(95%CI) 1 Month after Vaccination 3		86.8 (82.29, 91.50)	84.3 (77.54, 91.68)	85.1 (78.26, 92.47)	12.6 (11.96, 13.35)
		A56	N=1229			N=363
			222.5 (210.09, 235.56)			8.8 (7.63, 10.11)
		B24	N=1250	N=516	N=479	N=762
			24.1 (22.70, 25.48)	25.3 (23.08, 27.72)	25.2 (23.03, 27.58)	4.5 (4.37, 4.68)
		B44	N=1210			N=393
			50.9 (47.01, 55.16)			4.4 (4.21, 4.63)

Effect estimate per comparison	Co- Primary	Comparison groups	Group 1			
		Composite hSBA response	83.5 %			
		95% CI	81.3, 85.6			
		Lower Bound Threshold (Success criterion)	75%			
		P-value	ND			
	Co- Primary	Comparison groups (primary test strains)	A22	A56	B24	B44
		Four fold response	83.2	90.2	79.8	85.9
		95% CI	81.0, 85.2	88.4, 91.9	77.4, 82.0	83.8, 87.8
		Lower Bound Threshold (Success criterion)	75%	85%	65%	60%
		P-value	ND	ND	ND	ND

Co- Primary	Comparison groups		Group 1 to Group 2	Group 1 to Group 3	Group 2 to group 3
	Strain	Statistic			
	A22	GMR	1.03	1.02	0.99
		95% CI	0.93, 1.14	0.92, 1.13	0.88, 1.12
	B24	GMR	0.95	0.95	1.00
		95% CI	0.85, 1.06	0.86, 1.06	0.88, 1.14
	Equivalence margins		0.5, 2.0	0.5, 2.0	0.5, 2.0

Notes	The co-primary objectives were met: the lower limit of the 2-sided 95% CIs was greater than the corresponding pre-specified lower bound threshold for each of the 4 primary MnB strains and for the composite response, and lot to lot consistency was demonstrated. Of subjects vaccinated with bivalent rLP2086, 79.8%-90.2% had ≥ fourfold rise in hSBA titres against the four primary strains.					
Analysis description	**Secondary analysis (Primary strains)**					
Descriptive statistics and estimate variability	Treatment group		Group 1	Group 2	Group 3	Group 4
	hSBA Titre ⩾ LLOQ	A22				
	N / n (%)	Before vaccination	1238 / 411 (33.2) (30.6, 35.9)	502/175 (34.9) (30.7, 39.2)	479/152 (31.7) (27.6, 36.1)	748/85 (38.1) (34.6, 41.7)

	(95%CI)	1 month after vaccination 2	1263/1191 (94.3) (92.9, 95.5)	510/473 (92.7) (90.1, 94.8)	487/461 (94.7) (92.3, 96.5)	743/276 (37.1) (33.7, 40.7)
		1 month after vaccination 3	1266/1238 (97.8) (96.8, 98.5)	518/504 (97.3) (95.5, 98.5)	49/483 (98.2) (96.6, 99.2)	749/255 (34.0) (30.7, 37.6)
		A56				
		Before vaccination	1135/312 (27.5) (24.9, 30.2)			362/95 (26.2) (21.8, 31.1)
		1 month after vaccination 2	1222 1211 (99.1) (98.4, 99.5)			358/104 (29.1) (24.4, 34.1)
		1 month after vaccination 3	1229 1223 (99.5) (98.9, 99.8)			363/100 (27.5) (23.0, 32.5)
		B24				
		Before vaccination	1264/81 (6.4) (5.1, 7.9)	510/44 (8.6) (6.3, 11.4)	486/41 (8.4) (6.1, 11.3)	758/ 63 (8.3) (6.4, 10.5)
		1 month after vaccination 2	1216/807 (66.4) (63.6, 69.0)	499/350 (70.1) (65.9, 74.1)	470/330 (70.2) (65.9, 74.3)	758/ 62 (8.2) (6.3, 10.4)
		1 month after vaccination 3	1250/1089 (87.1) (85.1, 88.9)	516/452 (87.6) (84.4, 90.3)	479/431 (90.0) (86.9, 92.5)	762/ 53 (7.0) (5.3, 9.0)
		B44				
		Before vaccination	1230/44 (3.6) (2.6, 4.8)			391/16 (4.1) (2.4, 6.6)
		1 month after vaccination 2	1204/771 (64.0) (61.3, 66.8)			389/23 (5.9) (3.8, 8.7)
		1 month after vaccination 3	1210/1080 (89.3) (87.4, 90.9)			393/21 (5.3) (3.3, 8.1)
	Treatment group		Group 1	Group 2	Group 3	Group 4
	hSBA GMT **N** **GMT (95% CI)**	A22				
		Before vaccination	1238 12.6 (12.08, 13.14)	502 12.9 (12.06, 13.79)	479 12.2 (11.43, 13.04)	748 13.4 (12.63, 14.12)
		1 month after vaccination 2	1263 50.4 (47.76, 53.09)	510 47.7 (43.82, 51.97)	487 49.6 (45.58, 53.99)	743 13.2 (12.52, 14.00)
		1 month after vaccination 3	1266 86.8 (82.29, 91.50)	518 84.3 (77.54, 91.68)	492 85.1 (78.26, 92.47)	749 12.6 (11.96, 13.35)
		A56				

		Before vaccination	1135 8.4 (7.80,9.05)			362 8.3 (7.22, 9.46)
		1 month after vaccination 2	1222 131.2 (124.03, 138.70)			358 8.9 (7.77, 10.24)
		1 month after vaccination 3	1229 222.5 (210.09, 235.56)			363 8.8 (7.63, 10.11)
		B24				
		Before vaccination	1264 4.5 (4.37,4.60)	510 4.6 (4.43,4.85)	486 4.6 (4.43, 4.88)	758 4.6 (4.44, 4.78)
		1 month after vaccination 2	1216 14.3 (13.45,15.31)	499 14.5 (13.23, 15.98)	470 15.2 (13.75, 16.85)	758 4.5 (4.40, 4.70)
		1 month after vaccination 3	1250 24.1 (22.70, 25.48)	516 25.3 (23.08, 27.72)	479 25.2 (23.03,27.58)	762 4.5 (4.37,4.68)
		B44				
		Before vaccination	1230 4.3 (4.17, 4.34)			391 4.3 (4.16,4.54)
		1 month after vaccination 2	1204 17.1 (15.80, 18.60)			389 4.4 (4.22,4.58)
		1 month after vaccination 3	1210 50.9 (47.01, 55.16)			393 4.4 (4.21,4.63)
	Other secondary endpoints for the primary strains were in line with these results, with the Reverse Cumulative Distribution Curves showing increased responses following three doses compared to two doses - in particular against strain A56. These also illustrate that the response is maybe less robust for the B strains as the curve shows the steepest decline after hSBA titre 1:16 / 1:32 whilst other curves show a larger plateau.					
Secondary analysis, Secondary strains	For the 10 secondary strains, PMB3175 (A29), PMB3010 (A06), PMB3040 (A07), PMB824 (A12), PMB1672 (A15), PMB1989 (A19), PMB1256 (B03), PMB866 (B09), PMB431 (B15) and PMB648 (B16), pre-vaccination 3.9-43.1% of subjects had an hSBA titre≥LLOQ dependent on the strain. One month post dose 3 75.1-98.2% had an hSBA titre≥LLOQ, suggestive of a strong immune response against all strains tested.					

¥ *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 titre 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.*

Table 24. Summary of efficacy for trial B1971016

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	B1971016		
Design	This was a 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. Approximately 3300 subjects were to be randomly assigned to 1 of 2 groups in a 3:1 ratio (Group 1:Group 2). Group 1 received bivalent rLP2086 at Month 0 (Day 1) followed by subsequent vaccinations at Months 2 and 6. Group 2 received a saline injection at Month 0, Month 2, and Month 6.		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		12 months not applicable not applicable
Hypothesis	Superiority		
Treatments groups	Group 1		Bivalent rLP2086, N=2480
	Group 2		Saline, N=824
Endpoints and definitions	Co-Primary endpoint	composite hSBA response	*1)* The % subjects with hSBA titre ≥ lower limit of quantitation (LLOQ) for all 4 primary MnB test strains combined, 1 month after the 3rd dose with bivalent rLP2086. LLOQ: ≥ 1:8 for strains A56, B24, B44, ≥1:16 for strain A22
	Co-Primary endpoint	4-fold increase from baseline for each of the 4 primary test strains	*2-4)* % subjects achieving≥ 4-fold increase¥ in hSBA titre from baseline to 1 month after the 3rd vaccination with bivalent rLP2086 for each of the 4 primary MnB test strains.
	Secondary endpoints	hSBA ≥ LLOQ	% subjects with hSBA titres ≥ LLOQ for each of the test strains at baseline and 1 month after the third vaccination with bivalent rLP2086.
		4-fold increase from baseline for each of the 4 primary test strains	For the primary test strains, the number and proportions of subjects achieving at least 2-fold and 4-fold increases from baseline to each post-vaccination blood draw visit in hSBA titres with 95% exact CIs for Group 1 and Group 2.
		composite hSBA response	The composite responses for the 4 primary test strains were summarized similarly at each blood sampling time point.
		RCDCs	Empirical RCDCs showing the distribution of hSBA titres were presented graphically for each of the 4 primary MnB test strains, by each group, and at each sampling time point, for the evaluable immunogenicity population, and for secondary MnB strains at baseline and one month post dose 3.
		hSBA GMTs	GMTs for each of the 4 primary test strains at baseline and 1 month after the third vaccination with bivalent rLP2086.

		% hSBA ≥ thresholds	Proportions of subjects with hSBA titres ≥1:4, ≥1:8, ≥1:16, ≥1:32, ≥1:64, and ≥1:128 for each of the 4 primary test strains and for the 10 secondary strains at each applicable blood sampling time point,
Database lock	Last Subject Last Visit: 13 February 2015 Final Serology Date: 09 July 2015		

Results and Analysis

Analysis description	**Primary Analysis**			
Analysis population and time point description	Evaluable immunogenicity population: all eligible randomized subjects who had received investigational products at visit 1, 2 and 4 as randomized and had baseline and post vaccination 3 (within 28 to 42 days) blood draws available. Subjects were to have valid and determinate assay results for the proposed analysis, received no prohibited vaccines or treatment, and have no other major protocol violations as determined by the sponsor's global medical monitor.			
Descriptive statistics and estimate variability	Treatment group		Group 1 rLP2086	Group 2 Saline
	Number of subjects		(N=1723)	(N=535)
	Composite hSBA response; n (%)		1413 (84.9%)	40 (7.5%)
	(95%CI)		(83.1, 86.6)	(5.4, 10.0)
	Response by strain			
	hSBA fold rise ≥4 from baseline n/N (%) (95%CI)	*A22*	1365/1695 (80.5%) (78.6, 82.4)	36/568 (6.3%) (4.5, 8.7)
		A56	1477/1642 (90.0%) (88.4, 91.4)	*55/533* *(10.3%) (7.9, 13.2)*
		B24	1328/1675 (79.3%) (77.3, 81.2)	31/562 (5.5%) (3.8, 7.7)
		B44	1350/1696 (79.6%) (77.6, 81.5)	9/573 (1.6%) (0.7, 3.0)

Effect estimate per comparison						
	Co-Primary	Comparison groups	Group 1			
		Composite hSBA response	84.9% %			
		95% CI	83.1, 86.6			
		Lower Bound Threshold (Success criterion)	60%			
		P-value	ND			
	Co-Primary	Comparison groups (primary test strains)	A22	A56	B24	B44
		Four fold response	80.5%	90.0%	79.3%	79.6%
		95% CI	78.6, 82.4	88.4, 91.4	77.3, 81.2	77.6, 81.5

		Lower Bound Threshold (Success criterion)	55%	85%	50%	60%
		P-value	ND	ND	ND	ND
Notes	The primary objectives were met as the lower limit of the 2-sided 95% CIs was greater than the corresponding pre-specified lower bound threshold for each of the 4 primary strains and the composite hSBA response.					
Analysis description	**Secondary analysis (Primary strains)**					
	Treatment group		Group 1		Group 2	
	hSBA Titre ⩾ LLOQ **N/n (%) (95%CI)**	A22				
		Before vaccination	572/1704 (33.6) (31.3, 35.9)		192/573 (33.5) (29.6, 37.5)	
		1 month after vaccination 2	1437 /1697 (84.7) (82.9, 86.4)		198/570 (34.7) (30.8, 38.8)	
		1 month after vaccination 3	1602/1714 (93.5) (92.2, 94.6)		211/577 (36.6) (32.6, 40.6)	
		A56				
		Before vaccination	533/1657 (32.2) (29.9, 34.5)		186/563 (33.0) (29.2, 37.1)	
		1 month after vaccination 2	1656/1701 (97.4) (96.5, 98.1)		183/552 (33.2) (29.2, 37.3)	
		1 month after vaccination 3	1698/1708 (99.4) (98.9, 99.7)		189/552 (34.2) (30.3, 38.4)	
		B24				
		Before vaccination	562/1696 (33.1) (30.9, 35.4)		180/570 (31.6) (27.8, 35.6)	
		1 month after vaccination 2	1457/1685 (86.5) (84.7, 88.1)		183/570 (32.1) (28.3, 36.1)	
		1 month after vaccination 3	1618/1702 (95.1) (93.9, 96.0)		173/573 (30.2) (26.5, 34.1)	
		B44				
		Before vaccination	189/1716 (11.0) (9.6, 12.6)		64/578 (11.1) (8.6, 13.9)	
		1 month after vaccination 2	1157/1693 (68.3) (66.1, 70.6)		72/577 (12.5) (9.9, 15.5)	
		1 month after vaccination 3	1489/1703 (87.4) (85.8, 89.0)		66/577 (11.4) (9.0, 14.3)	

	Treatment group		Group 1	Group 2
	hSBA GMT N GMT (95% CI)	A22		
		Before vaccination	1704 12.8 (12.3, 13.3)	573 13.0 (12.2, 13.9)
		1 month after vaccination 2	1697 49.0 (46.2, 52.1)	570 13.2 (12.4, 14.1)
		1 month after vaccination 3	1714 74.3 (70.2, 78.6)	577 13.2 (12.4, 14.1)
		A56		
		Before vaccination	1657 8.8 (8.3, 9.3)	563 9.2 (8.3, 10.3)
		1 month after vaccination 2	1701 114.3 (107.9, 121.0)	552 9.2 (8.2, 10.2)
		1 month after vaccination 3	1708 176.7 (167.8, 186.1)	552 9.1 (8.2, 10.1)
		B24		
		Before vaccination	1696 7.6 (7.3, 8.0)	570 7.6 (7.0, 8.3)
		1 month after vaccination 2	1685 35.8 (33.7, 38.2)	570 7.4 (6.8, 8.1)
		1 month after vaccination 3	1702 49.5 (46.8, 52.4)	573 7.2 (6.6, 7.8)
		B44		
		Before vaccination	1716 4.8 (4.7, 4.9)	577 4.9 (4.6, 5.1)
		1 month after vaccination 2	1693 22.6 (20.9, 24.4)	577 4.9 (4.6, 5.1)
		1 month after vaccination 3	1703 47.6 (44.2, 51.3)	1703 47.6 (44.2, 51.3)
	Other secondary endpoints for the primary strains were in line with these results. As for study B1971009, the RCDCs illustrate the response is most robust for strain A56 and is possibly less robust for B-strains compared to A-strains.			

Secondary analysis: Secondary strains	Regarding the secondary strains (see Table 23 on study B1971009), between 5.0% (A12) to 55.8% (A07) of subjects had an hSBA titre ≥LLOQ pre-dose one. One month post dose 3, this increased to 71.3% (A12) to 99.3% (A29) depending on the strain. Six out of 10 strains had an hSBA ≥LLOQ >90%, 7/10 >85% and 9/10 >75%, suggesting an overall strong response.

¥ 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 titre 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.

Analysis performed across trials

Immunogenicity results from subjects who received bivalent rLP2086 (120 µg) administered using a 0, 2, 6-month schedule in 2 Phase 3 studies and 5 Phase 2 studies (B1971009, B1971010, B1971011, B1971012, B1971015, B1971016) against the four primary test strains were analysed in an integrated summary of efficacy. hSBA testing was conducted using the 4 primary test strains in each of these studies, except for Study B1971015, in which only the responses to 2 of the 4 primary test strains (PMB80 (A22) and PMB2948 (B24) were assessed.

A total of 10,232 subjects in these 7 studies were randomized to receive bivalent rLP2086 (120 µg dose) on a 0, 2, and 6-month schedule; of these, 8026 subjects were included in the evaluable immunogenicity population, and 10,187 subjects were included in the modified intent to treat (mITT) population. At EU sites, a total of 3,475 subjects were randomized; of these, 2983 (85.8%) subjects were included in the evaluable immunogenicity population, and 3465 (99.7%) were included in the mITT population. Except for age, the demographic characteristics were similar among these 7 studies. The demographic characteristics of subjects enrolled at EU sites were not notably different than those in the overall analysis.

The Forrest plots depicting hSBA GMTs one month after dose 2 and dose 3 in the seven primary studies included in this analysis against the four primary test strains are shown in the below figures.

Figure 7. Forrest Plot of GMTs 1 Month After Dose 2 and Dose 3 of Bivalent rLP2086 in Primary Studies, strain A22 (left) and A56 (right)

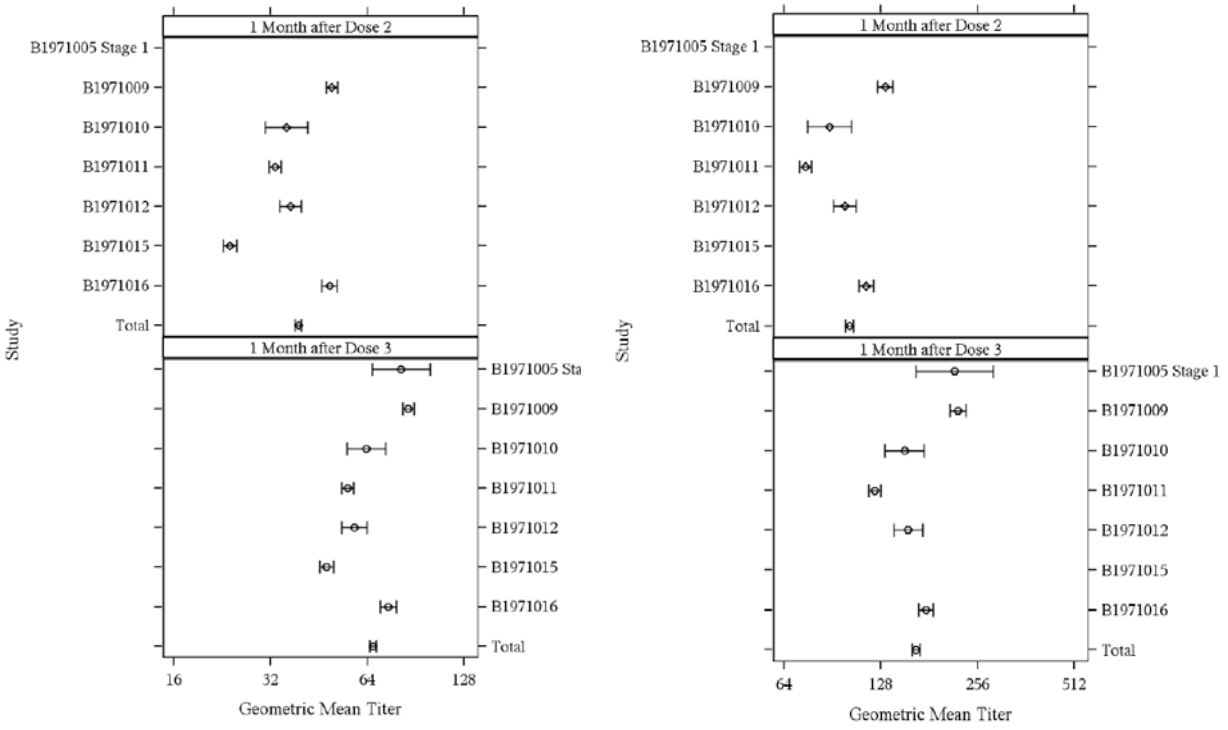
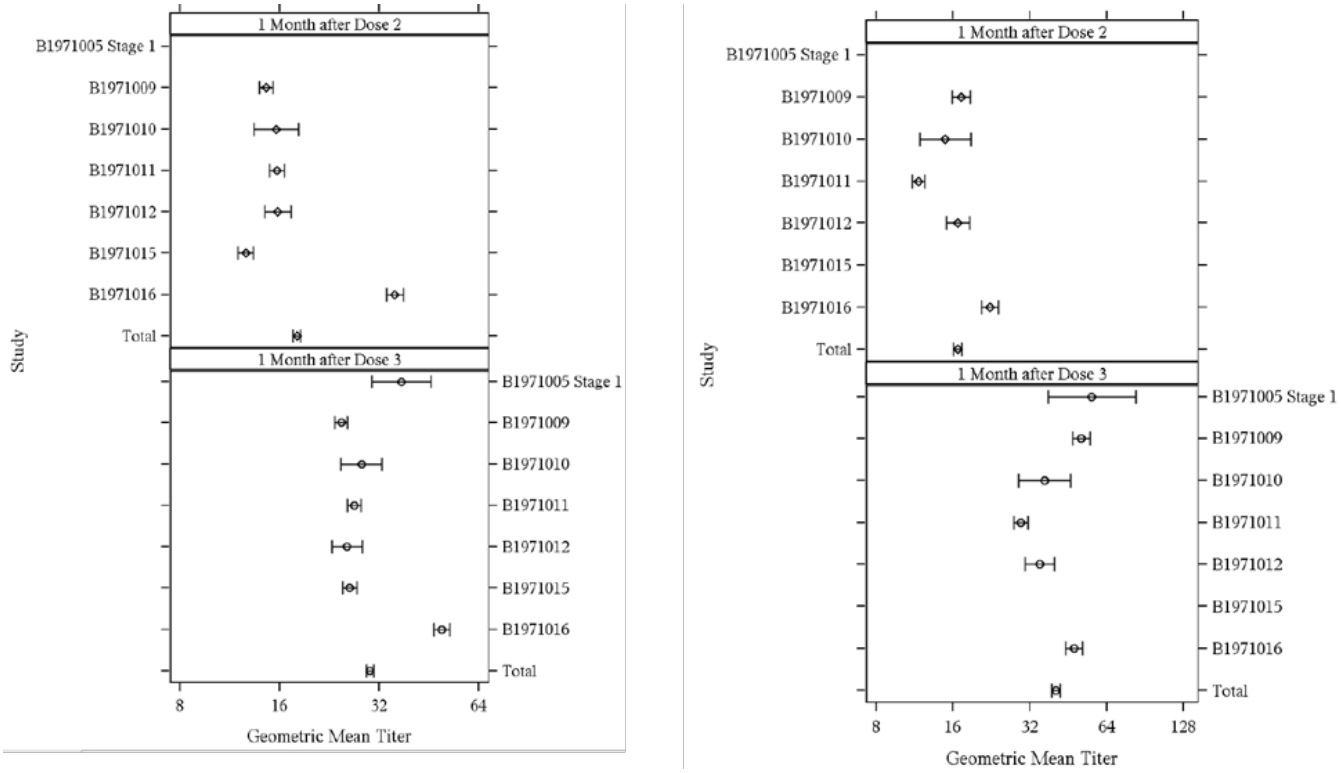


Figure 8. Forrest Plot of GMTs 1 Month After Dose 2 and Dose 3 of Bivalent rLP2086 in Primary Studies, B24 (left) and B44 (right)



The Forrest plots of the GMTs show some variation in response by study, in particular a higher response is seen in study B1971016 for strain B24 and for A22 – albeit less outspoken for the latter. Study B1971016 included persons aged 18 to 26 years, whilst all other studies presented in the Forrest plot included subjects aged 10-<13 (study B1971015) or 11-18 years (remaining studies), potentially

explaining the difference in GMT. Increasing GMTs with age as seen for these strains can be potentially explained by increasing baseline titres. For the A strains, among the studies in persons aged 10-18, a higher GMT is seen for study B1971009 and study B1971005 (wide CI). For study B1971009 again this might be partially explained by higher baseline titres in this study, but for B1971005 this is not apparent. However, for study B1971005, which has a smaller dataset, there is less precision around the point estimates.

See also the section on Ancillary analyses.

Clinical studies in special populations

Response in immunocompromised

The immunogenicity of bivalent rLP2086 has not been studied in patients with immune deficiencies such as complement deficiency or asplenia. Adequate warnings are included in the SmPC. Nonetheless, as persons with immune deficiencies represent an important target group for meningococcal vaccination, the Applicant has committed to investigate the immunogenicity and safety of bivalent rLP2086 in immunocompromised patients, including patients with complement deficiency or asplenia, as a category 3 study. The protocol and estimated timeline for study start and completion should be submitted within 12 months of authorisation (see RMP section).

Supportive studies

Early studies

Study B1971003 was a Phase 1/2 open-label study, in which 60 subjects (18 to ≤40 years of age) received 120 µg of bivalent rLP2086 using a 0, 1, 6-month schedule. This study was designed for serological assay development. An exploratory objective of this study was to assess the immunogenicity of 120 µg of bivalent rLP2086 as measured by hSBA and/or levels of antibody specific to antigens in bivalent rLP2086. Functional antibody responses using hSBA were performed using the following MnB test strains:

- PMB1745 (A05), which expresses an fHBP variant homologous to 1 of bivalent rLP2086 antigens, rLP2086-A05, and
- PMB17 (B02), which expresses an fHBP variant that is heterologous to the other vaccine antigen, rLP2086-B01.

The immune response data were determined using a qualified hSBA, and results were reported as interpolated titres. Sixty (60) subjects (mITT population) were included in the immunogenicity analyses. The mean age was 28.6 (SD: 6.74), median age was 26.0. The proportions of subjects with hSBA titres ≥1:4 to MnB test strains PMB1745 (A05) and PMB17 (B02) were 74.5% and 69.6% after Dose 2, respectively, and 94.3% and 94.1% after Dose 3, respectively.

Concomitant administration with other vaccines

Three clinical studies evaluated the effect of concomitant administration of bivalent rLP2086 with other vaccines which could likely be given to the same target group, i.e. Tdap, Tdap-IPV, conjugated meningococcal ACWY vaccine, and quadrivalent HPV vaccine (HPV serotypes 6, 11, 16, and 18).

Study B1971010 evaluated the impact of bivalent rLP2086 on the immune response to Repevax, a dTaP-IPV vaccine. Health subjects aged ≥11 to <19 Years were randomised to receive either 3 doses of bivalent rLP2086 using a 0, 2, 6-month schedule and 1 dose of dTaP-IPV given concomitantly with the first dose of bivalent rLP2086, or saline + dTaP-IPV for the first dose and saline for Doses 2 and 3 on a 0,

2, 6-month schedule. Non-inferiority was to be declared if the 2-sided 95% lower CI for the difference (bivalent rLP2086 / dTaP-IPV [Group 1] – dTaP-IPV Group 2]) was greater than -0.10 (-10%) for all of the 9 antigens in the dTaP-IPV vaccine.

Although the margin of 10% could be considered wide for the antigens in dTaP-IPV, results are well within this margin, with the difference in the response rate (percentages of subjects achieving prespecified antibody levels) being 0.0 (95% CI: -1.1, 1.1) for 7 out of 9 antigens. The lowest lower bound of the 95% CI on the proportion difference was -4.7% [pertussis toxoid].

There is no evidence of a potential interference of rLP2086 with the immune response to Tdap-IPV. As the response to Tdap-IPV was maximal in both groups, there was no difference between the groups. Considering the GMTs, for some antigens the GMTs were higher in the Tdap-IPV+saline group, most notably poliovirus 2, but differences were non-significant.

Study B1971011 evaluated the impact of concomitant administration of bivalent rLP2086 with quadrivalent HPV vaccine on the immune response (GMT to each of the 4 antigens) to the HPV vaccine and on the immune response to bivalent rLP2086 (as measured by hSBA performed with 2 primary MnB test strains, A22 and B24). Non-inferiority of both quadrivalent HPV vaccine and bivalent rLP2086 was to be considered achieved when the 2-sided 95% lower CI for the geometric mean ratios (GMRs) were greater than 0.67 for each of the 4 HPV antigens (Group 1/Group 3) and each of the 2 primary MnB test strains (Group 1/Group 2) among the evaluable immunogenicity population. Results are presented in Table 25.

Table 25. Comparison of Geometric Mean Titres at 1 Month After Vaccination 3 – Evaluable Immunogenicity Population (B1971011)

	Vaccine Group (as Randomized)										
	Group 1 rLP2086 + Gardasil			Group 2 rLP2086 + Saline			Group 3 Saline + Gardasil				
Antigen/Strain [Variant]	N[a]	GMT[b]	(95% CI)[c]	N[a]	GMT[b]	(95% CI)[c]	N[a]	GMT[b]	(95% CI)[c]	Ratio[d]	(95% CI)[e]
HPV antigens (Group 1 vs.Group 3)											
HPV-6	813	451.8	(417.50, 489.01)	NA	NA	NA	423	550.3	(490.44, 617.58)	0.82	(0.72, 0.94)
HPV-11	813	892.9	(839.52, 949.57)	NA	NA	NA	423	1084.3	(997.28, 1178.96)	0.82	(0.74, 0.91)
HPV-16	813	3695.4	(3426.32, 3985.67)	NA	NA	NA	423	4763.4	(4285.85, 5294.21)	0.78	(0.68, 0.88)
HPV-18	813	744.0	(687.67, 804.96)	NA	NA	NA	423	1047.4	(939.00, 1168.25)	0.71	(0.62, 0.81)
hSBA strains (Group 1 vs. Group 2)											
PMB80 [A22]	803	53.3	(50.22, 56.66)	801	57.8	(54.44, 61.44)	NA	NA	NA	0.92	(0.85, 1.00)
PMB2948 [B24]	788	25.8	(24.14, 27.56)	793	28.0	(26.24, 29.87)	NA	NA	NA	0.92	(0.84, 1.01)

The GMTs against HPV-6,-11, -16 and -18 were all numerically and statistically significantly higher when quadrivalent HPV vaccine was given without rLP2086 compared to when the two vaccines were given concomitantly. Although the 1.5-fold non-inferiority criterion of 0.67 (the 2-sided 95% lower CI of the GMR) was met for all HPV antigens except for HPV-18, which was marginally missed with a 95% LCI of 0.62, this does signal interference of the immune response and the clinical consequences are not known. One (1) month after Dose 3 with quadrivalent HPV vaccine, ≥99% of subjects seroconverted to all 4 HPV antigens in both the saline + quadrivalent HPV vaccine and the rLP2086 + quadrivalent HPV vaccine groups.

Similarly, the immune response to rLP2086 was higher (i.e. hSBA titres were higher) when rLP2086 was given with saline as compared to when it was given with HPV vaccine. Differences here were borderline significant with CIs overlapping marginally. The set non-inferiority criteria were all met.

Finally, **study B1971015** evaluated the safety, tolerability, and immunogenicity of MCV4 vaccine (Menactra), Tdap vaccine (Adacel), and bivalent rLP2086 when administered concomitantly in healthy subjects aged 10 to <13 years. A total of 2648 subjects were randomly assigned to 1 of 3 groups in a 1:1:1 ratio (Group 1- bivalent rLP2086 at 0, 2, 6 months, MCV4 and Tdap at 0 months; Group 2 – MCV4

and Tdap at 0 months, saline at 0, 2, 6 months; Group 3 - bivalent rLP2086 at a 0, 2, 6 months, MCV4 and Tdap at 7 month).

For assessment of the immune response to the MCV4 vaccine, functional antibodies were analysed in serum bactericidal assays using rabbit complement (rSBAs) with meningococcal strains representing serogroups A, C, Y and W. Assessments of diphtheria, tetanus, and pertussis antibody responses were performed using a validated, multiplexed Tdap LXA.

The results for the primary objective are presented in Table 26 below.

Table 26. Primary Immunogenicity Analysis – Comparison of Geometric Means (GM) at 1 Month After Last Vaccination – Evaluable Immunogenicity Populations (B1971015)

	Vaccine Group (as Randomized)										
	Group 1 MCV4+Tdap+rLP2086			Group 2 MCV4+Tdap+Saline			Group 3 Saline+Saline+rLP2086				
Antigen/Strain (Variant)	N[a]	GM[b]	(95% CI)[c]	N[a]	GM[b]	(95% CI)[c]	N[a]	GM[b]	(95% CI)[c]	Ratio[d]	(95% CI)[e]
Tdap antigens											
Diphtheria	778	9.3	(8.67, 9.92)	780	9.8	(9.23, 10.51)	N/A	N/A	N/A	0.94	(0.86, 1.03)
Tetanus	778	9.4	(8.95, 9.98)	780	10.3	(9.75, 10.85)	N/A	N/A	N/A	0.92	(0.85, 0.99)
Pertussis toxoid	778	13.2	(12.35, 14.14)	780	14.2	(13.28, 15.20)	N/A	N/A	N/A	0.93	(0.85, 1.02)
Pertussis filamentous hemagglutinin	778	112.0	(106.15, 118.14)	780	122.9	(116.42, 129.84)	N/A	N/A	N/A	0.91	(0.84, 0.98)
Pertussis pertactin	778	202.0	(187.77, 217.25)	780	228.9	(212.72, 246.35)	N/A	N/A	N/A	0.88	(0.80, 0.98)
Pertussis fimbriae agglutinogens types 2 + 3	778	138.1	(121.20, 157.33)	780	154.2	(135.30, 175.79)	N/A	N/A	N/A	0.90	(0.74, 1.08)
rSBA MCV4 antigens											
Serogroup A	763	4647.3	(4317.66, 5002.09)	772	5113.0	(4748.73, 5505.17)	N/A	N/A	N/A	0.91	(0.82, 1.01)
Serogroup C	768	1679.2	(1539.63, 1831.38)	767	1650.2	(1519.01, 1792.65)	N/A	N/A	N/A	1.02	(0.90, 1.15)
Serogroup Y	771	2212.6	(2056.08, 2381.08)	770	2244.9	(2088.70, 2412.89)	N/A	N/A	N/A	0.99	(0.89, 1.09)
Serogroup W-135	751	5925.1	(5469.77, 6418.33)	765	6367.9	(5872.68, 6904.88)	N/A	N/A	N/A	0.93	(0.83, 1.04)
hSBA MnB strains											
PMB80 (A22)	679	45.9	(42.74, 49.35)	N/A	N/A	N/A	674	49.7	(46.43, 53.30)	0.92	(0.84, 1.02)
PMB2948 (B24)	670	24.8	(23.11, 26.58)	N/A	N/A	N/A	656	27.4	(25.58, 29.41)	0.90	(0.82, 1.00)

The criterion for the non-inferiority margin of 1.5-fold, which corresponds to a value of 0.67 for the lower limit of the 2-sided 95% CI of the GMR, was met for all MCV4 and Tdap antigens (ranging from 0.88 to 1.02). The criterion for the non-inferiority margin was also met for both MnB test-strains. The lower limits of the 2-sided 95% CIs for the hSBA GMRs for Group 1 compared to Group 3 were 0.84 for PMB80 (A22) and 0.82 for PMB2948 (B24). Thus, the primary objectives for the study were met.

Numerically, GMTs were slightly higher for the Pertussis, Tetanus and Diphtheria antigens when Tdap + MCV4 were given together with saline as compared to when they were given together with bivalent rLP2086. This was statistically significant for the tetanus and two pertussis components and could be suggestive of some immune interference. Similarly, GMTs were slightly higher against serogroup A and W of the MCV4 vaccine when given with saline compared to rLP2086, however not for the C and Y components.

Considering the seroconversion rates for the different antigens, there was no difference between the groups for diphtheria and tetanus; response in group 1 was 98.6 and 97.7 for diphtheria and tetanus respectively and 98.3 and 97.4 in Group 2, Δ=0.2 for both antigens. For the pertussis antigens again there were some decreased responses in the Tdap+MCV4+rLP2086 group for two antigens however differences were small and the picture was not entirely consistent with the GMs. The response for pertussis toxoid was 68.1% in Group 1 compared to 72.7% in Group 2, Δ -4.6, 95% CI: -9.1, -0.1. The response for Pertussis filamentous hemagglutinin was 85.3% in Group 1 compared to 89.2% in Group 2, Δ -4.0%, 95%CI: -7.3, -0.6.

For the meningococcal ACWY antigens, here too some numerical differences can be seen between groups however these are small, and unlikely of clinical relevance.

The hSBA GMTs were higher against strains A22 and B24 when bivalent rLP2086 was given without MCV4+TdaP with the difference in GMTs between the group reaching borderline (non) significance. Considering the proportion of subjects with hSBA titre≥ LLOQ one month post vaccination 3, this was again numerically higher for those who received rLP2086 with saline compared to those who received rLP2086 with Tdap+MCV4, however differences were small and statistically not significant.

Persistence of the immune (antibody) response

Stage 2 of study B1971005 addressed the observational objective of assessing the duration of the immune response using the 4 primary MnB test strains. Only subjects receiving rLP2086 at dose levels selected for this study (120 µg and 200 µg) and placebo recipients during Stage 1 (see under dose finding section) were invited to continue into Stage 2. Blood samples for immunogenicity evaluation were collected from subjects participating in Stage 2 at the following 6 intervals after Dose 3: 6 months + 1 week, 12 months, 18 months, 24 months, 36 months, and 48 months. In 2012 a qualified hSBA was performed with 2 of the 4 primary strains, PMB2001 (A56) and PMB2707 (B44) for 6 months +1 week, 12 months and 18 months after Dose 3. Subsequently, the hSBA was modified slightly and validated. Serum samples from subjects in the 120 µg and control group were evaluated in hSBAs using MnB test strains PMB80 (A22) and PMB2948 (B24). Based on serum volume availability, serum samples from subsets of subjects in the 120 µg and control groups (selected in an unbiased fashion, albeit not random) were evaluated in hSBAs for MnB test strains for PMB2001 (A56) and PMB2707 (B44).

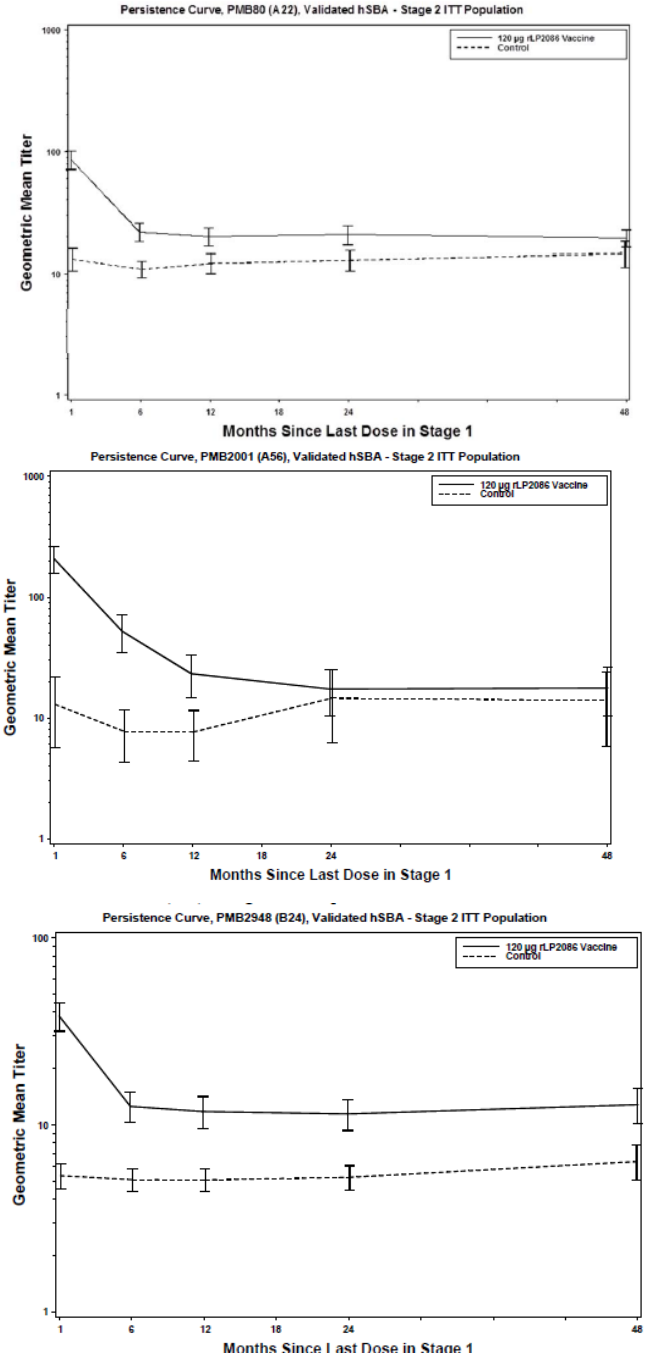
One of the descriptive immunogenicity endpoints for Stage 2 was measuring the proportion of subjects with hSBA titres ≥ LLOQ at selected time points through 48 months after Dose 3 for the 120ug dose. The LLOQs for the 4 primary MnB test strains in validated hSBAs were an hSBA titre equal to 1:16 for A22 and 1:8 for A56, B24, and B44. The 200 µg dose group was followed up to 18 months after dose 3; these samples were analysed with the hSBA against strains A56 and B44, using the qualified hSBA assay. The data available up to 18 m for both dose levels studied in B1971005 is against strain A56 and B44 is not shown but the two antibodies persistence curves overlap the entire observation period, further supporting the selection of the 120 µg dose for the final formulation. The data shown below are thus limited to the final dose of 120ug in comparison with the control.

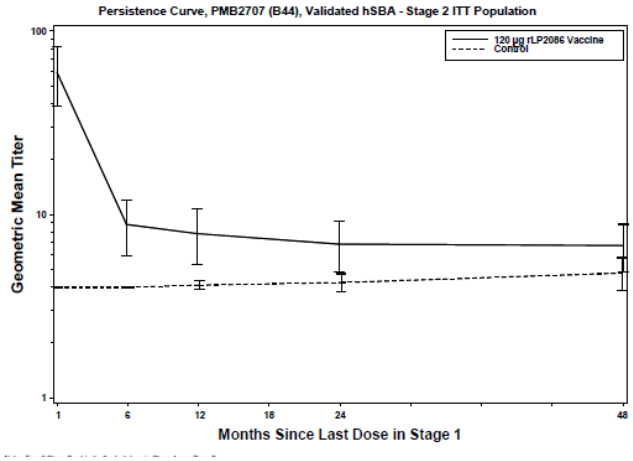
Table 27. Subjects With hSBA Titres ≥ LLOQ for the 120ug dose– Stage 2 ITT Population (B1971005)

	A22		A56		B24		B44	
Time	rLP2086	saline	rLP2086	saline	rLP2086	saline	rLP2086	saline
1 m	95.3% (90.5, 97.8)	28.8% (19.9, 39.6)	100% (85.5, 99.9)	34.8% (18.4, 55.7)	93.3% (88.0, 96.4)	15.2% (8.8, 24.9)	95.7% (84.5, 98.9)	0.0% (0.0, 24.7)
6 m + 1 wk	60.2% (52.5, 67.5)	20.3% (12.8, 30.5)	89.4% (76.9, 95.5)	21.7% (9.3, 42.8)	57.1% (49.3, 64.4)	13.8% (7.8, 23.1)	36.7% (24.5, 50.9)	0.0% (0.0, 24.7)
12 m	54.2% (46.3, 61.9)	28.9% (19.9, 40.1)	68.8% (54.4, 80.2)	26.1% (12.2, 47.2)	54.7% (46.6, 62.4	12.8% (7.0, 22.2)	29.2% (18.1, 43.4)	4.0% (0.6, 23.5)
24 m	53.6% (45.7, 61.3)	31.1% (21.6, 42.5)	53.1% (39.2, 66.5)	36.4% (19.3, 57.7)	53.9% (46.0, 61.7)	16.2% (9.4, 26.4)	22.4% (12.9, 36.2)	4.0% (0.6, 23.5)
48 m	59.0% (50.4, 67.0)	34.3% (24.0, 46.4)	51.1% (37.1, 64.9)	34.8% (18.4, 55.7	57.0% (48.3, 65.3)	23.5% (14.9, 35.0)	20.4% (11.3, 33.9)	12.0% (3.9, 31.3)

Antibody response curves displaying data for the hSBA GMTs using validated hSBAs for each of the 4 primary MnB test strains at approximately 1 month, 6 months + 1 week, 12, 24, and 48 months after Dose 3 are presented in Figure 9 below.

Figure 9. hSBA Antibody Persistence Curves, Validated for MnB Test Strains A22, A56, B24, B44 for 120 µg and control group. (B1971005)





The graphic illustrations in Figure 9 (note the different scales of GMTs for the subfamily A and B strains) of the persistence of hSBA GMTs following the 3rd dose of bivalent rLP2086 clearly show an initial decrease up to approximately month 6 followed by a plateau which is maintained above levels seen in the control group, although 95% CIs seem to overlap. The GMTs in the control groups tend to increase slightly over time for strains A22, B24 and B44. For strain A56 a more drastic increase is seen and the control group actually overlaps with the bivalent rLP2086 group after 24 months. Considering the % with titres >LLOQ, these are approximately 15% higher in the active group compared to the control group at month 48 after the 3rd dose against strain A56, CIs overlap (see Table 27 above).

The persistence of immunity is poor for strain B44. Although the initial response after the third dose is 95.7% with hSBA titre ≥ LLOQ, at 6 months this is 37% eventually falling back to 20% during the follow up period. There is no significant difference with the control group at 6 months and 1 week following the third dose, or any time-point thereafter but numbers are small and CIs wide. The numerical difference is approximately 20% (see Table 27 above).

The persistence of serum bactericidal antibodies was further studied following different dosing regimens in study B1971012 in the context of the extension study B1971033 (see below).

Study B1971033 is a Phase 3 Study to Assess the Persistence of hSBA Response up to 48 Months after Completion of a Primary Series of Bivalent rLP2086, and the Safety, Tolerability, and Immunogenicity of a Booster Dose of Bivalent rLP2086.

This study enrolled subjects who completed primary studies B1971010 (6108A1-2008) (Finland), B1971012 (6108A1-2003) (Czech Republic, Denmark, Germany, and Sweden), and B1971015 (6108A1-2005) (United States). Subjects were enrolled into Study B1971033 to evaluate the persistence of immunity for 48 months following receipt of 2 or 3 doses of Neisseria meningitidis serogroup B bivalent recombinant lipoprotein 2086 vaccine (bivalent rLP2086; subfamily A and B; Escherichia coli) in the primary study. Subjects who agreed to participate in the booster phase received a single booster dose of bivalent rLP2086 48 months after the second or third dose of the primary series and were then additionally followed for 12 months. Of the 3 primary studies above, Study B1971012 was the only 1 in which both a 2- or 3-dose schedule was used; the other two studies used a 3-dose primary schedule.

The interim report submitted in this application encompasses Stage 1 (Visit 1 [6 months after last primary study dose] through Visit 6 [48 months after last primary study dose]) and the booster vaccination phase of the booster stage (Visit 7 [booster vaccination] through Visit 8 [1 month after booster vaccination]).

Subjects enrolled from the other primary studies (Studies B1971010 and B1971015) had not completed all visits through Visit 8 at the cut-off date for this interim report. Thus, this interim analysis only includes

subjects from primary study B1971012 (referred to as Study B1971012 hereafter) who have completed all visits through 1 month after the booster vaccination (Visit 8).

Table 28. Study design overview

	Stage 1						Booster Stage			
							Vaccination Phase			
Visit number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
Approximate month	**6**	**12**	**18**	**24**	**36**	**48**	**48**	**1 Month after booster**	**6 Months after booster**	**12 Months after booster**
Visit purpose	Blood draw	Blood draw	Blood draw	Blood draw	Blood draw	Blood draw	Booster vaccination	Blood draw	6-Month telephone contact	Blood draw
Vaccination							Bivalent rLP2086			
Blood draw	20 mL	20 mL	20 mL	20 mL	20 mL	20 mL		20 mL		20 mL
SAE[a]	Nonactive reporting of SAEs to the primary study						From booster stage ICD to Visit 9			Nonactive reporting of SAEs to the B1971033 study
NDCMC[b]	From 6 month telephone call in the primary study to Visit 10									
MAE							From booster stage ICD to Visit 9			
RRI[c]	48 hr after blood draw	48 hr after blood draw	48 hr after blood draw	48 hr after blood draw	48 hr after blood draw	48 hr after blood draw				48 hr after blood draw
AE[d]	48 hr after blood draw	48 hr after blood draw	48 hr after blood draw	48 hr after blood draw	48 hr after blood draw	48 hr after blood draw	All AEs from booster stage ICD to Visit 8	48 hr after blood draw		48 hr after blood draw
Reactogenicity events							1-7 days			

ICD = informed consent document; MAE = medically attended event; NDCMC = newly diagnosed chronic medical condition; RRI = research-related injury.

a. Events with an onset during Stage 1 were reported under the primary study number. Events with an onset during the booster stage were reported under Study B1971033.
b. Events with an onset after the 6-month follow-up telephone call in the primary study.
c. Events reportable only within the first 48 hours following a blood draw.
d. Events with an onset in Stage 1, or from Visit 8 to Visit 10, were reportable only within the first 48 hours following a blood draw. From Visit 7 to Visit 8, all AEs were reportable.

Objectives

Primary: Immunogenicity

Stage 1

- To describe the immunogenicity of bivalent rLP2086 as determined by hSBA titres 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 primary study (i.e., a previously conducted Pfizer study using the final formulation and dose of bivalent rLP2086).

Booster Stage

- To describe the immune response as measured by hSBA titres 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, 1 month after a single booster dose of bivalent rLP2086, and 12 months after a single booster dose of bivalent rLP2086.

Primary: Safety

- To evaluate the safety profile of bivalent rLP2086 as measured by the incidence of local reactions, systemic events, adverse events (AEs), serious adverse events (SAEs), newly diagnosed chronic medical conditions (NDCMCs), medically attended events (MAEs), and immediate AEs following a booster vaccination of bivalent rLP2086

Exploratory:

Stage 1

- To describe the safety profile of bivalent rLP2086 as measured by the incidence of NDCMCs, AEs, and research-related injuries (RRIs) in Stage 1.

- The immune response may be further described as measured by hSBA titre levels and hSBA geometric mean titres (GMTs) with 4 primary MnB test strains measured at each blood draw visit in Stage 1.

Booster Stage

- The immune response may be further described as measured by a composite hSBA response to all 4 primary test strains at 1 month following the last vaccination with bivalent rLP2086 in the primary study, before booster vaccination (Visit 6), 1 month after a single booster dose of bivalent rLP2086, and 12 months after a single booster dose of bivalent rLP2086.
- The immune response may be further described as measured by hSBA titre levels and hSBA GMTs with 4 primary MnB test strains measured at each blood draw visit in the booster stage of the study.
- The immune response may be further described as measured by hSBA titres to secondary test strains 1 month following the last vaccination with bivalent rLP2086 in the primary study, before booster vaccination (Visit 6), 1 month after a single booster dose of bivalent rLP2086, and 12 months after a single booster dose of bivalent rLP2086.

Outcomes/endpoints

Immunogenicity

For assessment of the immune response to bivalent rLP2086, functional antibodies were analysed in hSBAs with MnB strains. The hSBA measures antibodies in human sera that initiate antibody-mediated complement-dependent killing of the target meningococcal strain. Four primary test strains, PMB80 (A22), PMB2001 (A56), PMB2948 (B24), and PMB2707 (B44), were used in the hSBAs for determination of the immunogenicity endpoints in sera obtained from all subjects at all study visits. The MnB hSBAs were validated before any testing was performed.

Sera obtained 1 month following the last vaccination with bivalent rLP2086 in the primary study were reassayed concurrently with sera obtained during B1971033 study visits.

Primary Endpoints in Stage 1

Proportions of subjects with hSBA titres ≥LLOQ for each of the 4 primary strains at each blood draw visit in Stage 1 (Visits 1 through 6).

Primary Endpoints Booster Stage

Proportions of subjects with hSBA titres ≥ 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).

Exploratory Endpoints Stage 1

- Proportions of subjects with hSBA titres ≥1:4, ≥1:8, ≥1:16, ≥1:32, ≥1:64, and ≥1:128 for each of the 4 primary strains at each blood draw visit in Stage 1.
- hSBA GMTs for each of the 4 MnB primary strains at each blood draw visit in Stage 1.

Exploratory Endpoints Booster Stage

- The composite endpoint is defined as the proportion of subjects achieving an hSBA titre ≥LLOQ for all 4 primary test strains simultaneously. The composite endpoint will be compiled for 1 month following the last vaccination with bivalent rLP2086 in the primary study, before booster vaccination (Visit 6), and 1 month after a single booster dose of bivalent rLP2086 (Visit 8).

- Proportions of subjects with hSBA titres ≥1:4, ≥1:8, ≥1:16, ≥1:32, ≥1:64, and ≥1:128 for each of the 4 primary strains at each blood draw visit in the booster stage of the study.
- hSBA GMTs for each of the 4 MnB primary strains at each blood draw visit in the booster stage of the study

The empirical reverse cumulative distribution curves (RCDCs) of hSBA titre are presented graphically for each of the 4 primary strains, and at each sampling time point.

Safety

See Safety section.

Sample size and randomisation

Study sample size was not based on statistical considerations. In recognition of the variability introduced with the inclusion of subject populations from various studies (such as population age, number of doses received, and concomitant vaccine usage), the study aimed to enrol up to 800 subjects to allow for sufficient numbers when describing findings with regard to particular variables. No specific sample size for subjects from Study B1971012 was determined. There was no randomisation step in the present study.

Statistical methods

Analysis populations

Full Analysis Set: The full analysis set for the interim analysis was the "As Enrolled" population, which included all of the subjects from Study B1971012 who enrolled in this study. This population was also called the intent-to-treat (ITT) population. The ITT population for the subjects who entered the booster stage was referred to as the booster stage ITT population.

Immunogenicity Analysis Set: Only subjects who were compliant with the primary study eligibility criteria while enrolled in the primary study were included in this study. Therefore, the modified intent-to-treat (mITT) population was used for Stage 1 immunogenicity analyses. The mITT population included subjects who had at least 1 valid and determinate assay result in Stage 1 of Study B1971033

The safety population for Stage 1 of the study will include all subjects who have at least 1 blood draw in the study. The safety population for the booster stage included all subjects who received the booster vaccination and for whom safety data were available.

Methods of Analysis

The LLOQs for the primary test strains were 1:16 for PMB80 (A22) and 1:8 for PMB2001 (A56), PMB2707 (B44), and PMB2948 (B24). For the calculation of GMT, hSBA values below the LLOQ were set to 0.5 × LLOQ.

The primary analysis included summaries of the primary immunogenicity endpoint (proportion of subjects with hSBA titre ≥LLOQ) at each blood sampling time point, including the blood draw assay performed 1 month after last vaccination from Study B1971012, in the primary analysis populations (mITT for Stage 1, evaluable population for booster stage) for each of the 4 primary test strains. Exact 95% confidence intervals (CIs) (Clopper-Pearson confidence limits) were displayed together with the proportion. For this interim report, the analyses included subjects from Study B1971012 for Visits 1 through 8.

The hSBA GMTs were summarized at each blood sampling time point in Stage 1, including the blood draw assay performed 1 month after last vaccination from Study B1971012, and the booster vaccination phase (blood sample taken at Visit 8), for each of the 4 primary test strains, along with 2-sided 95% CIs. The CIs were constructed by back transformation of the confidence limits computed for the mean of the logarithmically transformed assay data based on Student's t distribution. The proportion of subjects with

an hSBA titre ≥1:4, 1:8, 1:16, 1:32, 1:64, and 1:128 were descriptively summarized with exact 95% CIs for each of the 4 primary test strains at each blood sampling time point in Stage 1 and the booster vaccination phase up to Visit 8.

The empirical reverse cumulative distribution curves (RCDCs) of hSBA titre are presented graphically for each of the 4 primary strains, and at each sampling time point.

Missing data

As assay data were expected to be missing completely at random (MCAR), the primary immunogenicity analyses for the primary objectives were based upon the observed, determinate observations. Missing data were not imputed for analysis. As a sensitivity analysis, a mixed-effects model with repeated measurements (MMRM) was utilized for the immunogenicity analysis, which assumed the missingness was at random.

Results

Participant flow

Table 29. Disposition of all subjects enrolled from primary Study B1971012 through 1 month after booster vaccination

	Primary Study B1971012 Vaccine Group (as Randomized)									
	Group 1 0-, 1-, and 6-Month Schedule		Group 2 0-, 2-, and 6-Month Schedule		Group 3 0- and 6-Month Schedule		Group 4 0- and 2-Month Schedule		Group 5 0- and 4-Month Schedule	
	n[a]	%	n[a]	%	n[a]	%	n[a]	%	n[a]	%
Enrolled[b]	103		114		116		86		46	
Stage 1										
Completed	93	90.3	101	88.6	108	93.1	83	96.5	46	100.0
Withdrawn	10	9.7	13	11.4	8	6.9	3	3.5	0	0.0
Reasons for withdrawal during Stage 1										
Lost to follow-up	4	3.9	5	4.4	0	0.0	0	0.0	0	0.0
No longer meets eligibility criteria	0	0.0	0	0.0	2	1.7	0	0.0	0	0.0
No longer willing to participate in study	3	2.9	8	7.0	6	5.2	3	3.5	0	0.0
Protocol violation	3	2.9	0	0.0	0	0.0	0	0.0	0	0.0
Booster stage										
Entered booster stage[c]	60	100.0	59	100.0	64	100.0	56	100.0	32	100.0
Withdrawn before booster vaccination	1	1.7	0	0.0	0	0.0	2	3.6	0	0.0
Reason for withdrawal before booster vaccination										
Does not meet entrance criteria	0	0.0	0	0.0	0	0.0	1	1.8	0	0.0
No longer willing to participate in study	1	1.7	0	0.0	0	0.0	0	0.0	0	0.0
Other	0	0.0	0	0.0	0	0.0	1	1.8	0	0.0
Received booster vaccination	59	98.3	59	100.0	64	100.0	54	96.4	32	100.0
Completed booster vaccination phase	59	98.3	59	100.0	64	100.0	54	96.4	32	100.0
Withdrawn during booster vaccination phase	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Completed all study visits through 1 month after booster vaccination[d]	58	96.7	58	98.3	64	100.0	52	92.9	32	100.0

Note: Stage 1 refers to the long-term serologic assessment visits, Visits 1 (6 months after last primary study dose) - 6 (48 months after last primary study dose). The booster stage is from the booster vaccination (Visit 7) through the 12 month follow-up visit (Visit 10). The booster vaccination phase, a time frame within the booster stage, is from the booster vaccination (Visit 7) through Visit 8 (1 month after booster vaccination).

a. n = Number of subjects with the specified characteristic.
b. The values in this row are used as the denominators for percentages for Stage 1 section.

Baseline data and numbers analysed

Demographic characteristics were similar across the 5 groups.

From month 1 to month 48 in stage 1, loss to follow up was limited to around 10%, dependent on the group.

Outcomes and estimation

Table 30 below presents data on the proportion of subjects with hSBA titres ≥LLOQ up to 48 months (primary endpoint). The proportion of subjects with hSBA titres ≥LLOQ up to 48 months varied by strain but ranged across strains from approximately 16% to 60% from 12 months to 48 months after the last primary dose in the 0, 6-month schedule group and from approximately 17% to 76% in the 0, 2, 6 month schedule group. When evaluated over a 48-month period, the proportion of subjects achieving hSBA titres ≥LLOQ following the 2 dose schedule (0, 6 months) was similar to that observed following the 0, 2, 6-month schedule.

In addition, the response to the booster dose and the results of the composite endpoint are also included in the table. The proportions of subjects who achieved hSBA titres ≥LLOQ were similar across groups regardless of the B1971012 dosing schedule (those receiving 3 doses [Groups 1 and 2] and those receiving 2 doses [Groups 3, 4, and 5; the latter 2 are not shown]).

Table 30. Persistence of Immune and Booster Responses Among Individuals 11 to 18 Years of Age Administered a Primary Series of Trumenba on a 0-, 1-, 6-Month-; 0-, 2-, 6-Month- and 0-, 6-Month Schedule and a Booster 4 Years After Primary Series (Study B1971033)

		Primary Study B1971012 Vaccine Group (as Randomised)					
		Group 1 (0, 1, and 6 Months)		Group 2 (0, 2, and 6 Months)		Group 3 (0 and 6 Months)	
		N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
hSBA Strain (fHbp Variant)	**Time Point**						
PMB80 (A22)	**% hSBA ≥ 1:16**						
	1 Month after last primary Dose	100	91.0 (83.6, 95.8)	113	92.0 (85.4, 96.3)	115	96.5 (91.3, 99.0)
	12 Months after last primary Dose	99	41.4 (31.6, 51.8)	111	45.0 (35.6, 54.8)	113	36.3 (27.4, 45.9)
	48 Months after last primary Dose	90	41.1 (30.8, 52.0)	100	43.0 (33.1, 53.3)	101	39.6 (30.0, 49.8)
	1 Month after booster Dose	59	98.3 (90.9, 100.0)	58	100.0 (93.8, 100.0)	62	95.2 (86.5, 99.0)
PMB2001 (A56)	**% hSBA ≥ 1:8**						
	1 Month after last primary Dose	100	100.0 (96.4, 100.0)	112	99.1 (95.1, 100.0)	116	99.1 (95.3, 100.0)
	12 Months after last primary Dose	98	73.5 (63.6, 81.9)	109	76.1 (67.0, 83.8)	106	60.4 (50.4, 69.7)
	48 Months after last primary Dose	85	47.1 (36.1, 58.2)	99	58.6 (48.2, 68.4)	99	57.6 (47.2, 67.5)
	1 Month after booster Dose	59	100.0 (93.9, 100.0)	58	100.0 (93.8, 100.0)	62	98.4 (91.3, 100.0)
PMB2948 (B24)	**% hSBA ≥ 1:8**						
	1 Month after last primary Dose	100	90.0 (82.4, 95.1)	114	88.6 (81.3, 93.8)	113	81.4 (73.0, 88.1)
	12 Months after last primary Dose	98	40.8 (31.0, 51.2)	108	49.1 (39.3, 58.9)	103	36.9 (27.6, 47.0)
	48 Months after last primary Dose	90	41.1 (30.8, 52.0)	98	40.8 (31.0, 51.2)	105	30.5 (21.9, 40.2)
	1 Month after booster Dose	59	100.0 (93.9, 100.0)	58	100.0 (93.8, 100.0)	61	93.4 (84.1, 98.2)

		Primary Study B1971012 Vaccine Group (as Randomised)					
		Group 1 (0, 1, and 6 Months)		Group 2 (0, 2, and 6 Months)		Group 3 (0 and 6 Months)	
		N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
PMB2707 (B44)	% hSBA ≥ 1:8						
	1 Month after last primary Dose	99	88.9 (81.0, 94.3)	111	87.4 (79.7, 92.9)	113	77.9 (69.1, 85.1)
	12 Months after last primary Dose	100	24.0 (16.0, 33.6)	111	22.5 (15.1, 31.4)	115	16.5 (10.3, 24.6)
	48 Months after last primary Dose	92	20.7 (12.9, 30.4)	100	18.0 (11.0, 26.9)	106	18.9 (11.9, 27.6)
	1 Month after booster Dose	59	94.9 (85.9, 98.9)	57	98.2 (90.6, 100.0)	62	91.9 (82.2, 97.3)
Composite response (A response for all 4 hSBA strains combined)							
	1 Month after last primary Dose	57	80.7 (68.1, 90.0)	55	87.3 (75.5, 94.7)	57	77.2 (64.2, 87.3)
	12 Months after last primary Dose	55	10.9 (4.1, 22.2)	51	13.7 (5.7, 26.3)	49	20.4 (10.2, 34.3)
	48 Months after last primary Dose	51	15.7 (7.0, 28.6)	55	18.2 (9.1, 30.9)	55	16.4 (7.8, 28.8)
	1 Month after booster Dose	59	93.2 (83.5, 98.1)	57	98.2 (90.6, 100.0)	61	91.8 (81.9, 97.3)

Abbreviations: hSBA=serum bactericidal assay using human complement; fHbp=factor H binding protein.
Note: The lower limit of quantitation is an hSBA titre = 1:16 for PMB80 (A22) and 1:8 for PMB2001 (A56), PMB2948 (B24), and PMB2707 (B44).

The hSBA GMTs (exploratory endpoints) for each of the 4 primary strains for the Stage 1 mITT population from 1 month after the last dose (second or third dose) of bivalent rLP2086 in Study B1971012 through 48 months after the last dose and 1 month after the booster are presented in the table below.

Table 31. Persistence of Immune and Booster Responses Among Individuals 11 to 18 Years of Age Administered a Primary Series of Trumenba on a 0-, 1-, 6-Month-; 0-, 2-, 6-Month- and 0-, 6-Month Schedule and a Booster 4 Years After Primary Series (Study B1971033)

		Primary Study B1971012 Vaccine Group (as Randomised)					
		Group 1 (0, 1, and 6 Months)		Group 2 (0, 2, and 6 Months)		Group 3 (0 and 6 Months)	
		N	GMT (95% CI)	N	GMT (95% CI)	N	GMT (95% CI)
hSBA Strain (fHbp Variant) Time Point							
PMB80 (A22)	hSBA GMT						
	1 Month after last primary Dose	100	60.1 (48.6, 74.4)	113	56.6 (47.0, 68.2)	115	54.7 (47.3, 63.3)
	12 Months after last primary Dose	99	14.9 (12.6, 17.7)	111	15.8 (13.4, 18.6)	113	15.6 (13.0, 18.8)
	48 Months after last primary Dose	90	14.3 (11.9, 17.0)	100	15.1 (12.7, 18.0)	101	14.8 (12.5, 17.6)
	1 Month after booster Dose	59	90.0 (69.6, 116.3)	58	119.1 (90.0, 157.8)	62	140.0 (104.2, 187.9)

		Primary Study B1971012 Vaccine Group (as Randomised)					
		Group 1 (0, 1, and 6 Months)		Group 2 (0, 2, and 6 Months)		Group 3 (0 and 6 Months)	
		N	GMT (95% CI)	N	GMT (95% CI)	N	GMT (95% CI)
PMB2001 (A56)	**hSBA GMT**						
	1 Month after last primary Dose	100	199.5 (162.7, 244.5)	112	196.2 (161.8, 237.9)	116	142.5 (118.3, 171.7)
	12 Months after last primary Dose	98	25.7 (19.4, 34.0)	109	27.3 (21.0, 35.4)	106	18.5 (13.8, 24.7)
	48 Months after last primary Dose	85	11.5 (8.6, 15.5)	99	17.5 (13.2, 23.3)	99	16.0 (12.1, 21.1)
	1 Month after booster Dose	59	335.4 (262.1, 429.2)	58	370.8 (275.8, 498.6)	62	358.0 (262.1, 489.0)
PMB2948 (B24)	**hSBA GMT**						
	1 Month after last primary Dose	100	29.7 (23.9, 36.8)	114	30.9 (25.3, 37.7)	113	28.0 (22.0, 35.5)
	12 Months after last primary Dose	98	9.7 (7.5, 12.4)	108	11.5 (9.0, 14.6)	103	8.4 (6.7, 10.6)
	48 Months after last primary Dose	90	9.4 (7.3, 12.1)	98	9.7 (7.6, 12.3)	105	7.5 (6.1, 9.2)
	1 Month after booster Dose	59	74.6 (55.9, 99.5)	58	80.3 (62.6, 103.1)	61	86.0 (62.6, 118.2)
PMB2707 (B44)	**hSBA GMT**						
	1 Month after last primary Dose	99	50.1 (38.0, 66.1)	111	41.9 (32.3, 54.3)	113	31.4 (23.9, 41.3)
	12 Months after last primary Dose	100	6.4 (5.2, 7.8)	111	6.0 (5.1, 7.2)	115	5.6 (4.8, 6.5)
	48 Months after last primary Dose	92	6.0 (5.0, 7.2)	100	5.3 (4.6, 6.1)	106	5.1 (4.6, 5.7)
	1 Month after booster Dose	59	109.9 (74.5, 162.0)	57	117.6 (84.5, 163.5)	62	84.6 (57.8, 124.0)

Abbreviations: GMT = geometric mean titre; hSBA = serum bactericidal assay using human complement; fHbp = factor H binding protein.

There was a somewhat reduced response to the 2 dose schedule in particular for the B strains: approximately 5-10% less subjects had an hSBA ≥LLOQ following the two dose schedule (0,6 m) compared to the three dose schedules at different time points. However, the decline in antibodies followed a similar pattern with the 0,6 month schedule as the three dose schedules (i.e. the decline was not faster or more severe). Similar to the 3-dose schedule, the biggest decline following the 2-dose schedule occurred in the first 12 months after which the serum Ab levels appeared to stabilise.

Combined data suggested the persistence is moderate for three out of the four primary strains tested against (A22, B24, B44). Antibody levels at 12 months were relatively low. The persistence was particularly poor for primary strain B44, where only 16.5% to 24.0% of subjects still had hSBA ≥LLOQ 12 months following the last dose. For strain A56 persistence was better, varying from 60.4% to 76.1% at 12 months. When considering the % with the presumptive correlate of protection (hSBA ≥1:4) at 12 months after the last dose, these were a bit higher yet still low-moderate for strain B44: 19.1%-30.0% had hSBA ≥1:4, for strain A56 68.9%-80.7% had hSBA≥1:4. For the other two strains the response at 12 months after dose 1 was around 40%. For A56 however antibodies appeared to decline more gradually and 48 months post last dose %-s with hSBA ≥1:4 are 47.1% (0,1,6 m schedule), 58.6 (0,2,6 m schedule) and 57.6% (0,6 m schedule).

The hSBA GMTs confirmed that the larger decline in titres occurred during the first 12 months after vaccination after which antibody levels appeared to plateau, except for strain A56 where the decline was more gradual. A similar pattern was seen with the 2 and 3 dose schedules.

This trend is further supported by ancillary analysis looking at the proportions of subjects achieving hSBA titres ≥LLOQ for the 4 primary strains at each blood sampling time point and by age (data not shown). Although subgroups were small and confidence intervals therefore overlap, there was a trend of poorer persistence of immunity in individuals aged 10-14 years compared to those aged 15-18 years. Already at 12 months after the last dose of the primary vaccination schedule, the percentages of subjects aged 10-14 with hSBA ≥LLOQ were very low, ranging from 6.6 to 17.0% for strain B44, from 25.0 to 34.0% for strain B24, and from 17.3-36.7% for strain A22. Persistence was slightly better for the A56 strain, % hSBA≥LLOQ at 12 months after the last dose in those aged 10-14 years varied from 60.0-68.8%. This further strengthens the need for recommending a booster and providing clear information concerning the persistence of immunity following the different schedules in section 5.1 of the SmPC.

Based on these results, and also considering persistence data from B1971005, a booster dose should be considered especially in situations where immunity needs to be maintained. The results of the booster stage show that a primary series with bivalent rLP2086 administered on a 0, 6-month schedule, or on other 2-dose or 3-dose schedules evaluated in B1971012, induces immunologic memory, as demonstrated by substantial increases in bactericidal activity to a single booster dose given 4 years after a primary series with no notable difference in the booster responses after a primary vaccine series given at 0, 6 months or 0, 1-2, 6 months. Note that immunological memory alone is unlikely sufficient to convey protection against invasive meningococcal disease and that circulating serum antibodies are thought necessary.

Persistence following the booster dose has not been evaluated. The Applicant was requested to study post-authorisation the persistence of immunity following a booster dose to determine whether there is a need for any additional booster doses for longer term protection.

The final study results for study B1971033 will be submitted as soon as available.

2.5.3. Discussion on clinical efficacy

The Applicant conducted 10 clinical efficacy trials contributing to the substantiation of the vaccine's efficacy: two pivotal phase 3 studies B1971009 and B1971016; three phase 2 studies (B1971012, B1971004 & B1971005) to support the dose selection and dosing schedule proposed and which are discussed under the section on dose response studies (of these, study B1971005 also described the persistence of the immune response and these results are also discussed here). There were three studies to support concomitant administration with other vaccines (B1971010, B1971011, and B1971015), one early study in individuals 18-40 years of age (B1971003, not further discussed) and a study in laboratory workers which provided data in older subjects (B1971042).

To evaluate the functional immune response to bivalent rLP2086, the Applicant selected from a pool of clinical MnB isolates four primary strains (PMB80 (A22), PMB2001 (A56), PMB2948 (B24), and PMB2707 (B44)) and ten secondary strains (PMB3175 (A29), PMB3010 (A06), PMB3040 (A07), PMB824 (A12), PMB1672 (A15), PMB1989 (A19), PMB1256 (B03), PMB866 (B09), PMB431 (B15) and PMB648 (B16)) to be used in the hSBA for the pivotal immunogenicity studies in support of the MAA. Based on the fHbp variants expressed by the 4 primary and 10 secondary MnB test strains, such selected strains represent all 6 major fHBP phylogenetic subgroups and approximately 77% and 83% of disease causing MnB isolates in Europe and the US respectively.

All of these strains have moderate to high fHBP median surface levels. The lowest levels were reported for strain A07, with a median MFI of 1100 – 1379 dependent on strain pool. As mentioned in the non-clinical

section, at fHBP expression levels below 1100 MFI, the risk that a strain is not susceptible increases. Although fHBP expression on the MnB strain is a necessity for vaccine induced antibodies to be protective against that strain, there is no correlation between the levels of fHBP expression and vaccine response so that fHBP expression cannot be used to predict vaccine response.

Design and conduct of clinical studies

Pivotal efficacy studies

The two pivotal phase 3 studies, B1971009 and B1971016, assessed the hSBA response performed with 4 primary MnB test strains in two different age groups (11-18 and 18-26 years respectively), and evaluated the safety profile of bivalent rLP2086 compared to a control in these populations. The control in study B1971009 was hepatitis A vaccine, which has been used in many other studies where placebo control is inappropriate. The choice of comparator is acceptable considering that it was a paediatric study. Study B1971016 was placebo (saline) controlled which is considered appropriate. In addition, study B1971009 investigated the lot-to-lot consistency of three different lots of bivalent LP2086.

In general, the study design and methodology of the pivotal studies was appropriate. The inclusion and exclusion criteria were acceptable, i.e. representing healthy subjects in the respective age group in the pivotal studies.

Selected endpoints have been discussed and were agreed upon in CHMP scientific advice. Pre-defined success criteria were based on exploratory phase 2 data and on feasibility. The clinical relevance or expected impact of the vaccine, based on the targeted immune responses to the different test strains is difficult to determine. The hSBA data generated against the four primary and 10 secondary test strains provided robust evidence of the protection that might be expected during large-scale vaccine deployment programmes. Post marketing effectiveness studies are expected to confirm the observed efficacy of bivalent rLP2086 as a demonstration of real life use.

Although no justification is presented for the equivalence margins set in the lot to lot study, considering the results, with a narrow confidence interval around a point estimate suggesting no difference, this bears no consequences on the interpretation of the results and on the conclusions drawn.

Persistence of immunogenicity study

Stage 2 of B1971005 addressed the duration of the immune response using the 4 primary MnB test strains (observational objective). Subjects randomised to the 120 µg, 200 µg and control group in stage 1 were invited to remain enrolled in the study, and blood samples for immunogenicity evaluation were collected from subjects participating in Stage 2 at the following 6 intervals after Dose 3: 6 months + 1 week, 12 months, 18 months, 24 months, 36 months, and 48 months. Data is limited as groups are small in particular for strains A56 and B44. Overall, the methods were appropriate for an observational study whose aim is to describe the persistence of the hSBA response for the different vaccine groups.

The persistence of serum bactericidal antibodies was further studied following different dosing regimens in study B1971012 in the context of the extension study B1971033, currently ongoing. Study B1971033 was designed to provide immunogenicity and safety follow-up information on studies B1971010, B1971012, and B1971015, which used the final formulation and dose of bivalent rLP2086. The primary objective of the 'persistence stage' (Stage 1) of study B1971033 was to describe the immunogenicity of bivalent rLP2086 as determined by hSBA titres 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 primary study (B1971010, B1971012, B1971015).

Booster study

The response to a booster dose was evaluated in the booster stage of study B1971033, which also evaluated persistence. The primary objective was to describe the immune response as measured by hSBA titres to 4 primary test strains 1 month after the last dose (second or third dose) of bivalent rLP2086 in the primary study (B1971010, B1971012, B1971015), before the booster vaccination, 1 month after a single booster dose of bivalent rLP2086, and 12 months after a single booster dose of bivalent rLP2086. Currently, only interim data from subjects included in study B1971012 is available.

Concomitant vaccination studies

There were three clinical studies evaluating the effect of concomitant administration of bivalent rLP2086 with other vaccines which could potentially be given to the same target group, i.e. Tdap, Tdap-IPV, conjugated meningococcal ACWY vaccine, and quadrivalent HPV vaccine (HPV serotypes 6, 11, 16, and 18). Methods were generally acceptable.

Study B1971010 evaluated the impact of bivalent rLP2086 on the immune response to Tdap-IPV, but did not allow for evaluation of the impact of concomitant administration on the immune response to bivalent rLP2086 in health subjects aged ≥11 to <19 Years.

Study B1971011 evaluated the impact of concomitant administration of bivalent rLP2086 with quadrivalent HPV vaccine on the immune response to the HPV vaccine (GMT to each of the 4 antigens) and on the immune response to bivalent rLP2086 (as measured by hSBA performed with 2 primary MnB test strains, A22 and B24) in subjects age ≥11 to <18 Years.

Finally, study B1971015 evaluated the safety, tolerability, and immunogenicity of an conjugated tetravalent MenACWY vaccine, Tdap vaccine, and bivalent rLP2086 when administered concomitantly in healthy subjects aged 10 to <13 years. The effect of concomitant administration of either MenACWY or Tdap separately with rLP2086 was not evaluated.

Efficacy data and additional analyses

Two dose regimen

Although the immune response with the two dose schedule is lower for the B-strains, it was considered acceptable following this schedule. Furthermore the persistence is similar to the three dose schedule and a good booster response following both dosing regimens is seen, suggesting that protection can be maintained by administering a booster. The timeframe for such a booster would not be different for the two dose schedule compared to the three dose schedule, but will depend on the local epidemiology and aims of vaccination. The use of these two posologies gives flexibility to prescribers.

More data will be collected on the two dose schedule in a planned phase III randomised comparative study in which the immune response to the two dose schedule will be compared to that of an investigational meningococcal vaccine. The protocol was assessed. This data is not necessary to conclude that the benefit/risk of the two dose schedule is indeed positive, but will strengthen the evidence base.

B1971009

In study B1971009, 3596 persons were randomised, of which approximately 90% completed follow-up. The mean age at vaccination was 13.9 years, 48.5% of subjects were female. Overall, demographics were balanced amongst groups.

Of the subjects vaccinated with bivalent rLP2086, 79.8%-90.2% had ≥ 4 fold rise in hSBA titres against the four primary strains. The primary objectives were met: the lower limit of the 2-sided 95% CIs was greater than the corresponding pre-specified lower bound threshold for each of the 4 primary MnB strains (i.e. 75%, 85%, 65%, and 60% for A22, A56, B24 and B44 respectively) and for the composite response (75%), and lot to lot consistency was demonstrated.

Pre-vaccination, 26.2-38.1% of subjects had hSBA titres ≥LLOQ against the two A-strains, and 3.6-8.4% had hSBA titres ≥LLOQ against the two B-strains, depending on vaccination group and strain. One month after the second dose for the two A strains, 92.7-99.1% of subjects in the active groups and 29.1-37.1% in the control had hSBA titres ≥LLOQ. For the B-strains, 64.0-70.2% of subjects in the active groups had hSBA titres ≥ LLOQ one month after the second dose, compared to 5.9-8.2% in the control groups. One month after the third dose the percentage of subjects above the LLOQ raised to 97.3-99.5% and 87.1-90.0% in the active groups for the A and B strains respectively. Other secondary endpoints were in line with these results, with the RCDCs showing robust responses following three doses, in particular against strain A56.

For the 10 secondary strains, 3.9-43.1% of subjects had an hSBA titre≥LLOQ at baseline, with variation depending on the strain. One month post dose 3, 75.1-98.2% had an hSBA titre≥LLOQ, suggestive of a strong immune response against all strains included.

B1971016

In study B1971016, 3304 persons aged 18-26 years were randomised to receive bivalent rLP2086 at a 0,2,6 month schedule or saline (control). In total 2419 subjects (73.2%) completed follow up. The mean age at vaccination was 21.5 years, 60.8% was female. Demographics were balanced between the groups. In total, 999 (30.2%) of subjects were excluded from the EIP. The main reasons for exclusion from the EIP were similar as in B1971009 (missing blood-draws, no valid assay results and/or did not receive all vaccines as randomised). The % subjects with ≥ fourfold rise in hSBA titre ranged from 79.3 to 90.0 % depending on the strain. The primary objectives were met as the lower limit of the 2-sided 95% CIs was greater than the corresponding pre-specified lower bound threshold for each of the 4 primary strains (i.e. 55%, 85%, 50% and 60% for A22, A56, B24 and B44 respectively) and the composite hSBA response (>60%).

Secondary endpoints for the primary strains were in line with the primary endpoints. At baseline approximately 30% of subjects had hSBA ≥ LLOQ for strains A22, A56 and B24 – 11% of subjects had hSBA ≥LLOQ for strain B44. One month post dose 2, the % of subjects with hSBA ≥LLOQ increased to 94.7, 97.4, 86.5 and 68.3% for strain A22, A56, B24 and B44 respectively. The response further increased one month post dose 3, up to 93.5, 99.4, 95.1 and 87.4% for each of the 4 primary strains respectively.

Regarding the secondary strains, 5.0% (A12) to 55.8% (A07) of subjects had an hSBA titre ≥LLOQ at baseline. One month post dose 3 this increased to 71.3% (A12) to 99.3% (A29) depending on the strain. So there was some variation in the response between strains, but 6/10 strains had an hSBA ≥LLOQ >90%, 7/10 >85% and 9/10 >75%, suggesting an overall strong response.

Persistence of bactericidal antibodies

The persistence of hSBA GMTs following the 3rd dose of 120 µg bivalent rLP2086 as measured in stage 2 of study B1971005 show an initial decrease up to approximately month 6 followed by a plateau that is maintained above levels seen in the control group, although 95% CIs overlap for strain A22, A56 and B44 at later time points (see Figure 9). The GMTs in the control groups tend to increase slightly over time, with the exception of strain A56 where a more drastic increase is seen and where the bivalent rLP2086 group overlaps with the control group after m24.

The percentages of subjects with hSBA titres ≥ LLOQ at 48 months were 59%, 51%, 57% and 20% against strain A22, A56, B24 and B44 respectively. Considering the percentages with titres >LLOQ against strain A56, where a clear increase in the hSBA GMT in the control group was seen, these were approximately 15% higher in the active group compared to the control group at month 48 after the 3rd dose, and 95% CIs overlap.

The persistence of immunity was poor for strain B44. Although the initial response after the third dose was 95.7% of subjects having hSBA titre ≥ LLOQ, at 6 months this was 37%, down to 20% during the follow up period. There was no significant difference with the control group at 6 months and 1 week following the third dose, or any time-point thereafter, but numbers are small and CIs wide. The numerical difference ranges approximately from 10-20%.

Persistence of antibodies following vaccination in Protocols B1971010, B1971012, and B1971015 has further been studied in extension study B1971033. Preliminary data for subjects from study B1971012 included in study B1971033 was submitted as an interim study report. The immune response as measured by proportions of subjects with hSBA titres ≥ LLOQ, hSBA GMTs, hSBA titres achieving defined levels, and the composite hSBA response demonstrated that the immune response declined between 1 and 12 months after the last dose, after which it seemingly plateaued.

When evaluated over a 48-month period, the proportion of subjects achieving hSBA titres ≥LLOQ following the 2 dose schedule (0, 6 months) was similar to that observed following the 0, 2, 6-month schedule.

Combined data suggest the persistence is however moderate for three out of the four primary strains tested against (A22, B24, B44). Antibody levels at 12 months are relatively low. The persistence is particularly poor for primary strain B44, where, depending on the schedule, only 16.5% to 24.0% of subjects still had hSBA ≥LLOQ 12 months following the last dose. For strain A56 persistence is better, varying from 60.4% to 76.1% at 12 months. When considering the % with the presumptive correlate of protection (hSBA ≥1:4) at 12 months after the last dose, these are a bit higher yet still low-moderate for strain B44: 19.1%-30.0% had hSBA ≥1:4, for strain A56 68.9%-80.7% had hSBA≥1:4. For the other two strains the response at 12 months after dose 1 was around 40%. For A56 however antibodies appear to decline more gradually and 48 months post last dose percentages with hSBA ≥1:4 are 47.1% (0,1,6 m schedule), 58.6 (0,2,6 m schedule) and 57.6% (0,6 m schedule).

Furthermore, although subgroups are small and CIs therefore overlap, there is a clear trend of poorer persistence of immunity in individuals aged 10-14 years compared to those aged 15-18 years. Already at 12 months after the last dose of the primary vaccination schedule % subjects aged 10-14 years with hSBA ≥LLOQ are very low, ranging from 6.6 to 17.0% for strain B44, from 25.0 to 34.0% for strain B24, and from 17.3-36.7% for strain A22.

Considering the importance of circulating serum bactericidal antibodies for maintenance of protection (in theory memory alone might not provide protection against invasive meningococcal disease, which usually occurs 1–10 days after strain acquisition), the declined hSBA titres, in particular in younger individuals, questions whether long term protection will be maintained and points towards the need for a booster dose to maintain protection following either dosing regimen.

At what time point consideration should be given to a booster dose will be dependent on several factors in addition to declining hSBA titres, such as circulating strains and the antigen expression thereof as well as local epidemiology and possible herd-immunity. For this reason a booster dose may be considered in individuals at continued risk of invasive meningococcal disease. This is reflected in the SmPC.

Booster study

A primary series with bivalent rLP2086 administered on a 0, 6-month schedule, or on other 2-dose or 3-dose schedules evaluated in B1971012, induces immunologic memory, as demonstrated by substantial increases in bactericidal activity to a single booster dose given 4 years after a primary series (study B1971033). Furthermore, there was no notable difference in the booster responses after a primary vaccine series given at 0, 6 months or 0, 2, 6 months.

The Applicant has indicated that they have no further plans to follow persistence of immunity following either the three dose or the two dose schedule, which is acceptable. Persistence following the booster dose has not been evaluated. Considering a booster dose should be considered post-primary vaccination, the Applicant was requested to study the persistence of immunity following a booster dose to determine whether there is a need for any additional booster doses to maintain immunity after that.

Concomitant vaccination studies

Study B1971010 found no evidence of a potential interference of rLP2086 with the immune response to Tdap-IPV. As the immune response (percentages of subjects achieving prespecified antibody levels) to Tdap-IPV was maximal in both groups, there was no difference between groups. Considering the GMTs, which is a more sensitive endpoint, for some antigens the GMTs were higher in the Tdap-IPV+saline group, most notably poliovirus 2 GMTs, but differences were non-significant.

In study B1971011 the GMTs against HPV-6,-11, -16 and -18 were all numerically and statistically significantly higher when quadrivalent HPV vaccine was given without rLP2086 compared to when the two vaccines were given concomitantly. The 1.5-fold non-inferiority criterion of 0.67 (the 2-sided 95% LCI of the GMR) was met for all HPV antigens except for HPV-18, which was missed with a 95% LCI of 0.62 signalling potential interference of the immune response. However since one month after Dose 3 with quadrivalent HPV vaccine, ≥99% of subjects seroconverted to all 4 HPV antigens in both the saline + quadrivalent HPV vaccine group and the rLP2086 + quadrivalent HPV vaccine group, the potential interference is likely to be of limited clinical relevance. Similarly, the immune response to rLP2086 was higher (i.e. hSBA titres were higher) when rLP2086 was given with saline placebo as compared to when it was given with HPV vaccine. Differences were small and borderline significant with CIs overlapping marginally, the ratio between GMTs was 0.92 for both test strains, the lower bound for the 95% CI was 0.85 and 0.84 for the A22 and B24 strain respectively. The set non-inferiority criteria were all met.

Finally, study B1971015 evaluated the impact of concomitant administration of a conjugated quadrivalent meningococcal ACWY vaccine with Tdap and rLP2086. Predefined non-inferiority criteria were met for all MenACWY and Tdap antigens and for both MnB test strains. Numerically, GMs were slightly higher for the Pertussis, Tetanus and Diphtheria antigens when Tdap + MCV4 were given together with saline as compared to when they were given together with bivalent rLP2086. Similarly, GMTs were slightly higher against serogroup A and W of the MCV4 vaccine when given with saline compared to rLP2086, however not for the C and Y components. Considering the seroconversion rates for the different antigens, there was no difference between the groups for diphtheria and tetanus; some decreased responses were seen for the pertussis antigens when administered with bivalent, yet differences were small and the picture was not entirely consistent with the GMTs. For the meningococcal ACWY antigens, here too some numerical differences in % seroprotected can be seen between groups (differences between groups varied from -3.2% to 0.3 % dependent on the strain, LBI of the 95% CI from -6.7 to -1.9%), however these too were small and unlikely of clinical relevance.

For the two MnB test strains, the proportion of subjects with hSBA titre≥ LLOQ one month post vaccination 3, this was again numerically higher for those who received rLP2086 with saline compared to those who received rLP2086 with Tdap+MCV4: for strain A22 after 3 doses: 87.5%, 95% CI:84.8, 89.9 compared to 91.4%, 95% CI: 89.0, 93.4 in the rLP2086+saline group; for strain B24 this was 90.0%, 95% CI: 87.5, 92.2 compared to 92.7%, 95%CI: 90.4, 94.6. In conclusion, differences were small, statistically not significant, and unlikely bearing much clinical relevance.

Effect of covariates

Age

The immune responses in the 4 age subgroups (10 to 14, 15 to 18, 10 to 18, and 19 to 25 year age groups) after 3 doses of bivalent rLP2086 showed no substantial differences between age groups in the

subgroup analysis for any immunogenicity endpoint analysed, and were consistent with responses in the overall population. Available data did not point towards a clinically relevant effect of age on the hSBA response, for persons aged between 10-26 years.

There is limited data in individuals >26 years of age (n=67), in particular in persons aged 40-65 (n=9). There is no data in individuals aged ≥65 years. Whilst the available data can be extrapolated to adults, in older adults the immune response to vaccines can diminish with increasing age due to immunosenescence. Study B1971042 was the only study including subjects >40 years of age (13 subjects aged 24 to 62 years, of which 8 subjects were >40 years). The number of subjects is too limited for reliable inferences to be made based on this study results. However despite the paucity of data, it is unlikely that there would be no benefit from vaccination, i.e. no protective immune response against MnB strains, and it can thus be considered that the benefit/risk balance is positive in those over 40 years and over 65 years of age. Most importantly, if for example in an outbreak situation persons over 40 or over 65 would have to be vaccinated this should be possible considering the acceptable safety profile of bivalent rLP2086 and the likelihood of the vaccine eliciting a protective immune response.

Sex

There were small differences unlikely of clinical significance.

Analyses across studies

An analysis of responses across studies was performed and depicted in Forrest plots, showing some variation in response by study. This can be explained by a different history in exposure in MnB strains – either due to age or geographical region - and imprecision resulting from a more limited data set.

Follow up studies on effectiveness

Clinical studies measured targeted immune response to carefully selected test strains. The clinical relevance or expected impact of the vaccine, based on the targeted immune responses to the different test strains is difficult, to determine. The hSBA data generated against the four primary and 10 secondary test strains will only provide information of the protection that might be expected during large-scale vaccine deployment programmes however post marketing effectiveness studies are necessary to confirm the effectiveness of bivalent rLP2086.

Vaccine effectiveness and Vaccine failure are included as missing information in the RMP. The Applicant is committed to actively seek collaboration with any public health authority that has the capabilities to undertake a study to determine vaccine effectiveness of bivalent rLP2086 and to collaborate with the Applicant following introduction of the vaccine into a national or regional immunization program. Vaccine effectiveness studies are included in the Pharmacovigilance Plan (see RMP).

At the moment there is an important knowledge gap regarding the herd effect and risk on serotype and strain replacement following MnB vaccination with bivalent rLP2086. Specific data are needed on the molecular epidemiology of fHBP variants and protein surface expression in relation to the use of bivalent rLP2086. Therefore it cannot be completely ruled out that meningococcal strain replacement will not happen in the future in case the vaccine will be used more extensively (e.g. through use in national immunisation programs). The Applicant is committed to seek collaboration with the relevant public health authorities and have data on strain characterization made available for inclusion in any pharmacovigilance reports. This is adequately reflected in the RMP.

2.5.4. Conclusions on the clinical efficacy

The pivotal studies support the conclusion that 120 µg bivalent rLP2086 given at a 0,2,6 m dosing schedule elicits an immune response in individuals aged 11 to 26 years of age against a range of clinically

relevant MnB strains. The immune response after three doses was equally strong in the two main studies, 83.5% of subjects aged ≥10 to <19 years and 84.9% of subjects aged ≥18 to <26 years had an hSBA titre ≥ LLOQ for all 4 primary MnB test strains combined. Moreover, 71.3-99.3% had an hSBA titre≥LLOQ for the 10 secondary strains one month after dose 3, suggestive of an overall strong and broad response. The data available are suggestive that bivalent rLP2086 will provide broad protection against circulating MnB strains in Europe following a 3 dose schedule given at 0, 1-2 and 6 months.

Overall the immune response to the two dose schedule (0,6 m) are considered similar to the three dose schedules; the persistence of antibodies and the response to a booster dose given 4 years after a primary series showed no notable difference when the 0, 6 months schedule or the 0, 1-2, 6 months schedule were followed. The CHMP considered that the available 2 dose posology data is sufficient to recommend the use of this schedule. More data will be collected on the two dose schedule in a planned phase 3 randomised comparative study (B1971057). This additional data was not considered necessary to conclude that the benefit/risk of the two dose schedule and as a consequence the study will be conducted post-authorisation and the data generated is expected to further strengthen the evidence base.

In addition, based on the available data on persistence of antibodies, a booster dose should be considered following either dosing regimen for individuals at continued risk of invasive meningococcal disease. Further data was requested to understand if additional boosters are needed in order to maintain a continued protection.

Bivalent rLP2086 can be given concomitantly with any of the following vaccines: Tetanus Toxoid, Reduced Diphtheria Toxoid, Acellular Pertussis, and Inactivated Poliovirus Vaccine (TdaP-IPV), Quadrivalent Human Papillomavirus vaccine (HPV4), Meningococcal Serogroups A, C, Y, W conjugate vaccine (MenACWY) and Tetanus Toxoid, Reduced Diphtheria Toxoid, and Acellular Pertussis Vaccine Adsorbed (Tdap).

To further substantiate efficacy of the vaccine, the Applicant agreed to submit a plan to assess the effectiveness of bivalent rLP2086 in routine use, although the difficulties related to the type of study and the dependence upon product use and collaborations with stakeholders are acknowledged.

As there is no data in those aged over 65 years and limited data is available for those aged between 40 and 65, this is adequately reflected in the RMP and will be monitored post-authorisation. As the incidence of the invasive meningococcal serogroup B disease in adults and elderly populations is low and thus the expected use of the vaccine would be limited, more investigation could be of interest albeit not essential for approval.

The co-administration of vaccines foreseen in the vaccination schedule of adolescents and not studied in the clinical development plan, and lack of data in persons with immunodeficiency due to functional asplenia, HIV-infection or other immunosuppressant condition or therapy are adequately reflected in the RMP. The Applicant committed to investigate concomitant administration with measles, mumps, and rubella vaccine and 13-valent pneumococcal conjugate vaccine. The Applicant committed to investigate the immunogenicity and safety of bivalent rLP2086 in immunocompromised patients, including patients with complement deficiency or asplenia.

There are three planned or ongoing studies in the Post-Authorisation Pharmacovigilance Development Plan, which are relevant for efficacy:

- **B1971052,** a pregnancy and birth outcome assessment in a population-based cohort after exposure to bivalent rLP2086.
- Population-based surveillance of the incidence rates of IMD (serogroup B) in collaboration with national agencies if bivalent rLP2086 is used as part of a national immunization program with the aim to survey for cases of laboratory-confirmed serogroup B IMD in individuals who have received

the recommended number of doses of bivalent rLP2086 as part of a national immunization program.

- Population-based surveillance of the incidence rates of IMD (serogroup B) in collaboration with national agencies if bivalent rLP2086 is used as part of a national immunization program with the aim to measure bivalent rLP2086 effectiveness when used as part of a national immunization program.

Further clinical studies that are ongoing or planned are listed below:

B1971033 is an ongoing phase 3 extension study to assess the persistence of hSBA response up to 48 months after completion of vaccination with bivalent rLP2086, and the safety, tolerability, and immunogenicity of a booster dose of bivalent rLP2086. As mentioned, this is an extension study of Protocols B1971010, B1971012, and B1971015.

B1971053 is a dose-finding study to describe the immunogenicity, safety and tolerability of rLP2086 vaccine when administered to healthy *infants aged 2 months*.

B1971035 is a randomized, controlled, observer-blind trial, to describe immunogenicity, safety and tolerability of a meningococcal bivalent serogroup B (rLP2086) vaccine when administered to *healthy toddlers aged 12 to less than 24 months of age.*

B1971017 is a randomized, controlled, observer-blind trial, to describe immunogenicity, safety and tolerability of rLP2086 vaccine in *healthy children aged 24 months to less than 10 years.*

Finally, the Applicant submitted a synopsis for a proposed phase 3, randomized, observer-blinded trial (**B1971057**) to assess safety, tolerability, and immunogenicity of a meningococcal serogroup B bivalent rLP2086 vaccine administered on a 0-, 6-month schedule in healthy subjects aged ≥10 to <26 years.

2.6. Clinical safety

The safety of the final formulation of bivalent rLP2086 was investigated in the 11 completed clinical studies that contribute data: 8 controlled studies and 3 uncontrolled studies (see tabular overview in the clinical efficacy section). All of the studies evaluated the immunogenicity and safety of bivalent rLP2086, except for Study B1971014, which was solely a safety study. These 11 studies comprise:

- 6 studies in adolescents (age range, 10 to <19 years): B1971005, B1971009, B1971010, B1971011, B1971012, B1971015;
- 4 studies in adults: B1971003 (≥18 years to 40 years), B1971004 (≥18 years to 40 years), B1971016 (≥18 years to <26 years), B1971042 (≥18 years to ≥65 years);
- 1 study in adolescents and young adults (10 to <26 years): B1971014.

Safety was assessed on the basis of information regarding local and systemic events (collected by e-diary in all studies except Study B1971014). Frequencies of adverse events are discussed based on the findings in the core safety data set. The comparator group in the core safety data set reflects both active comparators and placebo (saline). The safety data is presented with rates among those receiving rLP2086 and those receiving a control. Comparisons between groups makes possible to differentiate between active comparators and between placebo groups.

Patient exposure

The safety data is discussed in terms of 2 groupings: core safety data and overall safety data.

In total, 15,294 subjects received at least one dose of bivalent rLP2086 (at any dose level and with any vaccination regimen) in any of the 11 completed clinical studies (overall safety dataset). In these studies, 5509 subjects were included in control groups and received either saline alone, licensed vaccine alone, or saline and a licensed vaccine. The vast majority of subjects in the overall safety data set received the 0,2,6 month schedule.

The core safety dataset as defined includes safety data from the 8 controlled studies (B1971004, B1971005, B1971009, B1971010, B1971011, B1971014, B1971015 and B1971016) for subjects who received at least one dose of the final formulation of bivalent rLP2086 on a schedule of 0,2,6 months (a total of 13,284 subjects) or who received a control vaccine. In the core safety dataset, among the 13,284 subjects who received 120 ug bivalent rLP2086, 4635 (34.89%) were enrolled at sites in the EU; and among the 5509 subjects who received control vaccine, 2144 (38.92%) were enrolled at EU sites.

Table 32. Number (%) of Vaccinated Subjects by Age Group (core safety data set)

	Dose 1		Dose 2		Dose 3	
Age Group	**n (%)**		**n (%)**		**n (%)**	
	rLP2086	**Control**	**rLP2086**	**Control**	**rLP2086**	**Control**
All vaccinated subjects	13284 (100.00)	5509 (100.00)	12271 (100.00)	5180 (100.00)	11441 (100.00)	4897 (100.00)
10-14 Years	6121 (46.08)	2645 (48.01)	5718 (46.60)	2531 (48.86)	5469 (47.80)	2446 (49.95)
15-18 Years	3301 (24.85)	1304 (23.67)	3134 (25.54)	1234 (23.82)	2968 (25.94)	1181 (24.12)
19-25 Years	3853 (29.00)	1552 (28.17)	3410 (27.79)	1408 (27.18)	2997 (26.20)	1264 (25.81)
≥26 Years	9 (0.07)	8 (0.15)	9 (0.07)	7 (0.14)	7 (0.06)	6 (0.12)

Overall the number of persons who have been exposed to bivalent rLP2086 is sufficiently large to evaluate the safety of bivalent rLP2086 in the targeted age group (11-26 years). Only very few subjects older than 25 years were exposed in clinical trials (in the core safety data set n=9 for dose 1). There is limited data for persons aged 26 to 40 and persons >40 years and no data in persons >65 years.

Safety Data Collection Methods

Standardized methods were used for collection of safety data. The safety endpoints evaluated in each study included unsolicited adverse events (AEs reported without prompting) and predefined, solicited AEs (local reactions at the injection site and systemic events) to be recorded by subjects/parents in an electronic diary (e-diary) in response to specific prompts. Solicited AEs, and the severity of each, were collected daily in the e-diary for 7 days after each vaccination in all studies, except in Phase 3 Study B1971014. In Study B1971014, since e-diaries were not used, reactogenicity events were reported in the same manner as unsolicited AEs.

In all studies, unsolicited AEs included nonserious AEs, serious adverse events (SAEs), newly diagnosed chronic medical conditions (NDCMC, disease or medical condition not identified prior to study entry and expected to persist), autoimmune diseases, and neuroinflammatory conditions; in addition, non-serious medically attended AEs (MAE) were collected in the 3 Phase 3 studies. These unsolicited AEs were collected by the investigator after clinical evaluation of the subject and clinical questioning of the subject or parent.

In all but the early development studies (B1971003, B1971004, B1971005), nonserious AEs were collected from the signing of the informed consent document to the study visit taking place 1 month after the third dose of study vaccine. SAEs, NDCMCs, MAEs, and autoimmune or neuroinflammatory conditions were collected throughout the studies and through the follow up visit approximately 6 months after the last dose of study vaccine.

Adverse events in the core dataset

Local reaction and systemic event data were collected in an e-diary from 7 of the 8 core studies (all studies except Phase 3 Study B1971014, reactogenicity data collected as other AEs, not by e-diary). Results for early Phase 1 Study B1971004 were excluded from this analysis due to the small sample size not allowing drawing meaningful conclusions.

Solicited adverse events: local and systemic reactions

Considering the local reactions, considerably more subjects reported pain, redness and swelling following vaccination with rLP2086 compared to subjects receiving saline or comparator vaccines HAV, quadrivalent HPV vaccine, TdaP, MCV4 or TdaP-IPV.

Pain at the injection site was a frequently experienced local reactogenicity event in subjects receiving bivalent rLP2086, reported by 89.6% to 98.1% across studies. It occurred more frequently among subjects receiving bivalent rLP2086 than among those receiving the control vaccine (18.2% to 64.8%). Severe pain was reported in 3.0-15.1% of subjects dependent on the study compared to 0-2.4% in control groups. Moderate pain was reported for 45.5% to 63.0% versus 1.7% to 17.5% of subjects in control groups; and mild pain after any dose was reported for 22.3% to 43.4% versus 16.2% to 46.1% of subjects in control groups. The median duration of pain at the injection site was generally 2 to 3 days in subjects receiving 120 µg bivalent rLP2086, compared to 1 day for the control vaccine.

The frequency of **redness** occurring within 7 days after any dose was higher among subjects receiving 120 µg bivalent rLP2086 (22.0% to 40.0% across studies) than among those receiving the control vaccine (0.0% to 8.1%). The frequency of **swelling** after any dose was also higher after 120 µg bivalent rLP2086 (25.1% to 40.7%, across studies) than after the control vaccine (0.0% to 12.2%).

An increase in severity of local reactions and increase in severity with potentiation (increased severity with *all* subsequent doses, i.e. 3>2>1) is reported at a higher frequency in the rLP2086 groups compared to control groups – albeit the percentages for the latter are small. This principle is illustrated in Table 33 below for pain, but was also seen for other solicited reactions.

Table 33. Subjects Reporting Increased Severity of Pain at Injection Site Within 7 Days After Vaccination – Core Studies – Safety Population

Study Vaccine Group	Any Severity Increase n[a]/N[b] (%)	 (95% CI)[c]	Severity Increase With Potentiation n[a]/N[b] (%)	 (95% CI)[c]	No Reaction After Any Vaccination n[a]/N[b] (%)	 (95% CI)[c]
B1971004 (0-, 2-, and 6-month schedule)						
120 µg rLP2086	4/10 (40.0)	(12.2, 73.8)	0/10 (0.0)	(0.0, 30.8)	1/10 (10.0)	(0.3, 44.5)
Tdap/saline	0/7 (0.0)	(0.0, 41.0)	0/7 (0.0)	(0.0, 41.0)	1/7 (14.3)	(0.4, 57.9)
B1971005 (0-, 2-, and 6-month schedule)						
120 µg rLP2086	95/188 (50.5)	(43.2, 57.9)	3/188 (1.6)	(0.3, 4.6)	13/188 (6.9)	(3.7, 11.5)
Saline	17/114 (14.9)	(8.9, 22.8)	0/114 (0.0)	(0.0, 3.2)	77/114 (67.5)	(58.1, 76.0)
B1971010 (0-, 2-, and 6-month schedule)						
120 µg rLP2086 + Repevax[d]	120/319 (37.6)	(32.3, 43.2)	2/319 (0.6)	(0.1, 2.2)	5/319 (1.6)	(0.5, 3.6)
Saline + Repevax[e]	54/345 (15.7)	(12.0, 19.9)	1/345 (0.3)	(0.0, 1.6)	123/345 (35.7)	(30.6, 41.0)
B1971011 (0-, 2-, and 6-month schedule)						
120 µg rLP2086+Gardasil[d]	304/834 (36.5)	(33.2, 39.8)	6/834 (0.7)	(0.3, 1.6)	20/834 (2.4)	(1.5, 3.7)
120 µg rLP2086+saline[d]	343/837 (41.0)	(37.6, 44.4)	8/837 (1.0)	(0.4, 1.9)	22/837 (2.6)	(1.7, 4.0)
Saline+Gardasil[e]	117/431 (27.1)	(23.0, 31.6)	2/431 (0.5)	(0.1, 1.7)	189/431 (43.9)	(39.1, 48.7)
B1971009 (0-, 2-, and 6-month schedule)						
120 µg rLP2086 (Lot 1)	545/1346 (40.5)	(37.9, 43.2)	14/1346 (1.0)	(0.6, 1.7)	86/1346 (6.4)	(5.1, 7.8)
120 µg rLP2086 (Lot 2)	217/530 (40.9)	(36.7, 45.3)	4/530 (0.8)	(0.2, 1.9)	48/530 (9.1)	(6.8, 11.8)
120 µg rLP2086 (Lot 3)	221/525 (42.1)	(37.8, 46.4)	4/525 (0.8)	(0.2, 1.9)	36/525 (6.9)	(4.8, 9.4)
HAV/saline	255/805 (31.7)	(28.5, 35.0)	3/805 (0.4)	(0.1, 1.1)	318/805 (39.5)	(36.1, 43.0)
B1971015 (0-, 2-, and 6-month schedule)						
MCV4+Tdap+120 µg rLP2086[d]	294/716 (41.1)	(37.4, 44.8)	6/716 (0.8)	(0.3, 1.8)	14/716 (2.0)	(1.1, 3.3)
MCV4+Tdap+saline[e]	146/732 (19.9)	(17.1, 23.0)	2/732 (0.3)	(0.0, 1.0)	326/732 (44.5)	(40.9, 48.2)
Saline+saline+120 µg rLP2086[d]	322/719 (44.8)	(41.1, 48.5)	7/719 (1.0)	(0.4, 2.0)	19/719 (2.6)	(1.6, 4.1)
B1971016 (0-, 2-, and 6-month schedule)						
120 µg rLP2086	740/1771 (41.8)	(39.5, 44.1)	20/1771 (1.1)	(0.7, 1.7)	131/1771 (7.4)	(6.2, 8.7)
Saline	59/606 (9.7)	(7.5, 12.4)	0/606 (0.0)	(0.0, 0.6)	488/606 (80.5)	(77.1, 83.6)

Systemic events were reported more frequently after 120 µg bivalent rLP2086 than after the control vaccine. The most frequently reported systemic events after any dose of 120 µg bivalent rLP2086 were fatigue and headache. In the rLP2086 groups versus the control groups, respectively, the proportion of subjects reporting **fatigue** after any dose ranged from 60.6% to 85.0% versus 41.7% to 79.6%; and the proportion reporting **headache** ranged from 59.1% to 83.9% versus 48.4% to 74.3%. For both fatigue and headache, in both the rLP2086 and control groups, reporting rates were highest after Dose 1, with lower rates observed after Dose 2 and dose 3. After any dose, severe fatigue was reported for 1.5% to 6.6% of subjects after rLP2086 versus 0.0% to 4.0% of subjects after the control vaccine; and rates for severe headache were 1.3% to 5.6% versus 0.0% to 2.9%, respectively. Increases in the severity of fatigue with potentiation were reported for ≤1.6% of subjects after administration of 120µg bivalent rLP2086 and for ≤0.7% after the control vaccine.

As for fatigue and headache, **muscle pain** was reported more frequently after 120 µg bivalent rLP2086 (34.3% to 61.8%) than after the control vaccine (18.3% to 52.4%), was observed more frequently after Dose 1 than after Dose 2 or Dose 3, and was most often reported as mild or moderate, with severe muscle pain reported for ≤5.2% of subjects after any dose of 120µg bivalent rLP2086. Increase in the severity of muscle pain with potentiation was reported for ≤1.2% of subjects after administration of 120µg bivalent rLP2086 and for ≤0.9% after the control vaccine.

Fever (≥38^{o}C) was also reported more frequently among subjects receiving 120µg bivalent rLP2086 (4.4% to 17.4%) than among those receiving the control vaccine (1.7% to 9.0%). In the 120µg bivalent rLP2086 group, the frequency of fever was consistently higher after Dose 1 than after Dose 2 or Dose 3. In both the bivalent rLP2086 and control vaccine groups, fever was most often mild (38^{o}C to <38.5^{o}C) or moderate (38.5^{o}C to <39^{o}C); severe fever (39.0^{o}C to 40.0^{o}C) was reported for 0.2% to 2.7% of subjects after any dose of 120 µg bivalent rLP2086 and for 0.4% to 1.7% of subjects after the control vaccine. Fever >40.0^{o}C was reported for 1 subject in Study B1971015 after Dose 1 of 120 µg bivalent rLP2086+MCV4+ Tdap (subject was withdrawn from the study as a result), for 1 subject in Study B1971016 after Dose 3 of 120 µg bivalent rLP2086, and for 1 subject in Study B1971009 after Dose 3 of control vaccine (HAV). Each of these 3 cases resolved after one day. Increases in the severity of fever with potentiation were reported for 3/2388 subjects (0.13%) who received 120 µg bivalent rLP2086 in Study B1971009; no subjects who received the control vaccine experienced increases in the severity of fever with potentiation.

Diarrhoea was reported for up to 25.7% of subjects receiving 120 µg bivalent rLP2086 and up to 25.2% receiving the control vaccine, while **vomiting** was reported for up to 15.0% of subjects after 120 µg bivalent rLP2086 and 11.1% after the control vaccine.

Chills and joint pain were reported more frequently after any dose of 120 µg bivalent rLP2086 than after any dose of control vaccine: chills, 20.7% to 55.8% versus 13.3% to 44.4% of subjects, respectively; and joint pain, 22.7% to 37.7% versus 14.2% to 30.7% of subjects, respectively.

Overall, in the core safety dataset, systemic events resulted in withdrawal of 31 subjects (0.23%) who received 120 ug bivalent rLP2086 and 2 subjects (0.04%) who received control vaccine. Among subjects receiving 120 ug bivalent rLP2086, the systemic events most frequently leading to withdrawal from study participation were headache (17 subjects, 0.13%) and pyrexia (11 subjects, 0.08%).

Reactogenicity data were not pooled, and were only presented for the individual studies. Based on the evaluation of individual studies, local and systemic reactogenicity events are more frequently reported among subjects receiving 120 µg of rLP2086 vaccine compared to saline or control vaccine. However, a pooled analysis of the reactogenicity data was provided during evaluation, in which the rLP2086 group was compared to a saline and a general control group, respectively. This analysis confirmed the findings previously observed in individual studies.

Unsolicited adverse events

The most frequently reported types of unsolicited AEs (reported by ≥2% of subjects) were reported at similar frequencies in the 120µg bivalent rLP2086 group and in the control group, as shown below.

Table 34. Adverse Events Reported During the Vaccination Phase – Subjects Who Received at Least 1 Dose of Bivalent rLP2086 Final Formulation (120 µg Dose Level) on a 0-, 2-, and 6-Month Schedule – Core Studies Pooled

	rLP2086	Control
	(N=13284)	(N=5509)
System Organ Class	n (%)	n (%)
Any event	5669 (42.68)	2296 (41.68)
Blood and lymphatic system disorders	65 (0.49)	26 (0.47)
Cardiac disorders	13 (0.10)	9 (0.16)
Congenital, familial and genetic disorders	10 (0.08)	3 (0.05)
Ear and labyrinth disorders	89 (0.67)	37 (0.67)
Endocrine disorders	10 (0.08)	3 (0.05)
Eye disorders	109 (0.82)	41 (0.74)
Gastrointestinal disorders	683 (5.14)	293 (5.32)
General disorders and administration site conditions	1568 (11.80)	385 (6.99)
Injection site pain	909 (6.84)	198 (3.59)
Pyrexia	347 (2.61)	79 (1.43)
Hepatobiliary disorders	7 (0.05)	4 (0.07)
Immune system disorders	70 (0.53)	37 (0.67)
Infections and infestations	3023 (22.76)	1314 (23.85)
Upper respiratory tract infection	659 (4.96)	291 (5.28)
Nasopharyngitis	448 (3.37)	208 (3.78)
Pharyngitis	326 (2.45)	131 (2.38)
Injury, poisoning and procedural complications	829 (6.24)	350 (6.35)
Investigations	56 (0.42)	27 (0.49)
Metabolism and nutrition disorders	46 (0.35)	15 (0.27)
Musculoskeletal and connective tissue disorders	585 (4.40)	227 (4.12)
Neoplasms benign, malignant and unspecified (inc cysts & polyps)	50 (0.38)	27 (0.49)
Nervous system disorders	751 (5.65)	278 (5.05)
Headache	502 (3.78)	191 (3.47)
Pregnancy, puerperium and perinatal conditions	6 (0.05)	2 (0.04)
Psychiatric disorders	183 (1.38)	81 (1.47)
Renal and urinary disorders	44 (0.33)	22 (0.40)
Reproductive system and breast disorders	102 (0.77)	43 (0.78)
Respiratory, thoracic and mediastinal disorders	654 (4.92)	262 (4.76)
Skin and subcutaneous tissue disorders	422 (3.18)	171 (3.10)
Social circumstances	2 (0.02)	1 (0.02)
Vascular disorders	13 (0.10)	11 (0.20)

Severe AEs, reported for 3.25% of subjects in the 120 µg bivalent rLP2086 group and 2.89% of subjects in the control group, were most frequently observed in the SOC of infections and infestations, which were reported by similar percentages of subjects in both groups (0.90%, 0.82%). Higher proportions of subjects in the 120 µg bivalent rLP2086 group compared with the control group reported severe AEs in the SOC of general disorders and administration site conditions (0.56% vs 0.29%), which includes AEs corresponding to local reaction and systemic event terms. Higher proportions of subjects in 120 µg bivalent rLP2086 group compared with the control group reported severe injection site pain (0.20% vs 0.04%) and severe headache (0.28% vs 0.16%).

Related AEs were reported by a higher percentage of subjects in the 120 µg bivalent rLP2086 group compared with the control group (11.37% vs 6.10%, respectively). Related AEs were most frequently observed in the SOC of general disorders and administration site conditions, which were reported by 9.58% of subjects in the 120 µg bivalent rLP2086 group and 4.50% of subjects in the control group. The

most frequently reported related AE in this SOC, injection site pain, was reported by a higher proportion of subjects in the 120 µg bivalent rLP2086 group (6.59%) than in the control group (3.30%).

Adverse events of special interest

Newly diagnosed chronic medical condition

A newly diagnosed chronic medical condition (NDCMC) was defined as a disease or medical condition that was not identified prior to study entry and was expected to be persistent or otherwise long lasting in its effects.

Data summarized for the core safety dataset (8 controlled studies), showed that the proportions of subjects diagnosed with NDCMCs throughout the studies were similar in the bivalent rLP2086 group (0.81%) and the control group (1.03%). In the overall safety dataset (11 studies), throughout the studies, NDCMCs were reported for 119 subjects (0.78%) who received any dose of bivalent rLP2086.

The most frequently reported NDCMC in the core safety dataset was asthma, reported for 9 subjects (0.07%) receiving rLP2086 and 4 subjects (0.07%) receiving control. Other NDCMCs reported most frequently in the bivalent rLP2086 group were scoliosis (7 subjects, 0.05%); myopia (6 subjects, 0.05%); attention deficit/hyperactivity disorder, polycystic ovaries (5 subjects, 0.04% each); and migraine (4 subjects, 0.03%). Among subjects receiving control vaccine, the most frequently reported NDCMCs included gastro-oesophageal reflux disease and migraine (each for 5 subjects, 0.09%); and eczema, attention deficit disorder, type 1 diabetes mellitus, and major depression (3 subjects, 0.05%).

Neuro-inflammatory Conditions

In the core safety dataset, neuro-inflammatory conditions were reported in 0.06% (95% CI: 0.03%, 0.12%) of subjects (8/13284) receiving 120 µg bivalent rLP2086 compared with 0.07% (95% CI: 0.02%, 0.19%) of subjects (4/5509) receiving control vaccine. No additional neuro-inflammatory conditions were reported in the overall safety dataset.

Of the 12 neuroinflammatory conditions reported in total, 8 subjects reported VIIth nerve paralysis (6 among bivalent rLP2086 recipients and 2 among controls) and 4 subjects reported multiple sclerosis (2 subjects in each group).

Among the 8 bivalent rLP2086 recipients who reported a neuroinflammatory condition, evidence of signs or symptoms suggestive of a pre-existing condition was evident for 1 subject (multiple sclerosis) and in a second subject (VIIth nerve paralysis) an infectious aetiology (Lyme disease) was identified as causative. A case of multiple sclerosis was reported during the follow-up phase for a third subject; the event, which occurred 134 days after the third dose of study vaccine, was not considered to be related to bivalent rLP2086 by the investigator. Of the remaining 5 neuroinflammatory cases (all VIIth nerve paralysis), the investigator considered the event to be possibly related to bivalent rLP2086 in 3 cases. In these cases, no evidence of pre-existing symptoms was reported and the paralysis resolved with or without treatment. The subjects in these studies were diagnosed with mild/moderate VIIth nerve paralysis 1 month after the first study dose (B1971014) / 144 days after the third study dose (B1971009), and 75 days after the second study dose (B1971016), respectively. Based on the background incidence of VIIth nerve paralysis/Bell´s palsy, it seems reasonable that a couple of background cases would be observed in the entire clinical trial population (15,294 and 5,509 subjects receiving at least one dose of bivalent rLP2086 vaccine and control vaccine, respectively). Of note, the subjects, (a 22 years old male [B1971014], a 21 years old female [B1971016], and an 11 years old female [B1971009]) belong to the peak age group for idiopathic facial paralysis. Based upon the available data from clinical trials and post marketing data (DLP 31 July 2016) the CHMP consider that there are no indications of a causal relationship between rLP2086 administration and mononeuritis, and consequently are not to be reflected in section 4.8 of the SmPC.

Among the 4 subjects in the control group, evidence of signs or symptoms suggestive of a pre-existing condition was found for 1 subject (multiple sclerosis) and not for the other 3 subjects (2 with VIIth nerve paralysis and one with multiple sclerosis).

Serious adverse event/deaths/other significant events in the core dataset

Serious adverse events

Similar percentages of subjects in the 120 ug bivalent rLP2086 group and the control group, reported SAEs during the vaccination phase (153 subjects, 1.15% vs 74 subjects, 1.34%), respectively.

At the EU sites only in the core safety dataset (5 controlled studies) Serious adverse events (SAEs) were reported during the vaccination phase for 65 of 4635 subjects (1.40%) who received 120 µg bivalent rLP2086 and for 43 of 2144 subjects (2.01%) in the control group.

For both the 120 µg bivalent rLP2086 group and control group, respectively, SAEs during the vaccination phase were most frequently observed in the SOCs of infections and infestations (33 subjects, 0.25% vs 24 subjects, 0.44%); injury, poisoning and procedural complications (30 subjects, 0.23% vs 12 subjects, 0.22%); and psychiatric disorders (29 subjects, 0.22% vs 9 subjects, 0.16%). Throughout the study, SAEs were most frequently observed in the SOCs of infections and infestations (52 subjects, 0.39%; 30 subjects, 0.54%), injury, poisoning and procedural complications (42 subjects, 0.32% vs 16 subjects, 0.29%); and psychiatric disorders (38 subjects, 0.29% vs 17 subjects, 0.31%).

In the core safety dataset, throughout the study period, SAEs considered by the investigator to be related to the study vaccine were reported for 5 subjects (0.04%) who received 120 µg bivalent rLP2086 and 2 subjects (0.04%) receiving control vaccine.

120µg bivalent rLP2086:

- One subject, a 13-year-old male in Study B1971014, was diagnosed with moderate neutropenia and mild leukopenia 4 days after Dose 2 of 120 µg bivalent rLP2086. He reported moderate malaise, moderate headache, moderate nausea, moderate myalgia, and moderate abdominal pain as well as moderate depressed mood one day after Dose 2 of 120 µg bivalent rLP2086. He was diagnosed with moderate neutropenia and mild leukopenia 4 days after Dose 2. Values were: neutrophils, 2.2 x 103 cells/µL (normal range: 2.5-6 x 103 cells/µL) and leukocytes, 3.92 x 103 cells/µL (normal range: 4-10 x 103 cells/µL). Approximately 7 weeks later the subject was hospitalized for continuing neutropenia. The subject was evaluated by a haematologist, whose opinion was that the laboratory abnormalities were probably caused by a concomitant infection. This interpretation is reasonable and since no further cases of neutropenia were identified, there is no reason to believe there is a causal association between the vaccine and the development of neutropenia. Approximately 2 months later, the subject was withdrawn from the study because his parents declined further participation in the study. The SAE of neutropenia was continuing at that time.
- A 15-year-old female in Study B1971014 was reported to have had an anaphylactic reaction beginning approximately 3 hours after the first dose of 120 µg bivalent rLP2086. The investigational product was permanently discontinued, and the subject was withdrawn from the study.
- One subject, a 22-year-old female, in Study B1971016 developed severe pyrexia after the first vaccination with 120 µg bivalent rLP2086.
- In Study B1971016, a 25-year-old female was reported to have severe dystonia 3 hours after vaccination with 120 µg bivalent rLP2086 and was diagnosed with "reactive confusion".
- A 21-year-old female in Study B1971016 had a reported AE of possible multiple sclerosis 48 days after her second dose of bivalent rLP2086.

Control vaccine:

- One subject, a 19-year-old female, was diagnosed with demyelination 3 days after receiving one dose of control vaccine (HAV); approximately 3 months later a diagnosis of multiple sclerosis was confirmed by a neurologist.
- A 14-year-old female experienced a SAE of spontaneous abortion 54 days after receiving the second study vaccination with saline, which was administered 2 months after receiving HAV at the first study vaccination.

In addition to the related SAEs reported for 5 subjects who received bivalent rLP2086 in the core safety dataset, in the overall safety data set related SAEs were reported for 2 subjects who received 120 µg bivalent rLP2086 (Study B1971012, vertigo, chills, and headache in one subject; and pyrexia and vomiting in the other subject) and 1 subject who received 200 µg bivalent rLP2086 (B1971005, anaphylactic reaction).

Deaths in the overall safety dataset

Among the 13,284 subjects who received 120 µg bivalent rLP2086, 5 subjects (0.04%) died, while there were no deaths among the 5509 subjects who received control vaccine. Among the subjects who died, 3 died as a result of road traffic accidents (2 were passengers, 1 was the driver), 1 subject died due to a gunshot wound (not self-inflicted), and 1 subject committed suicide. None of the deaths were considered related to study vaccine. The overall safety dataset included no additional deaths.

Laboratory findings

Clinical laboratory parameters were evaluated in Study B1971004 only. In this Phase 1 study, adults 18 to 40 years of age received 60 µg, 120 µg, or 200 µg bivalent rLP2086 at 0, 2, and 6 months, or control vaccine (Tdap at 0 months, saline at 2 and 6 months). A total of 12 subjects were vaccinated in each vaccine group. Blood and urine samples were collected at screening and again 2 to 3 days (48 to 72 hours) after each vaccination to evaluate chemistry, haematology, electrolytes, coagulation, and urinalysis parameters.

While laboratory abnormalities were reported in Study B1971004, none were considered to be related to the rLP2086 vaccine, and there were a similar number of laboratory abnormalities in the control group. There was no consistent pattern of laboratory abnormalities as examined by mean changes from baseline by dose group, nor did abnormalities worsen with additional administrations of the vaccine. Overall, laboratory abnormalities were intermittent, resolved without intervention, and did not recur upon repeat testing.

Safety in special populations

AEs were summarized by the intrinsic factors of age (10-14 years, 15-18 years, 19-25 years, and ≥26 years), sex (male or female), and race (white, black, Asian or other races). Among the 13,284 subjects who received 120 µg rLP2086, 11,222 (84.48%) were white, 1,519 (11.43%) were black, 172 (1.29%) were Asian, and 371 (2.79%) were of other races. As the majority of vaccinated subjects were white (84.84%), it was noted that it was not possible to evaluate differences in different types of AEs among racial groups, i.e. Asians and other groups. In the core safety dataset, the proportion of subjects receiving 120 µg rLP2086 who reported at least 1 AE was approximately 45% for white subjects and 28% for black subjects. While the frequency of AEs was lower among black subjects than among white subjects, the types of AEs reported most frequently were similar in the two racial groups. The incidence rate of AEs per category per vaccination group (LP2086 vs control) is provided in Table 35 below.

Table 35. Adverse Event Incidence Rates During the Vaccination Phase by Sex, Race, and Age Group – Subjects Who Received at Least 1 Dose of Bivalent rLP2086 Final Formulation (120 µg Dose Level) on a 0-, 2-, and 6-Month Schedule – Core Studies Pooled

	rLP086		Control		
Category	Incidence Rate	(95%CI)	Incidence Rate	(95%CI)	p-Value
Total	189.41	(186.15, 192.70)	165.44	(160.80, 170.15)	0.0143
Sex					
Female	209.02	(204.15, 213.96)	184.34	(177.45, 191.40)	0.0985
Male	170.30	(165.97, 174.70)	146.40	(140.24, 152.73)	0.0464
Age					
10-18 Years	193.26	(189.42, 197.15)	171.09	(165.62, 176.68)	0.0512
10-14 Years	200.81	(195.95, 205.75)	172.26	(165.57, 179.11)	0.0012
15-18 Years	179.39	(173.17, 185.74)	168.69	(159.21, 178.50)	0.6332
19-25 Years	176.88	(170.80, 183.10)	144.76	(136.29, 153.55)	0.0027
10-25 Years	188.90	(185.65, 192.19)	164.27	(159.65, 168.97)	0.0134
≥26 Years	774.62	(567.12, 1033.23)	889.82	(641.31, 1202.78)	NE
Race					
White	195.45	(191.89, 199.05)	167.76	(162.76, 172.84)	0.0122
Black	132.22	(123.63, 141.18)	150.78	(136.20, 166.30)	0.1093
Asian	208.61	(179.17, 241.51)	99.01	(69.71, 136.48)	0.0154

The percentages of subjects reporting severe AEs during the vaccination phase were low for all age groups: ≤3.82% for bivalent rLP2086 in each age group and ≤3.22% for control vaccine in each age group (except that for subjects aged ≥26 years the rates were 22.22% in the bivalent rLP2086 group and 25.00% in the control groups).

Table 36. Summary of AEs and SAEs by Age Group – Subjects Who Received at Least 1 Dose of 120µg bivalent rLP2086 on any schedule – All Studies Pooled

MedDRA Terms	**Age 10-14 number percentage 95%CI**	**Age 15-18 Number percentage 95%CI**	**Age 19-25 Number percentage 95%CI**	**≥26 Number percentage 95%CI**
AE reported during the vaccination phase	3127/6983 **44.78** 95%CI: 43.61, 45.96	1678/4134 **40.59** 95%CI: 39.09,42.11	1473/3883 **37.93** 95%CI: 36.41,39.48	38/53 **71.70** 95%CI: 57.65, 83.21
Related AE reported during the vaccination phase	675/6983 **9.67** 95%CI: 8.98, 10.38	360/4134 **8.71** 95%CI: 7.87, 9.61	560/3883 **14.42** 95%CI: 13.33, 15.57	10/53 **18.87** 95%CI: 9.44, 31.97
Severe AE reported during the vaccination phase	217/6983 **3.11** 95%CI: 2.71, 3.54	142/4134 **3.43** 95%CI: 2.90, 4.04	105/3883 **2.70** 95%CI: 2.22, 3.26	8/53 **15.09** 95%CI: 6.75, 27.59
Serious AEs – Total	110/6983 **1.58** 95%CI: 1.30, 1.90	88/4134 **2.13** 95%CI: 1.71, 2.62	257/15000 **1.71** 95%CI: 1.51, 1.93	0/53 **0.00** 95%CI: 0.00,6.72

An increase in related AEs and severe AEs in those older than 26 years compared to those aged 10-25 can be suggested. However it should be noted that the 22% of those >26 years that reported related AEs is based on 9 subjects (2/9). The 3-4% reporting related AEs <26 years of age is based on over 13.000 subjects. Furthermore, comparing safety data across studies is impeded by differences in collection methods that can impact rates of AEs reported and those ≥26 years were only included in several smaller studies. The Applicant compared the reporting of solicited adverse events in study B1971003, which included both subjects ≥26 years and <26 years. This comparison points towards similar, if not lower, frequencies of AEs in those ≥26 years of aged compared to younger subjects. Rates of AEs in young adults (19-25 years) were further compared to rates in adolescents (10-18 years), which point towards a decrease in AEs with age. The higher rate of AEs reported in those >26 years is mirrored in the control

groups (i.e. 89% of ≥26 year olds reported any AE during the vaccination phase vs. 88% in the control arm). The higher rate of AEs seen in subjects ≥26 years of age is most likely a result of small numbers and more intensive collection/reporting methods rather than representative of a higher risk of AEs with increased age. Comparing age related rates of AEs within studies does not point towards an increased rate of AEs. Considering age related changes in subjects <26 years of age, with increasing age the rates of AEs decline slightly or remain the similar. Further, rates of AEs are similar in the control group, suggesting the high rates are due to reporting patterns rather than actual occurrence of AEs. Therefore the data available albeit limited do not indicate an increased risk of AEs with age.

Safety in subjects with chronic conditions

Subjects with chronic medical conditions were not excluded from participation in bivalent rLP2086 clinical trials except for subjects with known autoimmune diseases, neuroinflammatory conditions, or any medical or psychiatric condition or laboratory abnormality that suggested they would be unable to participate in a clinical trial or could interfere with the interpretation of study results. In the core safety database, among the 13,284 subjects who received bivalent rLP2086, the most frequently reported terms were in the SOCs of Immune system disorders (2376 subjects, 17.89%) and Respiratory, thoracic and mediastinal disorders (2310 subjects, 17.39%). In the SOC of Immune system disorders, the most commonly reported prior medical condition was seasonal allergy (1490 subjects, 11.22%) or allergy/hypersensitivity to a known product. In the Respiratory, thoracic and mediastinal disorders SOC, the most commonly reported prior medical condition was asthma (1217, 9.16%). Safety in chronic medical conditions will be monitored post-authorisation.

Safety in immunocompromised patients

The safety of bivalent rLP2086 has not been studied in patients with immune deficiencies. Adequate warnings are included in the SmPC. Nonetheless, as persons with immune deficiencies represent an important target group for meningococcal vaccination, the Applicant has committed to investigate the immunogenicity and safety of bivalent rLP2086 in immunocompromised patients, including patients with complement deficiency or asplenia. This is adequately reflected in the RMP.

Immunological events

Autoimmune Conditions

In the core safety dataset, autoimmune conditions were reported in 0.14% (95% CI: 0.08%, 0.21%) of subjects receiving 120 µg bivalent rLP2086 compared with 0.11% (95% CI: 0.04%, 0.24%) of subjects receiving control vaccine. Incidence rates for autoimmune conditions were similar between the 120 µg bivalent rLP2086 and the control groups, with 0.16 (95% CI: 0.09, 0.25) events versus 0.14 (95% CI: 0.06, 0.30) events per 100 subject-years, respectively. In the overall safety dataset, among subjects receiving 120 µg bivalent rLP2086, the incidence was 0.20 (95% CI: 0.13, 0.29) events per 100 subject-years.

An overview of autoimmune conditions reported following bivalent rLP2086 given at a 0, 2 and 6 months schedule in all pooled studies is provided in the table below.

Table 37. Autoimmune Conditions Reported Throughout the Study – Subjects Who Received at Least 1 Dose of Bivalent rLP2086 Final Formulation (120 µg Dose Level) on a 0-, 2-, and 6-Month Schedule – All Studies Pooled

	rLP2086			
	120 µg	60 µg	200 µg	Total
	(N=15053)	(N=34)	(N=207)	(N=15294)
System Organ Class				
Preferred Term	n (%)	n (%)	n (%)	n (%)
Any event	25 (0.17)	0 (0.00)	0 (0.00)	25 (0.16)
Blood and lymphatic system disorders	1 (0.01)	0 (0.00)	0 (0.00)	1 (0.01)
Idiopathic thrombocytopenic purpura	1 (0.01)	0 (0.00)	0 (0.00)	1 (0.01)
Endocrine disorders	6 (0.04)	0 (0.00)	0 (0.00)	6 (0.04)
Autoimmune thyroiditis	2 (0.01)	0 (0.00)	0 (0.00)	2 (0.01)
Basedow's disease	2 (0.01)	0 (0.00)	0 (0.00)	2 (0.01)
Hypothyroidism	2 (0.01)	0 (0.00)	0 (0.00)	2 (0.01)
Gastrointestinal disorders	4 (0.03)	0 (0.00)	0 (0.00)	4 (0.03)
Coeliac disease	3 (0.02)	0 (0.00)	0 (0.00)	3 (0.02)
Crohn's disease	1 (0.01)	0 (0.00)	0 (0.00)	1 (0.01)
Infections and infestations	1 (0.01)	0 (0.00)	0 (0.00)	1 (0.01)
Arthritis infective	1 (0.01)	0 (0.00)	0 (0.00)	1 (0.01)
Metabolism and nutrition disorders	3 (0.02)	0 (0.00)	0 (0.00)	3 (0.02)
Type 1 diabetes mellitus	2 (0.01)	0 (0.00)	0 (0.00)	2 (0.01)
Diabetic ketoacidosis	1 (0.01)	0 (0.00)	0 (0.00)	1 (0.01)
Musculoskeletal and connective tissue disorders	1 (0.01)	0 (0.00)	0 (0.00)	1 (0.01)
Rheumatoid arthritis	1 (0.01)	0 (0.00)	0 (0.00)	1 (0.01)
Nervous system disorders	1 (0.01)	0 (0.00)	0 (0.00)	1 (0.01)
Sydenham's chorea	1 (0.01)	0 (0.00)	0 (0.00)	1 (0.01)
Renal and urinary disorders	1 (0.01)	0 (0.00)	0 (0.00)	1 (0.01)
IgA nephropathy	1 (0.01)	0 (0.00)	0 (0.00)	1 (0.01)
Skin and subcutaneous tissue disorders	6 (0.04)	0 (0.00)	0 (0.00)	6 (0.04)
Psoriasis	4 (0.03)	0 (0.00)	0 (0.00)	4 (0.03)
Alopecia areata	2 (0.01)	0 (0.00)	0 (0.00)	2 (0.01)
Vascular disorders	1 (0.01)	0 (0.00)	0 (0.00)	1 (0.01)
Raynaud's phenomenon	1 (0.01)	0 (0.00)	0 (0.00)	1 (0.01)

Note: Studies B1971003, B1971004, B1971005, B1971009, B1971010, B1971011, B1971012, B1971014, B1971015, B1971016, and B1971042 are summarized in this table. **Note**: Autoimmune and neuroinflammatory conditions were identified from a potential list of autoimmune/neuroinflammatory conditions. Confirmation was determined by sponsor's global medical monitor after review of diagnostic testing and medical history. **Note**: For B1971012 Group 5 subjects, any AE reported prior to first dose of rLP2086 was not counted. **Note**: The 120 µg group included subjects from B1971003, B1971004, B1971005, B1971009, B1971010, B1971011, B1971012, B1971014, B1971015, B1971016, and B1971042; the 60 and 200 µg groups included subjects from B1971004 and B1971005. B1971010 subjects received Repevax at Month 0 in addition to rLP2086 at Months 0, 2, and 6; B1971011 subjects received quadrivalent HPV vaccine (Group 1) or saline (Group 2) at Months 0, 2, and 6 in addition to rLP2086 at Months 0, 2, and 6. B1971015 subjects received MCV4 and Tdap (Group 1) or saline (Group 3) in addition to rLP2086 at Months 0, 2, and 6.

Autoimmune conditions were reported for a total of 25 subjects; 24 of these subjects were 10 to 25 years old, and 1 subject was 38 years old. Among 25 subjects who had autoimmune condition and who received at least one dose of bivalent rLP2086 from the overall safety dataset, 17 subjects (68%) had evidence

either that the autoimmune condition pre-existed prior to enrolment, that there was a documented cause of the condition, or that the autoimmune condition was likely pre-existing, based on the timing of vaccination and the known pathophysiology of the disease.

Autoimmune conditions were considered by the investigator not to be related to study vaccine in 88% (22 of 25) of bivalent rLP2086 subjects.

Three events in 3 subjects were considered by the investigator to be possibly related to study vaccine. One (1) case from Study B1971003 was considered related: a 38-year-old female subject, with known history of psoriasis prior to study entry experienced a mild flare of disease 14 days after the third dose of bivalent rLP2086. Of note, Study B1971003 was the only clinical trial in this MAA for which autoimmune diseases was not an exclusion criterion. In Study B1971015 there was an 11-year-old female who reported mild Raynaud's phenomenon 56 days after the last study dose. The subject was diagnosed by a rheumatologist, after presenting with painful, cyanotic episodes involving all of her fingers (distally from the proximal interphalangeal joint), induced upon exposure to cold weather). The last subject, who participated in Study B1971014, was a 24-year-old male without significant relevant medical history who was diagnosed with mild alopecia areata (localized to the left frontal area of the head) 81 days after his second dose of bivalent rLP2086. He had no history of alopecia prior to study entry and no family history of alopecia.

Hypothyroidism

Adverse events of hypothyroidism or diagnostic tests suggestive of hypothyroidism were reported for 14 subjects: 12/15,294 (0.08%) who received bivalent rLP2086 (8 female and 4 male) and 2/5509 (0.04%) who received control vaccine (both female).

Hypothyroidism is a common endocrine disorder characterized by reduced thyroxine (T4) levels. The most common cause of hypothyroidism worldwide is iodine deficiency, but in parts of the world where this is not an issue, autoimmune disease (Hashimoto's thyroiditis) and iatrogenic causes (treatment of hyperthyroidism) are the most common causes. Autoimmune hypothyroid disease is more common in women and in some studies has been estimated to occur 5 to 10 times more often in women than men in areas where iodine is readily available.

Autoimmune hypothyroidism occurs as the process of autoimmune attack of the thyroid gland gradually reduces thyroid function. For a time, T4 levels can be maintained by elevated thyroid stimulating hormone (TSH) levels. As the disease progresses, T4 levels fall and TSH levels rise further, at which time symptoms typically become more apparent. The relationship between the presence of autoantibodies and the development of hypothyroidism is complex, as there is typically a long lag time between autoimmune thyroiditis and overall thyroid failure.

In the bivalent rLP2086 group, the events were reported as hypothyroidism in 9 subjects, autoimmune thyroiditis in 2 subjects, and thyroxine decreased in 1 subject. An autoimmune aetiology was confirmed for 4 of these cases. Evidence of pre-existing disease was obtained through medical history or testing of pre-vaccination serology samples in each of the 4 autoimmune hypothyroidism cases.

Safety related to drug-drug interactions and other interactions

Concomitant administration of bivalent rLP2086 with other vaccines was studies in B1971010 (+DTaP/IPV), B1971011 (HPV) and B1971015 (MCV4+Tdap). Local reactions were not collected for the injection sites of DTaP/IPV, HPV and MCV4+Tdap control vaccines.

In **Study B1971010** (concomitant vaccine at Dose 1 only), the frequency of both fatigue and headache after Dose 1 were higher after 120 µg bivalent rLP2086+DTaP/IPV than after DTaP/IPV alone: 76.6% versus 71.6% for fatigue; and 72.6% versus 63.7% for headache. The frequency of fever was higher after

Dose 1 of bivalent rLP2086+dTaP/IPV (12.1%) than after Dose 1 of dTaP/IPV alone (5.3%) alone. The frequency of muscle pain after Dose 1 was similar among subjects receiving 120 µg bivalent rLP2086+dTaP/IPV and among those receiving dTaP/IPV alone.

In **Study B1971011**, concomitant administration of bivalent rLP2086 + HPV vaccine as compared with saline + HPV vaccine had a higher proportion of subjects (91.6% and 80.9%, respectively) who reported any systemic events within 7 days after all vaccinations, but did not result in substantially higher rates of systemic reactogenicity compared with administration of bivalent rLP2086 + saline (91.6% vs 91.1%, respectively). Slightly higher reactogenicity rates were observed for bivalent rLP2086 + HPV vaccine as compared to bivalent rLP2086 + saline for all systemic events, including fever (11.6% vs 8.3%), vomiting (11.6% vs 11.0%), diarrhoea (24.7% vs 23.9%), headache (73.4% vs 70.3%), fatigue (77.7% vs 73.6%), chills (41.5% vs 39.6%), muscle pain (61.8% vs 58.4%), and joint pain (35.2% vs 33.3%).

In **Study B1971015**, concomitant administration of MCV4+Tdap+bivalent rLP2086 resulted in slightly higher rates of systemic events compared to administration of saline+saline+bivalent rLP2086 (87.0% vs 81.7%, respectively). Concomitant administration of MCV4+Tdap+bivalent rLP2086 Group 1) as compared to MCV4+Tdap+saline Group 2) had a higher proportion of subjects (87.0% and 74.8%, respectively) who reported any systemic events within 7 days after vaccination.

For subjects receiving 120 µg bivalent rLP2086+MCV4+Tdap at Dose 1 compared to those receiving 120 µg bivalent rLP2086+saline+saline at Dose 1, a higher or comparable incidence of systemic events was observed for fever (13.2% vs 11.6%), vomiting (9.2% vs 9.3%), headache (61.9% vs 56.4%), fatigue (66.4% vs 59.7%), chills (35.7% vs 31.5%), muscle pain (46.2% vs 43.3%), joint pain (23.0% vs 20.6%), and diarrhoea (15.4% vs 14.1%).

The frequency of antipyretics use in study B1971015 in the groups receiving rLP2086 was about double as high as in the group receiving routine vaccines only. The Applicant was asked to perform an analysis of the rate of fever in subjects treated and not treated with antipyretics in the pooled data sets. Among the 9,182 subjects who received rLP2086, 24% used antipyretics and 76% did not. Of the untreated subjects, only a few percent reported fever ≥38^{o}C after dose 1 (and even less after subsequent doses). Moreover, the majority of subjects with no fever (80 %) after rLP2086 vaccination did not use antipyretics, which indicates that the rate of high fever in untreated subjects is not markedly underestimated in the originally performed analyses.

When bivalent rLP2086 vaccine was given concomitantly with another vaccine, the pattern of AEs was similar to the pattern of AEs reported after concomitant vaccine alone or after bivalent rLP2086 vaccine alone and was similar to what was observed for the 120 µg bivalent rLP2086 groups in the 8 controlled core safety studies.

In conclusion, the frequency of systemic events was generally slightly higher after rLP2086 + Tdap/IPV than after Tdap/IPV alone.

Overall rates of systemic adverse events were slightly higher when rLP2086 was administered with other vaccines in studies B1971011 (HPV) and B1971015 (MCV4+Tdap). Differences in rates between groups are small (mostly <5%) and is not considered to be a substantial increase.

Discontinuation due to adverse events

Among the 13,284 subjects who received 120 µg bivalent rLP2086 in the 8 controlled studies (core safety dataset), 46 subjects (0.35%) were withdrawn from the studies due to local reactions; and among the 5509 subjects who received control vaccine in these studies, 2 subjects (0.04%) were withdrawn due to local reactions. Some of these subjects were withdrawn because of more than 1 local reaction type and some were withdrawn because of both local reactions and systemic events.

The local reaction most frequently resulting in withdrawal from the studies was injection site pain, which led to withdrawal of 40 subjects (0.30%) in the bivalent rLP2086 group. Among subjects receiving 120 µg bivalent rLP2086, the systemic events most frequently leading to withdrawal from study participation were headache (17 subjects, 0.13%) and pyrexia (11 subjects, 0.08%).

Consistent with the data from the 8 controlled studies, 1.07% of subjects (163/15,294) of the overall safety dataset (11 completed clinical studies) who received bivalent rLP2086 at any dose level and using any regimen were withdrawn from the studies because of AEs. The most common events leading to subject withdrawal in the overall safety dataset were in the SOC general disorders and administration site conditions (71 subjects, 0.46%), most frequently injection site pain, pyrexia, chills, fatigue, injection site erythema, and injection site swelling).

Most people who discontinue due to an AE do so following the first dose: 0.72% (n=96) compared to 0.34% (n=42) following the second dose. There is no indication of an increased rate of discontinuations with subsequent doses.

Additional studies

Interim data for **Study B1971033** was submitted during the procedure (see details in the section on supportive studies). This was an extension study providing 4 years follow up after primary series for persistence of antibodies and responses to a booster dose. Final results of this study are in December 2018. The safety was also investigated as follows.

Safety assessment included physical examination, measurement of solicited local and systemic reactions, including fever, after vaccination, the recording of use of antipyretic medication and the recording of unsolicited AEs and SAEs.

Solicited adverse events were recorded with use of an e-diary during the 7 days after administration of the investigational product:

- Local reactions at the site of investigational product administration (redness, swelling, and pain at the injection site).
- Systemic events (fever, vomiting, diarrhoea, headache, fatigue, chills, muscle pain other than muscle pain at the injection site, and joint pain).

Main 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, SAE, NDCMC or MAE occurring during the period between visit 7 and visit 8.

Results

There were no new safety signals from this study and the reactogenicity and safety profile after the booster dose appears consistent with the findings observed for the safety profile of the product from earlier studies and as described in the product information.

Post marketing experience

Bivalent rLP2086 has been licensed in the US for use in subjects aged 10-26 years since 2014. Post-marketing, approximately 170,000 doses have been distributed up to 30 November 2015, but it is not yet possible to determine with certainty the exact number of individuals who received bivalent rLP2086 vaccine during the period of this review. The post-marketing data are derived from the Applicant's safety database. The safety database contains cases of Adverse Events (AEs) spontaneously reported, cases reported by the health authorities, cases published in the medical literature, cases from marketing programs sponsored by the Applicant, non-interventional studies, and cases of serious adverse events reported from clinical studies, regardless of causality. The safety database was searched to identify post-marketing non-clinical study sourced adverse events for patients receiving bivalent rLP2086. Upon review, the analysis of the reported events did not show any new significant safety findings and the most frequently reported adverse events are consistent with clinical study observations for reactogenicity. There were no cases from spontaneous sources reporting anaphylactic reactions. Overall there are no new emerging safety concerns identified in this dataset.

Given the limited exposure, adverse events that occur very rarely (~ <1/10,000 – 1/100,000) and adverse events with a (significant) delay in onset are difficult to exclude based upon the data available.

2.6.1. Discussion on clinical safety

The safety profile of bivalent rLP2086 is supported by data from 15,294 subjects who received at least one dose of bivalent rLP2086 (overall safety dataset). Of these, 13,284 subjects were included in controlled studies in which they received at least one dose of the final formulation on a schedule of 0,2,6 months (a total of 8 controlled studies forming the core safety dataset).
The number of subjects included for safety analysis is considered adequate for adolescents and young adults. As there is no data in those aged over 65 years and limited data for those aged between 40 and 65, appropriate warning s are included in the SmPC as well an adequate post-authorisation pharmacovigilance activities.
Solicited adverse events show that bivalent rLP2086 is a reactogenic vaccine, with a relatively high proportion of subjects reporting local reactions following vaccination, in particular pain which was reported by 89.6% to 98.1% of subjects across studies. Severe pain was reported in 3.0-15.1% of subjects depending on the study compared to 0-2.4% in control groups. The median duration of pain at the injection site was generally 2 to 3 days in subjects receiving 120 µg bivalent rLP2086 and 1.0 day in subjects receiving a control. An increase in severity of pain within 7 days after vaccination was reported by 36.5-50.5% of subjects who received bivalent rLP2086. An increase in severity with potentiation (increased severity with all subsequent doses, i.e. 3>2>1) for local reactions is reported at a higher frequency in the rLP2086 groups compared to control groups.
The most frequently reported systemic events after any dose of 120 µg bivalent rLP2086 were fatigue, reported by 60.6% to 85.0%, and headache, reported by 59.1% to 83.9%. Severe fever (39.0^{o}C to 40.0^{o}C) was reported for 0.2% to 2.7% of subjects after any dose of 120 µg bivalent rLP2086 (vs 0.4% to 1.7%). Increases in the severity of fever with potentiation were reported for 3/2388 subjects (0.13%) who received 120 µg bivalent rLP2086 in Study B1971009; no subjects who received control vaccine experienced increases in the severity of fever with potentiation.
Unsolicited AEs were reported at similar frequencies in the 120 µg bivalent rLP2086 group and in the control group with the exception of AEs in the SOC 'General disorders and administration site conditions' which were reported more frequently for subjects receiving bivalent rLP2086. Similarly, related AEs were reported more often by subjects receiving rLP2086 compared to those receiving control vaccines (11.4% vs 6.1%) and were mostly observed in the SOC of 'General disorders and administration site conditions' (9.6% vs 4.5%). Higher proportions of subjects in 120 µg bivalent rLP2086 group compared with the control group reported severe injection site pain (0.20% vs 0.04%) and severe headache (0.28% vs

0.16%).
Special attention was paid to newly diagnosed chronic medical conditions and neuro-inflammatory conditions as well as auto-immune conditions. Overall, rates were similar between subjects who received rLP2086 and those who received control vaccines or saline placebo.
Eight subjects reported VIIth nerve paralysis (6 among bivalent rLP2086 recipients and 2 among controls). Considering bivalent rLP2086 recipients, in one subject with VIIth nerve paralysis, an infectious aetiology (Lyme disease) was identified as causative. Of the remaining 5 cases of VIIth nerve paralysis, the investigator considered the event to be possibly related to bivalent rLP2086 in 3 cases. For these three cases, the diagnosis was made 29 days after the first dose, 75 days after the second dose and 144 days after the third dose respectively.
A higher proportion of subjects in the rLP2086 groups reported hypothyroidism (0.08% vs 0.04%). In the bivalent rLP2086 group, the events were reported as hypothyroidism in 9 subjects, autoimmune thyroiditis in 2 subjects, and thyroxine decreased in 1 subject. An autoimmune aetiology was confirmed for 4 of these cases. Evidence of pre-existing disease was obtained through medical history or testing of pre-vaccination serology samples in each of the 4 autoimmune hypothyroidism cases.
In some studies, vertigo was reported as a severe AE related to rLP2086 vaccine. Moreover, dizziness and malaise were frequently reported (>4%) in the U.S. post marketing data. In the clinical trials, the frequency of dizziness and vertigo were similar between the rLP2086 and control groups. Malaise, on the other hand, was reported more frequently in the rLP2086 groups. Confounding factors make a proper causality assessment of the cases difficult, including cases of malaise. Moreover, the cases of malaise tend to be rather unspecific and could also be explained as being an indirect effect of other AEs known to be associated with rLP2086 (fever, nausea, pain). Causality cannot be assessed based on post marketing reports.
In conclusion, there are no clear indications of a causal relationship between the vaccine and the development of vertigo/dizziness and/or malaise and thus no inclusion of these events in the SmPC is considered necessary based on current knowledge.
SAEs that were considered related to study vaccine were reported for 8 subjects who received bivalent rLP2086 at any dose level and using any regimen. These include two subjects with anaphylactic reactions, one subject with severe pyrexia, one subject with severe dystonia, one subject with vertigo, chills, and headache, one subject reporting vomiting and pyrexia, one report of possible multiple sclerosis 48 days after her second dose of bivalent rLP2086 and finally one subject who was diagnosed with moderate neutropenia and mild leukopenia 4 days after Dose 2 of 120 µg bivalent rLP2086. There were no deaths that were possibly related to rLP2086.
Further, discontinuations due to AEs were also driven by the reactogenicity of bivalent rLP2086. The most common events leading to subject withdrawal in the overall safety dataset were in the SOC general disorders and administration site conditions (71 subjects, 0.46%), most frequently injection site pain, pyrexia, chills, fatigue, injection site erythema, and injection site swelling). Discontinuations due to AEs decreased with subsequent doses.
Concerning coadministration, the frequency of systemic events was generally slightly higher after rLP2086 + Tdap/IPV than after Tdap/IPV alone. Overall rates of systemic adverse events were slightly higher when rLP2086 was administered with other vaccines in studies B1971011 (HPV) and B1971015 (MCV4+Tdap). Differences in rates between groups are small (mostly <5%) and is not considered to be a substantial increase.
The majority of vaccinated subjects were white (84.8%) making it difficult to evaluate differences in different types of AEs among racial groups, i.e. Asians and other groups. In the core safety dataset, the proportion of subjects receiving 120 µg rLP2086 who reported at least 1 AE was approximately 45% for white subjects and 28% for black subjects. While the frequency of AEs was lower among black subjects than among white subjects, the types of AEs reported most frequently were similar in the two racial groups.
Due to the limited data for persons aged 26 to 40, persons >40 years and persons >65 years, the safety

for these age group was extrapolated from younger age groups. No outstanding safety issues have been identified among the few subjects ⩾26 years of age. The data available, albeit limited, do not point towards increased risk of AEs with age. As mentioned safety in persons over the age of 40 and over the age of 65 is included as missing information in the Risk Management Plan (RMP) and monitored appropriately.
The safety of bivalent rLP2086 has not been studied in patients with immune deficiencies. Adequate warnings have been proposed in the SmPC. Nonetheless, as persons with immune deficiencies represent an important target group for meningococcal vaccination, the Applicant has committed to investigate the immunogenicity and safety of bivalent rLP2086 in immunocompromised patients, including patients with complement deficiency or asplenia, as a category 3 study (see RMP).

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

2.6.2. Conclusions on the clinical safety

Overall, 120µg bivalent rLP2086 vaccine is a relatively reactogenic vaccine, and it is the local and systemic reactions to vaccination that largely drive the safety profile. The most common adverse reactions observed were injection site pain, redness and swelling at the vaccination site, headache, fatigue, chills, diarrhoea, muscle pain, joint pain and nausea. No significant safety issues have been identified which would indicate an increased risk for use of bivalent rLP2086 in the targeted age group.

The Applicant has committed to investigate the immunogenicity and safety of bivalent rLP2086 in immunocompromised patients, including patients with complement deficiency or asplenia.

2.7. Risk Management Plan

Safety concerns

Important identified risks	None
Important potential risks	None
Missing information	Use in pregnancy and lactation
	Use in individuals 40 years and older
	Use in co-administration with MMR and pneumococcal vaccines
	Use in immunocompromised individuals (eg, individuals with terminal complement deficiency or asplenia)
	Autoimmune conditions (Potential MnB vaccine class effect)
	Vaccine effectiveness
	Vaccine failure
	Potential for strain replacement

Pharmacovigilance plan

Study / Activity Type, Title and Category (1-3)	Objectives	Safety Concerns Addressed	Status	Date for Submission of Final Study Report
B1971052 Pregnancy and birth outcome assessment in a population-based cohort after exposure to bivalent rLP2086	- Estimate the incidence and risk ratios of pregnancy outcomes in women exposed and not exposed to bivalent rLP2086 up to 28 days prior or during	Use in pregnancy and lactation.	Planned.	31 October 2023.

(Category 3)	pregnancy. - Estimate the prevalence and risk ratios of birth outcomes among infants exposed and not exposed to bivalent rLP2086 vaccine in utero.			
Investigation of safety and immunogenicity in co-administration of bivalent rLP2086 with MMR and Pneumococcal vaccines (Category 3)	To evaluate the safety and immunogenicity of bivalent rLP2086 when co-administered with MMR and pneumococcal conjugate vaccine.	Use in co-administration of bivalent rLP2086 with MMR and Pneumococcal vaccines.	Feasibility is under evaluation.	Protocol submission: 31 May 2018
Investigation of safety and immunogenicity in immunocompromised patients (Category 3)	To evaluate safety and immunogenicity of rLP2086 in immunocompromised individuals (eg, individuals with terminal complement deficiency or asplenia).	Use in immunocompromised individuals (eg, individuals with terminal complement deficiency or asplenia).	A protocol is being developed.	Protocol submission: 31 May 2018
Investigation of bivalent rLP2086 effectiveness. Collaborate with relevant public health authorities and clinical investigators with access to integrated clinical and epidemiological databases containing data on IMD in regions where bivalent rLP2086 is used as part of a national immunisation program or in response to hyperendemic or large outbreak situations. (Category 3)	To evaluate the effectiveness of bivalent rLP2086 in reducing the incidence of IMD (serogroup B) in the indicated population.	Vaccine effectiveness.	Feasibility assessment dependant on the use as part of national immunisation program(s) or in response to large outbreak situations.	Effectiveness plan submission: 31 May 2019
Investigation of vaccine failure: As an adjunct to routine pharmacovigilance activities, a review of population-based national surveillance programs for meningococcal disease including molecular epidemiological data (specifically, characterization of fHbp) when available, in collaboration with	To evaluate laboratory-confirmed serogroup B IMD in individuals who have received the recommended number of doses of bivalent rLP2086.	Vaccine failure.	Feasibility assessment dependant on the use as part of national immunisation program(s).	Review of available publications and national surveillance data reports will be discussed with all PSUR submissions.

national agencies using bivalent rLP2086 as part of a national immunization program. (Category 3)				
Investigation of potential for strain shift: Review of population-based national surveillance programs for meningococcal disease including molecular epidemiological data (specifically, characterization of fHbp) when available, in collaboration with national agencies using bivalent rLP2086 as part of a national immunization program. (Category 3)	To evaluate any changes in epidemiology of IMD due to strain shift in regions where bivalent rLP2086 is used as part of a national immunisation program.	Potential for strain replacement.	Feasibility assessment, dependant on the use as part of national immunisation program(s).	Review of available publications and national surveillance data reports will be discussed with all PSUR submissions.
B1971033: A study on duration of immunity to assess persistence of hSBA response for up to 48 months after completion of vaccination with bivalent rLP2086 and the immunogenicity, safety, and tolerability of a booster dose of bivalent rLP2086. (Category 3)	To investigate the persistence of the immune response following a primary series and to investigate the immunogenicity, safety, and tolerability of a booster dose. The B1971033 protocol will be amended in order to assess the persistence of immunity through 26 months after a booster dose.	Persistence data.	Ongoing.	Final study report: 31 December 2018.

Risk minimisation measures

Safety Concerns	**Proposed Risk Minimisation Activities (Routine and Additional)**
Missing Information	
Use in pregnancy and lactation	**Routine: SmPC** (Section 4.6) states that there are no data from the use of bivalent rLP2086 in pregnant women nor on the excretion of the vaccine in human milk; however reproduction studies performed in female rabbits have revealed no evidence of impaired female fertility or harm to the foetus due to bivalent rLP2086. **SmPC** (Section 5.3): Non-clinical data revealed no special hazard for humans based on conventional studies of repeated dose toxicity, and reproduction and developmental toxicity.
Use in individuals 40 years and older	**Routine: SmPC** (section 4.4) states that there are no data on the use of bivalent rLP2086 in subjects above 65 years of age.

Safety Concerns	Proposed Risk Minimisation Activities (Routine and Additional)
Use in Co-administration with MMR and pneumococcal vaccines	**Routine: SmPC** (Section 4.5) states the vaccines that have been studied in co-administration with bivalent rLP2086 and that when given concomitantly with other vaccines bivalent rLP2086 must be administered at a separate injection site and should not be mixed with other vaccines in the same syringe.
Use in immunocompromised individuals (eg, individuals with terminal complement deficiency or asplenia)	**Routine: SmPC** (Section 4.4) communicates that there are no data on the use of bivalent rLP2086 in immunocompromised individuals, including individuals receiving immunosuppressant therapy and that they may have a diminished response to bivalent rLP2086.
Autoimmune conditions (Potential MnB vaccine class effect)	None.
Vaccine effectiveness	**Routine: SmPC** (Section 5.1), provides information information on the immune response to bivalent rLP2086 based on clinical studies. Human serum bactericidal antibody response (hSBA) is the recognized surrogate of efficacy and hSBA titers of greater than or equal 1:4 is considered to be protective against invasive meningococcal disease.
Vaccine failure	**Routine: SmPC** (Sections 4.4) communicates the possible variability of immune responsiveness in individuals.
Potential for strain replacement	None.

Conclusion

The CHMP and PRAC considered that the risk management plan version 1.4 is acceptable.

2.8. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the Applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.9. New Active Substance

The Applicant declared that the bivalent lipoprotein (also referred to as bivalent rLP2086) consisting of *Neisseria meningitidis* serogroup B recombinant lipidated factor H binding protein (fHbp) subfamily A and *Neisseria meningitidis* serogroup B recombinant lipidated factor H binding protein (fHbp) subfamily B contained in Trumenba has not been previously authorised in a medicinal product in the European Union.

The active substance components of bivalent rLP2086 are both members of the Neisseria meningitidis family of proteins called factor H binding proteins (fHBP). Bexsero, the only Meningococcal B vaccine that is authorized for use in the European Union, contains a fHBP fusion protein as one of its components.

Several features differentiate the fHBP antigen components of bivalent rLP2086 (in Trumenba) from fHBP fusion protein (variant B24) in Bexsero. This includes a divergent amino acid sequence, the presence /absence of an N-terminal lipid tail and expression as recombinant non-fusion proteins vs. a fusion protein.

The CHMP, based on the available data, considers the bivalent lipoprotein (also referred to as bivalent rLP2086) consisting of *Neisseria meningitidis* serogroup B recombinant lipidated factor H binding protein (fHbp) subfamily A and *Neisseria meningitidis* serogroup B recombinant lipidated factor H binding protein (fHbp) subfamily B to be a new active substance as it is not a constituent of a medicinal product previously authorised within the Union.

2.10. Product information

2.10.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the Applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.10.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Trumenba (meningococcal group B vaccine (recombinant, adsorbed)) is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU.

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

N. meningitidis is an obligate human pathogen that colonizes the upper respiratory tract. Under certain not well understood conditions, *N. meningitidis* is capable of invading the human host, leading to bacteraemia which then manifests as life-threatening invasive meningococcal disease. Transmission with *N. meningitidis* is via contact with droplets from the upper respiratory tract, typically resulting in colonization and asymptomatic carriage in otherwise healthy individuals. See section 2.4.1 for the clinical presentation.

Trumenba is a vaccine that consists of two purified recombinant lipoprotein 2086 (rLP2086) antigens, from each of the two factor H binding protein (fHBP) subfamilies A and B (A05 and B01). Trumenba is intended for active immunisation to prevent invasive meningococcal disease caused by *Neisseria meningitidis* serogroup B in individuals aged 10 years and older.

Since the introduction of conjugated Meningococcal C vaccines in Europe, *Neisseria meningitidis* serogroup B (MnB) has been a leading cause of invasive meningococcal disease (IMD).

The notification rate for MnB in Europe was 0.3/100,000 in 2014, 7.7/100,000 in children <1 year and 0.4/100,000 in persons 15-24 years of age. Whilst the peak for MnB cases is in children under one years of age, a smaller peak is seen in adolescents and young adults. During the 2013/2014 epidemiological year in England, 17% of the total MnB cases were observed in those aged 10 to 24 years old. This relatively higher incidence in adolescents and young adults, targeted in the indication proposed for Trumenba, is believed to be due to increased social mixing and exposure to new strains of *N. meningitidis* while in closed, crowded communities such as classrooms, dormitories, and military institutions.

3.1.2. Available therapies and unmet medical need

IMD is treated with antibiotics. The case fatality ratio of IMD remains high (10% to 15%) even with appropriate antibiotic treatment, and of those who survive, 11% to 19% will experience long-term

sequelae. For prevention of IMD, antimicrobial chemoprophylaxis (e.g. ciprofloxacin) can be used to prevent transmission from infected individuals to close contacts. However the cornerstone of prevention is represented by vaccines.

There is only one other vaccine available in Europe against IMD due to MenB, Bexsero. Bexsero was approved in 2013 for the prevention of MnB disease in individuals 2 months of age and older and is based on four different MnB antigens: NHBA, NadA, fHbp, and PorA P1.4.

While the incidence of endemic IMD has decreased in all age groups and is currently at a relatively low level globally, the rapid progression to serious illness or death, potentially life-changing long-term morbidities associated with IMD, and the shortcomings of mass chemoprophylaxis, emphasize the need for availability of safe and effective MnB vaccines to reduce the impact of MnB disease and to cover the needs of the EU population.

3.1.3. Main clinical studies

This application is based on 11 clinical studies, including two pivotal phase 3 clinical studies (B1971009 and B1971016). As it is not feasible to demonstrate clinical efficacy for MnB vaccines, the demonstration of protective efficacy is based on a serological marker, serum bactericidal antibody (SBA). Serum bactericidal antibody assays measure functional antibody activity in human sera that results in the complement-dependent killing of the target meningococcal strains. A hSBA titre ≥ 1:4 is a presumptive correlate for protection for MnB. Throughout the studies the lower limit of quantitation (LLOQ) corresponded with an hSBA titre ≥ 1:8 or higher, depending on strain. Therefore, this measure can be considered relatively conservative.

B1971009 was a phase 3, randomized, active-controlled, observer-blind multicentre trial in healthy subjects aged ≥10 to <19 years, designed to assess the safety, tolerability, and immunogenicity of 3 lots of bivalent rLP2086 and compare the immune response across lots. Subjects were randomised to receive either one of three lots of bivalent rLP2086, administered at Months 0, 2, and 6, or a single dose of hepatitis A vaccine followed by two doses of saline.

B1971016 was a Phase 3, randomized, placebo-controlled, observer-blind, multicentre trial in healthy subjects aged ≥18 to <26 years, designed to assess the safety, tolerability, and immunogenicity of bivalent rLP2086 when administered as a 3-dose regimen. Subjects were randomly assigned to receive bivalent rLP2086 or a saline injection at Month 0, 2, and 6.

In these main pivotal studies, the functional immune response was demonstrated against four primary MnB test strains (A22, A56, B24, and B44) and ten secondary MnB test strains (A29, A06, A07, A12, A15, A19, B03, B09, B15 and B16), which were selected using a random approach that took into account the in vitro fHBP surface expression level and ensured the inclusion of strains expressing fHBP variants identified frequently in MnB IMD isolates in Europe and the US. Selected test strains represent all 6 major fHBP phylogenetic subgroups and approximately 77% and 83% of disease causing MnB isolates in Europe and the US respectively, based on the fHBP variants expressed by MnB strains.

3.2. Favourable effects

Three dose schedule (0,2,6 months)

In study B1971009, one month after the 3rd dose, 83.5% (95%CI: 81.3-85.6) achieved the composite endpoint for hSBA response, meaning a hSBA titre ≥LLOQ for all four primary test strains compared to 2.8% (95%CI: 1.4-5.1) in the control group. The proportions of subjects with an hSBA titre fold rise ≥4 from baseline for the four primary test strains in the rLP2086 group compared to the control group were 83.2 vs 9.6, 90.2 vs 11.3, 79.8 vs 2.7 and 85.9 vs 1.0 for strains A22, A56, B24 and B44 respectively. For

the 10 secondary strains, pre-vaccination 3.9-43.1% of subjects had an hSBA titre ≥ LLOQ depending on the strain. One month post dose 3, 75.1-98.2% had an hSBA titre ≥ LLOQ.

In study B1971016, one month after the 3rd dose, 84.9% (95% CI: 83.1, 86.6) achieved the composite endpoint for hSBA response, compared to 7.5% (95%CI: 5.4, 10.0) in the control group. The percentage subjects with an hSBA titre fold rise ≥4 from baseline for the four test primary strains in the rLP2086 group compared to the control group were 80.5% vs 6.3%, 90.0% vs 10.3%, 79.3% vs 5.5% and 79.6% vs 1.6% for strains A22, A56 , B24 and B44 respectively. Against the 10 secondary strains prior to vaccination 5.0% (A12) to 55.8% (A07) had a hSBA titre ≥LLOQ. One month post dose 3 this had increased to 71.3% (A12) and 99.3% (A29) depending on the strain. Six out of 10 strains had an hSBA ≥LLOQ >90%, 7/10 >85% and 9/10 >75%.

Two dose schedule (0,6 months)

In study B1971012 several two and three dose schedules, including a 0,6 m schedule, were evaluated in 427 healthy subjects aged 11 to 18 years inclusive. The composite response of 73.5% was achieved with the 0 and 6-month schedule in the evaluable population. The composite responses after a 0, 1, 6-month schedule and a 0, 2-, and 6-month schedule in study B1971012 were, respectively, 83.1% and 81.7%. The percentage subjects achieving an hSBA titre ≥1:8 (LLOQ) one month after 2 doses of bivalent rLP2086 given at 0 and 6 was 93.5%, 98.4%, 81.1% and 77.5% for the 4 primary MnB test strains A22, A56, B24 and B44 respectively.

Persistence

The proportion of subjects with hSBA titres ≥ LLOQ at 48 months after the third dose of bivalent rLP2086 as measured in study B1971005 was 59.0%, 51.1%, 57.0% and 20.4% for strains A22, A56, B24 and B44 respectively compared to 34.3%, 34.8%, 23.5% and 12.0% in the control group.

In study B1971033, the proportion of subjects with hSBA titres ≥ LLOQ at 48 months after the last dose of bivalent rLP2086 was 41.1%, 43.0% and 39.6% for strain A22 and 47.1%, 58.6%, 57.6% for strain A56 following the 0,1,6 m, 0,2,6 m or 0,6 m schedule respectively. For the B-strains the proportion of subjects with hSBA titres ≥ LLOQ at 48 months after the last dose was 41.1%, 40.8%, and 30.5% for strain B24 and 20.7%, 18.0% and 18.9% for strain B44 following the 0,1,6 m, 0,2,6 m or 0,6 m schedule respectively.

Booster response

Substantial increases in bactericidal activity to a single booster dose given 4 years after a primary series as measured in study B1971033 show that a primary series with bivalent rLP2086 induces immunologic memory. Furthermore, there was no notable difference in the booster responses after a primary vaccine series given at 0, 6 months or 0, 2, 6 months.

Interactions

Concomitant administration of bivalent rLP2086 with Tdap-IPV, quadrivalent HPV vaccine, and with conjugated MenACWY vaccine and Tdap did not have a clinically relevant effect on the immune response to any of the vaccines, as determined in studies B1971010, B1971015 and B1971011.

Age effect

The immune responses in the four age subgroups (10 to 14, 15 to 18, 10 to 18, and 19 to 25 year age groups) after 3 doses of bivalent rLP2086 showed no substantial differences between age groups in the subgroup analysis for any immunogenicity endpoint analysed, and were consistent with responses in the overall population.

3.3. Uncertainties and limitations about favourable effects

Clinical efficacy data are not available. The determination of favourable effects for bivalent rLP2086 is based on functional antibody data from hSBA assays that employ carefully selected strains and human complement. There is no established immunological correlate of protection for MnB, however a hSBA titre ≥ 1:4 is generally assumed to be protective against meningococcal disease.

The hSBA response has been determined against four primary test strains and, in the two pivotal phase III studies, ten secondary test strains. It has not been demonstrated that a protective immune response has been elicited against all MenB strains circulating in the EU, but based on the methodology used to select the strains it can be assumed that these strains are representative of the overall population.

Dose schedule

The response for different dose schedules was not compared across groups in study B1971012. Therefore inferences from this study have some limitations. Sera from this study were only tested against the four primary strains. The Applicant has committed to conduct a phase 3 study to further investigate the 2 dose posology.

Persistence

Persistence of serum bactericidal antibodies was measured up to 48 months after the last dose in several studies.

Available data show poor persistence for strain B44, with no significant difference in the percentages of subjects with hSBA titre ≥ LLOQ for the bivalent rLP2086 group compared to the control group at 6 months plus 1 week following the third dose, or any time-point thereafter. Against strains A22 and B24, persistence of hSBA titres is modest. There is an age effect noticeable, with persistence being generally poorer in younger individuals (aged 10-14 years) compared to older individuals (15 to 18 years). A booster dose should be considered for individuals at continued risk of invasive meningococcal disease.

There is limited data in individuals aged 40-65 (n=9). There is no data in individuals aged ≥65 years. Although the benefits of the vaccine can largely be extrapolated to the adult population, there are uncertainties on the magnitude of the benefit in older adults due to immunosenescence.

There is no data in persons at particular risk of IMD due to immune deficiencies, but studies are planned. Persistence of immunity following the booster dose shall be studied further in order to determine whether additional booster doses might be necessary to maintain protection.

The potential impact of bivalent rLP2086 on carriage of *N. meningitidis* is unknown. The Applicant has confirmed interest in evaluating potential collaborations to assess vaccine impact on carriage.

3.4. Unfavourable effects

The main adverse reactions observed following rLP2086 administration are injection site reactions and systemic reactions to vaccination, which were reported more frequently following rLP2086 than following either saline or control vaccines. The most common adverse reactions observed were injection site pain, redness and swelling at the vaccination site, headache, fatigue, chills, diarrhoea, muscle pain, joint pain and nausea.

Pain at the injection site was the most common local reaction reported. Pain was reported across studies by 89.6% to 98.1% of subjects compared to 18.2% to 64.8% in the control groups. Severe pain was reported in 3.0-15.1% of subjects compared to 0-2.4% in control groups, moderate pain was reported for 45.5% to 63.0% versus 1.7% to 17.5% of subjects. The median duration of pain at the injection site was

2 to 3 days following rLP2086. An increase in severity of reactions with subsequent doses was seen across all local reactions.

The most frequently reported systemic events after any dose of bivalent rLP2086 were fatigue, reported by 60.6% to 85.0% compared to 41.7% to 79.6% in control groups, and headache, reported by 59.1% to 83.9% compared to 48.4% to 74.3% in control groups. Severe fever (39.0°C to 40.0°C) was reported for 0.2% to 2.7% of subjects after any dose of bivalent rLP2086 compared to 0.4% to 1.7% of subjects in control groups.

Among the 13,284 subjects who received bivalent rLP2086 in the 8 controlled studies (core safety dataset), 46 subjects (0.35%) were withdrawn from the studies due to local reactions. In the overall safety dataset, among the 15,053 subjects who received 120 µg bivalent rLP2086, a total of 44 subjects (0.29%) were withdrawn from the studies because of injection site pain.

3.5. Uncertainties and limitations about unfavourable effects

Bivalent rLP2086 has been evaluated in 15,294 subjects who received at least one dose of bivalent rLP2086 in clinical trials (overall safety dataset). Additionally, bivalent rLP2086 has been licensed in the US for use in subjects aged 10-26 years since 2014. Post-marketing, approximately 170,000 doses have been distributed up to 30 November 2015. Due to the small exposure yet, adverse events that occur very rarely (~ <1/10,000 – 1/100,000) adverse events with a (significant) delay in onset are difficult to exclude.

Overall, safety data in persons older than 26 years is limited. There is very limited data in persons aged between 40 and 65 years and no data in persons over 65 years of age. There is no data in immunosuppressed subjects; however this will be addressed post-authorisation.

Bivalent rLP2086 is a fairly reactogenic vaccine. An increase in reaction severity can be seen with subsequent doses.

3.6. Effects Table

Table 38. Effects Table for Trumenba as indicated for prevention of invasive disease due to *Neisseria meningitidis* serogroup B in persons aged 10 and older (data cut-off: 31 October 2015)

Effect	Short description	Unit	Treatment	Control	Uncertainties	References
Favourable Effects						
% of sbjs 10-18 years achieving a protective immune response	hSBA titre ≥LLOQ for all four primary test strains (A22, A56, B24, B44) (composite endpoint)	%	81.7 (3 doses, given at 0,2,6 m) 73.5 (2 doses, given at 0,6 m) 95% CI (77.3, 85.7) (68.5, 78.1)	n/a	Exploratory endpoint in a phase 2 study	B1971012
% of sbjs 10–18 years achieving a protective immune response	hSBA titre ⩾LLOQ for all four primary test strains (A22, A56, B24, B44) (composite endpoint)	%	83.5 (3 doses given at 0,2,6 m) 95% CI (81.3,85.6)	2.8 95% CI (1.4,5.1)	Demonstration of efficacy against IMD based on assumed hSBA protective titre	B1971009
% of sbjs 18-26 years achieving a protective immune response	hSBA titre ⩾LLOQ for all four primary test strains (A22, A56, B24, B44) (composite endpoint)	%	84.9 (3 doses given at 0,2,6 m) 95% CI (83.1, 86.6)	7.5 95% CI (5.4, 10.0)	as above	B1971016
Unfavourable Effects						
Severe fever	Temperature (39.0°C to 40.0°C) solicited within 7 days after vaccination	%	0.2 - 2.7	0.4 - 1.7	No pooling of data performed	Core safety dataset (8 controlled studies)

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Within the main clinical studies a functional immune response has been demonstrated against four primary strains and 10 secondary strains which have been selected from a MnB SBA strain pool of invasive disease isolates collected in Europe and the US. The fHBP variants expressed by the 4 primary and 10 secondary MnB test strains represent all 6 major fHBP phylogenetic subgroups which represent approximately 77% and 83% of disease causing MnB isolates in Europe and the US respectively, based on the fHBP variants expressed by MnB strains. The MnB strain pool from which test strains were selected is similar in makeup and distribution of fHBP variants compared to contemporary, recently (2011-2014) collected MnB strains from the UK, the Netherlands, Canada and the US, therefore results of the main clinical trials can be considered relevant to the current epidemiological situation.

Responses following three doses given at 0,2 and 6 months were relatively strong against all the strains tested. One month after the third dose of bivalent rLP2086, 83.5% of subjects aged ≥10 to <19 years had an hSBA titre ≥ LLOQ for all 4 primary MnB test strains combined, and 75.1-98.2% had an hSBA titre ≥ LLOQ against the secondary strains. Between 84.9% and 71.3-99.3% of subjects aged ≥18 to <26 years had an hSBA titre ≥ LLOQ against the ten secondary strains, which points towards a strong and broad immune response elicited by Trumenba.

Similar responses can be seen following a 0,1,6 month schedule, although these data are descriptive in nature. Overall the data on the 0,2,6 month schedule observed by 11 clinical trials provide sufficient evidence for the approval of three dose schedule. Data in immunocompromised persons, including complement deficient persons, is lacking but will be studied post-authorisation.

It has to be noted that even though the response to the B-strains following the 0,6 m schedule appears reduced compared to the response with the 0,2,6 m, a high proportion of subjects achieved an immune response against each test strain (from 80% to 98% across strains) after two doses given at 0, 6 months. Despite the more limited data, the immune response to the two dose schedule (0,6 m) are considered similar to the three dose schedules; the persistence of antibodies and the response to a booster dose given 4 years after a primary series showed no notable difference when the 0, 6 months schedule or the 0, 1-2, 6 months schedule were followed. Based on the overall data the 2 dose posology is approvable. More data will be collected on the two dose schedule in a planned phase 3 randomised comparative study, B1971057. These data are not necessary to conclude that the benefit/risk of the two dose schedule is indeed positive so the study can be conducted post-authorisation, but the data are expected to further strengthen the evidence base.

The persistence data for the 0,2,6 m schedule show that persistence is moderate to poor for the B44 strain with no significant difference with the control group at 6 months plus 1 week following the third dose. Persistence data for the 0,6 m schedule shows a similar decline in antibodies as seen following the 0,2,6 m schedule. At 48 months following the last dose, levels of serum bactericidal antibody are similar between the two schedules.

The significance of the decline in antibodies in relation to efficacy or effectiveness is currently unknown. However, as circulating serum bactericidal antibodies are considered important for protection against invasive meningococcal disease, this decline suggests that a booster is necessary to maintain protection following either dosing regimen. The need for further boosters is planned to be investigated post-approval.

Bivalent rLP2086 is a fairly reactogenic vaccine with a relatively high proportion of subjects reporting pain, headaches and fatigue following vaccination. The severity of local reactions can increase with subsequent doses.

Regarding the benefit/risk balance, the limited data available in persons > 26 years of age (and especially above 40 years of age) suggest that the immunogenicity and safety profile is acceptable, and likely similar to that seen in younger adults. Concerning individuals above 65 years of age, the main uncertainty is that the immune response to vaccination may diminish with age due to immunosenescence. However, based also upon experience with other vaccines, the impact of this is unlikely to be of such a degree that it would render the benefit/risk negative for the whole population over 65 years. In conclusion the benefit/risk is considered positive for those aged 26 years and above, including the ederly population.

3.7.2. Balance of benefits and risks

The benefit/risk balance for bivalent rLP2086 vaccine is positive for use in individuals above 10 years of age and older.

The available data indicate that bivalent rLP2086 should provide broad protection against circulating MenB strains in Europe following a 3 dose schedule given at 0, 1-2 and 6 months and following a 2 dose schedule at 0, 6 months. The data assessed for this application do not allow the determination of the impact or effectiveness that this vaccine will have in Europe. This will have to be confirmed in post-authorisation effectiveness studies. Bivalent rLP2086 is a fairly reactogenic vaccine with high proportions of subjects reporting mostly mild reactions to vaccination across studies, but the reactogenicity is within limits of acceptability. Overall bivalent rLP2086 has an acceptable safety profile.

Despite limited data above 40 years of age and lack of data in those above 65 years of age, the benefit/risk profile of the vaccine is considered positive across age groups. The uncertainties in elderly that due to immunosenescence the vaccine could be less protective than adults should be taken into account when recommending vaccination in this age group.

Considering the totality of the available persistence data, a booster dose should be considered following either dosing regimen for individuals at continued risk of invasive meningococcal disease. Persistence of immunity following a booster dose is planned to be investigated to evaluate the potential need for further boosters.

3.7.3. Additional considerations on the benefit-risk balance

Not applicable

3.8. Conclusions

The overall benefit/risk of Trumenba for active immunisation of individuals 10 years and older to prevent invasive meningococcal disease caused by *Neisseria meningitidis* serogroup B is positive.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit/risk balance of Trumenba is favourable in the following indication:

Trumenba is indicated for active immunisation of individuals 10 years and older to prevent invasive

meningococcal disease caused by Neisseria meningitidis serogroup B.

See section 5.1 for information on the immune response against specific serogroup B strains.

The use of this vaccine should be in accordance with official recommendations.

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Other conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription

Official batch release

In accordance with Article 114 Directive 2001/83/EC, the official batch release will be undertaken by a state laboratory or a laboratory designated for that purpose.

Conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that *Neisseria meningitidis* serogroup B bivalent lipoprotein (recombinant lipidated fHbp (factor H binding protein) subfamily A and B) is considered to be a new active substance as it is not a constituent of a medicinal product previously authorised within the European Union.

Paediatric Data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan PIP P/0304/2015 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.