Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Meningococcal group B vaccine

Proprietary Product Name: Trumenba

Sponsor: Pfizer Australia Pty Ltd

August 2018

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance) when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website < https://www.tga.gov.au>.

About AusPARs

- An Australian Public Assessment Report (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations and extensions of indications.
- An AusPAR is a static document; it provides information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

Common abbreviations

Abbreviation	Meaning
Ab	Antibody
4CMnB	Multicomponent meningococcal serogroup B vaccine (Bexsero)
ABN	Australian Biological Name
ACIP	Advisory Committee on Immunization Practices
Adacel	Tetanus, low-dose diphtheria, and low-dose acellular pertussis vaccine (Tdap)
AE	Adverse event
ARTG	Australian Register of Therapeutic Goods
ACV	Advisory Committee on Vaccines
ATAGI	Australian Technical Advisory Group on Immunisation
BLA	Biologic License Application
CBER	Center for Biologics Evaluation and Research
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CRM197	Cross-reactive material-197
dTaP	Low-dose diphtheria, tetanus, and low-dose acellular pertussis vaccine
e-diary	Electronic diary
EU	European Union
FDA	Food and Drug Administration
Factor H binding protein	Bacterial lipoprotein expressed on surface of N meningitidis
Gardasil	Human papilloma virus vaccine (HPV)
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
GMR	Geometric mean ratio

Abbreviation	Meaning
GMT	Geometric mean titre
HAV	Hepatitis A virus vaccine
HPV	Human papilloma virus vaccine
hSBA	Serum bactericidal assay using human complement
ICH	International Conference on Harmonization
IgG	Immunoglobulin G
IMD	Invasive meningococcal disease
IPV	Inactivated poliomyelitis virus vaccine
LCI	Lower bound confidence interval
LLOQ	Lower limit of quantitation
LP2086	Lipoprotein or fHBP vaccine antigen
MAA	Marketing authorization application
MCV4	Quadrivalent meningococcal polysaccharide conjugate vaccine
Menactra	Meningococcal (Groups A, C, Y, and W-135) polysaccharide diphtheria toxoid conjugate vaccine (MCV4)
mITT	Modified intent-to-treat
MLST	Multi-locus sequence type
MnB	*Neisseria meningitidis* serogroup B
MPSV4	Meningococcal polysaccharide vaccine
NDCMCs	Newly diagnosed chronic medical conditions
PPV	Positive predictive value
Repevax	Low-dose diphtheria, tetanus, acellular pertussis, and inactivated poliomyelitis virus vaccine (dTaP/IPV)
rLP2086	Recombinant lipoprotein 2086
rSBA	Serum bactericidal assay using baby rabbit serum as complement source
SAE	Serious adverse event

Abbreviation	Meaning
SBA	Serum bactericidal assay
SOC	System Organ Class
Tdap	Tetanus, low-dose diphtheria, and low-dose acellular pertussis vaccine
UK	United Kingdom
US	United States
WHO	World Health Organization

I. Introduction to product submission

Submission details

Type of submission:	New biological entity
Decision:	Approved
Date of decision:	12 September2017
Date of entry onto ARTG:	14 September 2017
ARTG number:	276920
Active ingredients:	Neisseria meningitidis serogroup B recombinant lipidated factor H binding subfamily A; and Neisseria meningitidis serogroup B recombinant lipidated factor H binding subfamily B
Product name:	Trumenba
Sponsor's name and address:	Pfizer Australia Pty Ltd 38-42 Wharf Rd West Ryde NSW 2114
Dose form:	Suspension for injection
Strength:	60 µg of Neisseria meningitidis serogroup B recombinant lipidated factor H binding subfamily A; and and 60 µg of Neisseria meningitidis serogroup B recombinant lipidated factor H binding subfamily B
Container:	Prefilled syringe
Pack size:	1
Approved therapeutic use:	*Trumenba is indicated in individuals 10 years and older for active immunisation to prevent invasive meningococcal disease caused by Neisseria meningitidis serogroup B.*
Route of administration:	Intramuscular
Dosage:	Standard schedule for routine immunisation: 2 doses (0.5 ml each) administered at 0 and 6 months. Schedule for individuals at increased risk of invasive meningococcal disease: 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. The choice of dosing schedule may depend on the risk of exposure and the patient's susceptibility to meningococcal B disease.

Product background

This AusPAR describes the application by Pfizer Australia Pty Ltd (the sponsor) to register Trumenba Meningococcal group B vaccine suspension for injection prefilled syringe 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.*

Trumenba is a new *N. meningitidis* serogroup B recombinant bivalent rLP2086[1] vaccine (MnB rLP2086). It composed of two recombinant lipidated factor H binding protein (fHBP) variants from *Neisseria meningitidis (N. meningitidis)* serogroup B; lipidated factor H binding protein subfamily A and lipidated factor H binding protein subfamily B protein. The vaccine is provided in pre-filled syringes.

N. meningitidis serogroup B (MnB) is a significant cause of serious endemic meningococcal disease worldwide and can epidemiologically manifest as prolonged outbreaks or as sudden, unpredictable outbreaks. MnB disease is often devastating with sudden onset, fast progression and may result in permanent significant clinical long term sequelae (neurological impairment, hearing loss, renal failure, and/or skin, digit and limb loss) in those that survive.

The main treatment option is antibiotics for meningococcal infection. It still however has a significant mortality and morbidity associated with it despite even early antibiotic therapy. There is one licensed MnB vaccine currently available in Australia which is now routinely being offered to groups 'at risk' for outbreaks.

The role of the recombinant lipoproteins, formulated in the vaccine, is to elicit functional bactericidal antibodies against Meningococcal B strains in vaccinated subjects. The native molecules were identified as members of a family of outer membrane proteins known to bind factor H, which is a key down regulator of the alternative complement pathway. Binding of factor H by pathogens is thought to provide significant resistance to complement attack, and therefore increased virulence. In an immune response to MnB infection, vaccine derived antibodies will interfere with factor H binding by the pathogen and that this will lead to bactericidal effects from complement action.

Regulatory status

The product received initial registration on the Australian Register of Therapeutic Goods (ARTG) on 14 September 2017.

At the time the TGA considered this application; a similar application had been approved or was under consideration in countries as described in Table 1.

Table 1: International regulatory status

Country	Status	Indications
European Union	Approved Submitted 22 April 2016 Approved 24 May 2017	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

[1] rLP2086: recombinant lipoprotein 2086

Country	Status	Indications
		serogroup B strains. The use of this vaccine should be in accordance with official recommendations.
USA	Initial Biologic License Application (BLA) 16 June 2014 sBLA 27 March 2016	Trumenba is indicated for active immunization to prevent invasive disease caused by Neisseria meningitidis serogroup B. Trumenba is approved for use in individuals 10 through 25 years of age. Approval of Trumenba is based on demonstration of immune response, as measured by serum bactericidal activity against four serogroup B strains representative of prevalent strains in the United States. The effectiveness of Trumenba against diverse serogroup B strains has not been confirmed.
Canada	Under Evaluation Submitted 30 May 2016	Indication submitted is identical to the proposed Australian indication

Product Information

The Product Information (PI) approved with the submission which is described in this AusPAR can be found as Attachment 1. For the most recent PI, please refer to the TGA website at < https://www.tga.gov.au/product-information-pi> .

II. Registration time line

The following table captures the key steps and dates for this application and which are detailed and discussed in this AusPAR and Attachment 2.

Table 2: Registration timeline for Submission PM-2016-02079-1-2

Description	Date
Submission dossier accepted and first round evaluation commenced	29 July 2016
First round evaluation completed	3 January 2017
Sponsor provides responses on questions raised in first round evaluation	28 February 2017
Second round evaluation completed	31 May 2017
Delegate's Overall benefit-risk assessment and request for Advisory Committee advice	3 July 2017

Description	Date
Sponsor's pre-Advisory Committee response	17 July 2017
Advisory Committee meeting	2 August 2017
Registration decision (Outcome)	12 September 2017
Completion of administrative activities and registration on ARTG	14 September 2017
Number of working days from submission dossier acceptance to registration decision*	202

*Target timeframe for standard applications is 220 working days

III. Quality findings

Introduction

The *N. meningitidis* serogroup B recombinant lipidated factor H binding protein subfamily A and *N. meningitidis* serogroup B recombinant lipidated factor H binding protein subfamily B proteins are composed of 258 and 261 amino acids respectively. The primary amino acid sequences of recombinant lipoproteins were provided. Both proteins are covalently lipidated at the N-terminus. The nature of the lipidation was described along with structural diagrams and details of molecular mass for both subfamilies.

All isoforms of the recombinant lipidated factor H binding protein drug substance were characterised and described.

The role of the recombinant lipoproteins, formulated in the vaccine, is to elicit functional bactericidal antibodies against Meningococcal B strains in vaccinated subjects. The native molecules were identified as members of a family of outer membrane proteins known to bind factor H, which is a key down regulator of the alternative complement pathway. Binding of factor H by pathogens is thought to provide significant resistance to complement attack, and therefore increased virulence.

The implication, therefore, seems to be that, in an immune response to MnB infection, vaccine derived antibodies will interfere with factor H binding by the pathogen and that this will lead to bactericidal effects from complement action.

The presence of functional epitopes in the protein moieties of the recombinant lipoproteins is considered to be critical to their function in eliciting the production of protective antibodies in vaccinated subjects. The lipid moieties are considered to be critical to the immunogenicity of the recombinant molecules. These properties of the two immunogens are controlled at the drug substance and drug product level by the antigenicity and purity tests.

The structural, physicochemical and functional characterisation of the lipidated recombinant factor H binding proteins subfamilies A and B were provided.

Drug substance (active ingredient)

Commercial scale drug substance (DS) batches are fermented at a production culture scale. The entire batch is processed for purification. The DS proteins (subfamily A and B) are individually expressed in E coli and the fermentation and recovery processes are identical.

The production of the recombinant lipoproteins consists of 3 stages: shake flask, seed fermenter 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 fermenter, where expression of the rLP2086 protein is induced.

The cells are harvested by centrifugation and lysed by homogenisation. 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. For the fermentation and recovery process, In-process tests for control and in-process tests for monitoring have been implemented throughout the process to ensure consistency of the manufacturing process.

The purified protein pools are concentrated into drug substance buffer, sterile filtered, filled and stored frozen. All manufacturing steps are validated.

Potency, conformation and structural integrity of the DS immunogens in the final product are controlled by the appropriate release tests. All analytical procedures are validated.

Drug product

Assurance is provided that all sites associated with manufacture hold current Good Manufacturing Practice (GMP) clearance covering the steps requested.

The proposed commercial shelf life of Trumenba is 36 months at 5 ± 3 °C.

This shelf life is supported by information for the filled vaccine syringes.

Stability studies were conducted in accordance with relevant International Conference on Harmonization (ICH) guidelines.

Quality summary and conclusions

Changes to original name and consequent changes to labelling and PI

At the time of submission of this application a single Australian Biological Name (ABN) had been approved for the two drug substances in Trumenba; recombinant lipoprotein rLP2086 subfamily A and B. During the course of evaluation, it was considered that this ABN was not suitable and the following replacement names were proposed by the company and approved by TGA ABN committee:

- Neisseria meningitidis serogroup B recombinant lipidated factor H binding protein subfamily A and
- Neisseria meningitidis serogroup B recombinant lipidated factor H binding protein subfamily B

The proposed labels and PI have been amended to reflect these changes. The name on the main label for the proposed carton now reads:

Trumenba Meningococcal group B vaccine Neisseria meningitidis serogroup B recombinant lipidated factor H binding protein subfamily A 60 µg factor H binding protein subfamily B 60 µg Suspension for intramuscular injection.

Potential pyrogenic effects of Trumenba

Both the immunogens in Trumenba are intrinsically pyrogenic. The lipid moieties that are critical to the immunogenicity of the drug substance molecules are thought to achieve their effect in vaccinated subjects by stimulation of the release of a number of cytokines that are pyrogenic.

[Information redacted]

This characteristic of the vaccine is brought to the Delegate's attention in case there has been any indication of pyrogenicity or any signal that might be associated with pyrogenicity observed in the clinical trials.

Control of the drug product

For reasons covered in the evaluation process, the company has proposed that the potency test, [information redacted], should be treated only as a characterisation test in Australia until [information redacted]. The company has undertaken to provide the full Manufacturing Summary Protocol submitted to EMA, containing results of the potency test, for all batches of vaccine imported into Australia.

The proposal to treat the potency test as a characterisation test is recommended with the following conditions:

- The standard Batch Release conditions relating to the shipping of vaccines to Australia should be applied with an additional requirement that Summary Manufacturing Protocols of all batches imported into Australia will contain results of potency testing of the vaccine that meet acceptance criteria detailed in the application.
- The company will submit a Category 3 application to transition the potency test to a release test [information redacted].

IV. Nonclinical findings

Introduction

The sponsor has applied to register a new chemical entity, *N. meningitidis* serogroup B bivalent recombinant lipoprotein rLP2086 (subfamily A and B, *E. coli*) vaccine (Trumenba). rLP2086 is a lipidated form of bacterial factor H binding protein (fHBP). Trumenba is indicated for individuals 10 years and older for active immunisation to prevent invasive meningococcal disease caused by *N. meningitidis* serogroup B (MnB). Routine immunisation with Trumenba involves IM administration of 2 doses (0.5 mL each) at 0 and 6 months. Individuals at increased risk of invasive meningococcal disease are given 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. Each 0.5 mL dose of Trumenba contains 60 µg of lipidated subfamily A and 60 µg of lipidated subfamily B rLP2086 (120 µg total protein).

The amount of rLP2086 in a dose of Trumenba is comparable with another MnB vaccine, 4CMnB (Bexsero; registered by the TGA in August 2013), which contains 50 µg of a non lipidated subfamily B form of fHBP. Each dose of Trumenba also contains 0.25 mg of the adsorbent aluminium as aluminium phosphate. This level is well within the limits

specified by the 'US FDA Code of Federal Regulations Title 21 (revised as of 1 April 2016)' and the European Pharmacopoeia of 0.85 and 1.25 mg of aluminium per dose, respectively.

All studies, except one, were performed by the sponsor or by the initiator of the product (Wyeth Research, a company that was subsequently purchased by the sponsor). The sponsor submitted the following nonclinical studies:

- Primary pharmacology; 26 studies.
- Repeat dose toxicity; 2 studies (both to GLP standard).
- Reproductive and developmental toxicity; 2 studies (both to GLP standard).

All submitted studies have been reviewed.

Pharmacology

Primary pharmacology

Reports were provided on an extensive body of studies performed in the sponsor's laboratories. These studies examined:

1. the background to the identification of fHBP as a candidate antigen
2. the development of a monoclonal antibody for flow cytometric-based quantification of surface expression of subfamily A or B type fHBP on MnB strains
3. the immunogenicity of different forms of fHBP
4. the characterisation of fHBP variant type and other genetic markers in the sponsor's large panel (n = 1,814) of MnB strains collected in America and Europe from invasive meningococcal disease (IMD) cases occurring from 2000 to 2006
5. comparison of the fHBP variant type of the sponsor's panel of 1,814 MnB strains with that of more recent IMD derived MnB strains collected in America, Canada, Europe, and the United Kingdom (UK) and with carriage isolates collected in Canada, Europe, and the UK from adolescents and young adults
6. the sensitivity in the hSBA[2] of MnB strains, from both the sponsor's 2000 to 2006 panel and more recent collections, to rabbit and human immune sera.

The sponsor provided no data on the fHBP status of MnB strains isolated from Australian IMD cases. In a response, the sponsor provided a paper, which reported *fHbp* gene sequence results for 227 IMD derived MnB strains collected in Western Australia over the period 2000 to 2014.[3] All MnB strains, except for 2 that contained a stop codon in the *fHbp* gene, were predicted to produce functional fHbp protein. The sequence data was converted to the sponsor's fHbp variant nomenclature using the PubMLST[4] database[5] and comparison was then made between the variants present in the Western Australian strains and in the sponsor's pool of 1,814 MnB strains collected in USA and Europe. The eleven most common fHbp variants in the USA/Europe MnB pool, in declining order of frequency, were: B24, B16, A22, B03, B44, B09, A19, A12, A05, A06, and A07. Whilst the most common variants in the Western Australian MnB strains were: A22, B24, B16, B09, B44, A47, B03, B192, A05, A19, and A06. As well as showing a close qualitative

[2] hSBA = serum bactericidal assay using human complement
[3] Mowlaboccus S et al. (2016) Temporal changes in BEXSERO® antigen sequence type associated with genetic lineages of Neisseria meningitidis over a 15-year period in Western Australia. *PLoS One,* 2016; 11: e0158315.
[4] MLST; multi-locus sequence type
[5] www.pubmlst.org/neisseria

correspondence, there was also a quantitative correspondence between the pools, with the eleven most common fHbp variants in the USA/Europe MnB strain pool representing 78.6% (1,425/1,814) of that pool and 74.0% (168/227) of the Western Australian MnB pool. The test strains used for hSBA testing in the clinical studies were therefore representative of fHBP variants in Western Australia from 2000 to 2014. No data were available for the eastern Australian states.

As detailed in various literature reports, meningococcal fHBP is an outer membrane protein that has the potential to serve as the basis for either mono or multivalent vaccines. fHBP binds complement factor H, which circulates in human plasma at high concentrations and modulates the alternative complement pathway, thereby protecting the meningococcal cell against destruction by the complement system.[6] [7]A potential challenge, however, with the use of fHBP in vaccines is that MnB strains express many sequence variants of fHBP, commonly divided into two major groups designated subfamilies A and B. Accordingly, the sponsor's vaccine, rLP2086, is bivalent and contains both a subfamily A and a subfamily B form of fHBP. Consistent with this approach, studies in rabbits showed that monovalent subfamily A or B vaccines produced high titres in hSBA assays using a MnB strain expressing an fHBP variant from the same subfamily, but low or no activity towards MnB strains expressing the alternate fHBP subfamily. In addition, the fHBP in rLP2086 is lipidated, which represents the native form of the protein and was shown in mice, rabbits, and monkeys to increase the immunogenic response incidence as compared with non-lipidated protein. Another issue related to the use of fHBP in vaccines is that expression levels of this protein can vary markedly between MnB strains. The sponsor developed a validated flow cytometric procedure for the assay of fHBP surface expression levels, using a monoclonal antibody that recognises both subfamilies of fHBP, and showed that < 5% of strains in a large panel (n = 1814) were below the limit of detection. Expression levels of fHBP varied markedly between strains, although subfamily B expressing strains tended to have higher surface expression as compared with subfamily A expressing strains. Such differences in fHBP expression could be partly related to the sequence of the promoter region.[8]

Testing of a randomly selected panel of IMD MnB strains in the hSBA using human post rLP2086 vaccination serum pools showed that 82% (89/109) were susceptible to killing, as defined by a ≥ 4 fold difference in titre between pre and post vaccination serum samples. The latter definition derives from the finding that failure of protection against IMD can occur when the hSBA titre is below 4.[9] The susceptibility of MnB strains in the hSBA, using rabbit or human post immune sera, was shown to correlate with their surface expression of fHBP. MnB strains expressing subfamily A or B fHBP at greater than a threshold level were consistently sensitive to killing, whereas killing of strains below the threshold could not be predicted, but nearly 50% of strains below the threshold were killed. The resistance to immune serum of MnB strains with low/undetectable expression of fHBP suggests that there may be other mechanisms for evading killing by the alternative complement pathway. For example, Neisserial surface protein A (NspA), which is expressed at variable levels in MnB strains, can bind factor H and may provide protection

[6] Fletcher L.D., et al. (2004) Vaccine potential of the *Neisseria meningitidis* 2086 lipoprotein. *Infection and Immunity*, 2004; 72: 2088-2100.
[7] McNeil L.K. et al. (2013) Role of factor H binding protein in *Neisseria meningitidis* virulence and its potential as a vaccine candidate to broadly protect against meningococcal disease. *Microbiology and Molecular Biology Reviews*, 2013; 77: 234-252
[8] Biagini M., et al. (2016) Expression of factor H binding protein in meningococcal strains can vary at least 15-fold and is genetically determined. *Proceedings of the National Academy of Sciences (USA)*,2016; 113: 2714-2719.
[9] Holst J. et al. (2003) Serum bactericidal activity correlates with the vaccine efficacy of outer membrane vesicle vaccines against *Neisseria meningitidis* serogroup B disease. *Vaccine* 2003; 21: 734-737.

against complement mediated killing.[10] Surface expression of fHBP was found to be the only marker providing some level of prediction of MnB strain susceptibility in the hSBA.

fHBP sequence diversity in MnB carriage isolates was compared with the sponsor's panel of IMD isolates (n = 1814). Whereas subfamily B predominated in IMD isolates (29% subfamily A and 71% subfamily B), carriage MnB isolates from different countries predominantly (77 to 87%) expressed subfamily A fHBP. These results emphasise that a MnB vaccine needs to induce a potent immune response against both subfamilies of fHBP variants in order to impact invasive disease and disrupt carriage.

The focus of several studies was demonstrating that the genotype and/or surface expression level of fHBP variants found in the 2000 to 2006 panel of MnB strains, which had been used for initial testing of the immunogenicity of rLP2086, was still representative of more recently isolated MnB strains. It was shown that large contemporary pools of MnB strains from both North America and Europe were comparable with the sponsor's older panel of strains.

Secondary pharmacodynamics and safety pharmacology

Specific studies in these categories were not performed and the World Health Organization (WHO) (2005) vaccine guideline suggests that they are not normally necessary for the safety assessment of a vaccine.

Pharmacokinetics

Pharmacokinetic studies were not performed and would not normally be considered relevant to the testing/development of a vaccine (WHO 2005).[11]

Pharmacokinetic drug interactions

Such studies were not performed and would not normally be considered relevant to the testing/development of a vaccine.

Toxicity

Acute toxicity

No studies of this type were performed. This is consistent with the suggestion in the WHO (2005) vaccine guideline that '*the number of doses administered to the test animals should be equal to or more than the number of doses proposed in humans*'.[11]

Repeat dose toxicity

Two repeat dose toxicity studies were performed using rabbits of both sexes given five IM doses of bivalent rLP2086 at two week intervals. Groups received 100 or 400 µg total protein per dose in the first study and 400 µg per dose in the second study. The 400 µg dose is twice the highest dose used in clinical trials. The WHO (2005) vaccine guideline suggests use of the highest dose to be used in clinical trials.[11] Appropriate saline and vehicle control groups were included in the rabbit studies. Half the animals were euthanised at 2 or 3 days after the last dose and the other half were euthanised after a 30 day recovery period. A difference between the studies was that the second study used

[10] Lewis L.A. et al. (2010). The meningococcal vaccine candidate neisserial surface protein A (NspA) binds to factor H and enhances meningococcal resistance to complement. *PLoS Pathogens*, 2010; 6: e1001027.
[11] WHO (2005) WHO guidelines on nonclinical evaluation of vaccines. WHO Technical Report Series, No. 927.

the vehicle for Trumenba whereas a vehicle with lower aluminium concentration and a different buffer was used in the first study.

Very high titres of anti-rLP2086 antibodies were shown to be induced by the vaccine in all treated rabbits. This immune response was not consistently associated with vaccine-related effects on body weight, organ weights, or gross pathology.

Injection site irritation was monitored by scoring erythema and oedema after dosing and by examining histopathological changes at injection sites. Both studies suggested that rLP2086 dosing produced only a slight, transient increase in irritation as quantified by erythema/oedema scoring. Histopathology of the first study suggested that the incidences of slight to moderate subacute and chronic inflammation were increased by vehicle and by vaccine dose but that both were reversed after the recovery period, whilst in the second study (which used a different vehicle) inflammation appeared largely attributable to the vehicle. In addition, an increase (< 0.5 °C) in body temperature compared with vehicle control animals was noted after the first vaccination in both studies. As body temperature was only measured at 4 and 24 hours post dose, it is possible that the peak of the pyrogenic response was missed. Nevertheless, the sponsor's conclusion that the small transient increase was not an adverse event appears reasonable.

In both studies, vaccine dosing at 400 µg produced an approximate doubling of fibrinogen concentration at two days post dose. This increase is suggestive of an acute phase inflammatory reaction. More modest increases of fibrinogen concentration have been noted after inoculation of humans with various vaccines, including outer membrane vesicles from *N. meningitidis;*[12] [13] although vaccination of horses could produce more marked increases of fibrinogen concentration.[14] Hence, it is possible that such increases are species and vaccine dose dependent. The dose producing this response in rabbits is, however, much higher than the recommended dose for humans and the effect was transitory. Although increased fibrinogen concentration can cause RBC aggregation,[15] it has been noted that there is a lack of evidence associating vaccine-induced increases of fibrinogen concentration with thrombotic events in humans.[13]

The conduct of these studies was generally consistent with the WHO (2005) vaccine guideline.

Genotoxicity

No genotoxicity studies were performed. This is consistent with the WHO (2005) guideline which states that such studies are not normally needed for vaccines.

Carcinogenicity

No carcinogenicity studies were performed. This is consistent with the WHO (2005) guideline which states that such studies are not normally needed for vaccines.

Reproductive toxicity

Two reproductive and developmental toxicity studies were performed using female rabbits given four IM doses of bivalent rLP2086 (two doses given pre mating plus doses on GD 10 and GD 24) at 200 µg total protein per dose (equal to the highest dose used in clinical trials), which exceeds the clinical dose of 120 µg. In the first study, half the does were

[12] Verschuur M., et al (2004) Interindividual variation in the response by fibrinogen, C-reactive protein and interleukin-6 to yellow fever vaccination. *Blood Coagulation & Fibrinolysis* 2004; 15: 399-404
[13] Keiser P.B., et al (2009) Plasma fibrinogen levels after vaccination with a native outer membrane vesicle vaccine for *Neisseria meningitidis*. *Vaccine* 2009; 27: 6809-6813.
[14] Andersen S.A., et al. (2012) Vaccination elicits a prominent acute phase response in horses. *Veterinary Journal* 2012; 191: 199-202.
[15] Davalos D. and Akassoglou K. (2012) Fibrinogen as a key regulator of inflammation in disease. *Seminars in Immunopathology* 2012; 34: 43-62

sacrificed on GD 29 and the other half were allowed to deliver, whilst in the second study all does were sacrificed on GD 29. Another difference between the studies was that the second study used the vehicle for Trumenba whereas a vehicle with lower aluminium concentration and a different buffer was used in the first study. It was shown in both studies that female rabbits developed a very strong immune response to the vaccine. On GD 29, antibody titres in the maternal and fetal circulation were similar, indicating that antibodies to rLP2086 can cross the placenta. Antibodies to rLP2086 were still detectable in serum from pups on PND 21, but were present at about 10 fold lower than fetal titres. Both studies showed no effect of rLP2086 dosing on mating or fertility rates or on various other maternal and fetal/pup parameters including fetal variations/malformations and pup development. Both vehicle and vaccine treated groups showed a low incidence of minimal severity oedema and/or erythema at injection sites. Such irritation was generally transient. These studies were generally conducted in conformity with the WHO (2005) guideline.

Pregnancy classification

The sponsor has proposed Pregnancy Category B2[16]. It is suggested that Pregnancy Category B1;[17] ('*Studies in animals have not shown evidence of an increased occurrence of fetal damage*.') is more appropriate based on the lack of animal findings. The previously registered MnB vaccine Bexsero was categorised as B1. The USA category for Trumenba is B.

Local tolerance

Injection site irritation was monitored as part of both the repeat dose and reproductive toxicity studies. This is consistent with the WHO (2005) guideline. No adverse findings were reported.

Immunotoxicity

No specific immunotoxicity studies were performed, although the repeat dose toxicity studies did not indicate rLP2086-related changes in circulating levels of immune system cells or changes in immune system organs.

Phototoxicity

No phototoxicity studies were performed. There is no apparent basis for thinking that rLP2086 could be phototoxic.

Impurities

The proposed limits for the process-related impurities endotoxin and residual DNA are acceptable and results for host cell protein levels in several batches of rLP2086 suggest that the sponsor is using an 'appropriate manufacturing process'.

Paediatric use

Trumenba is indicated for individuals 10 years and older. No specific studies were performed with juvenile animals; however, dosing of pregnant rabbits with rLP2086 indicated no apparent effects of the vaccine or induced antibodies on fetal development.

[16] Pregnancy Category B2 is defined as: Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed.
Studies in animals are inadequate or may be lacking, but available data show no evidence of an increased occurrence of fetal damage.

[17] Pregnancy Category B1 is defined as: Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed.
Studies in animals have not shown evidence of an increased occurrence of fetal damage.

the nonclinical evaluator is in general concordance with the sponsor's draft Risk Management Plan (RMP).

Nonclinical summary and conclusions

- The submitted nonclinical dossier was in accordance with the WHO (2005) guideline on the nonclinical evaluation of vaccines.[11] The overall quality of the nonclinical dossier was high. The pivotal repeat dose and reproductive toxicity studies were GLP compliant, used the clinical vaccine administration route, and were performed in a species that has a strong immune response to rLP2086.
- An extensive panel of primary pharmacology studies were performed that examined: (1) the identification of fHBP as a candidate antigen; (2) the development of methods for the quantification of surface expression of fHBP on MnB strains; (3) the immunogenicity of different forms of fHBP; (4) the characterisation of fHBP variant type and other genetic markers in a large panel of MnB strains collected in America and Europe from IMD cases occurring from 2000-2006; (5) the comparison of the fHBP variant type of the sponsor's panel of MnB strains with that of more recent IMD derived MnB strains collected in America, Canada, Europe, and the UK and with carriage isolates collected in Canada, Europe, and the UK from adolescents and young adults; and (6) the sensitivity in the serum bactericidal assay (SBA) of MnB strains, from both the sponsor's 2000–2006 panel and more recent collections, to sera from rabbits and humans vaccinated with Trumenba. These studies support the proposed clinical indication for Trumenba.
- Clinical hSBA testing (a surrogate marker of efficacy) was based on 4 primary MnB test strains and 10 secondary strains from the 'Extended MnB SBA strain pool' (n = 1814) selected from disease causing strains isolated in Europe and/or the United States (US). In a response to a request for Australian strain data, the sponsor provided a publication which indicated that these strains were representative of disease causing strains in circulation in Western Australia during 2000 to 2014. No data were available for the eastern Australian states.
- Active protection studies were not performed as *N. meningitidis* is a human specific pathogen. The effectiveness of Trumenba in humans was determined using the human complement serum bactericidal assay (hSBA). Post-vaccination human serum pools showed bactericidal activity against 82% (89/109) of strains in a randomly selected MnB panel.
- Secondary pharmacodynamics and safety pharmacology studies were not performed. The WHO (2005) vaccine guideline[18] suggests that they are not normally necessary for the safety assessment of a vaccine.
- Pharmacokinetic studies were not performed and would not normally be considered relevant to the testing/development of a vaccine (WHO 2005).
- Pharmacokinetic drug interaction studies were not performed and would not normally be considered relevant to the testing/development of a vaccine.
- Two repeat dose toxicity studies were performed using rabbits of both sexes given five IM doses of bivalent rLP2086 at two week intervals. Groups received 100 or 400 µg total protein per dose in the first study and 400 µg per dose in the second study. Such doses produced no consistent effects on body weight, organ weights, or gross pathology. Slight to moderate inflammation could be induced by the vaccine at injection sites. Such events were generally reversible and not considered adverse.

[18] WHO guidelines on nonclinical evaluation of vaccines. WHO Technical Report Series No. 927, Annex 1, 2005.

Dosing at 400 µg did, however, produce an approximate doubling of fibrinogen concentration at two days post dose. This increase is suggestive of an acute phase inflammatory reaction. More modest increases of fibrinogen concentration have been noted previously in humans following vaccination (including with other vaccines against *N. meningitidis*). The response seen in rabbits is not considered adverse as it occurred at much higher doses than are recommended for humans and the effect was transitory. Dosing at 400 µg also produced a modest (< 0.5 °C) pyrogenic response, although because body temperature was only measured at 4 and 24 hours post dose it was possible that the peak of the response was missed.

- No genotoxicity or carcinogenicity studies were conducted. This is considered acceptable.
- Two reproductive toxicity studies using female rabbits given four IM doses of bivalent rLP2086 (two doses given pre-mating plus doses on GD 10 and GD 24) at 200 µg total protein per dose. Post dosing antibody titres in the maternal and fetal circulation were similar, indicating that antibodies to rLP2086 cross the placenta. Both studies showed no effect of vaccine dosing on mating or fertility rates or on various other maternal and fetal/pup parameters including fetal variations/malformations and pup development.
- Local tolerance at the injection site was monitored as part of both the repeat dose and reproductive toxicity studies. This is consistent with the WHO (2005) nonclinical guideline for vaccines. No adverse findings were reported.
- The proposed limits for the process-related impurities endotoxin and residual DNA are acceptable and results for host cell protein levels in several batches of rLP2086 suggest that the sponsor is using an 'appropriate manufacturing process'.

Conclusions and recommendation

- The studies presented comply with the requirements of the WHO (2005) vaccine guideline.
- Vaccine clinical efficacy was assessed using a panel of MnB strains representative of those found in America, Canada, United Kingdom, and Europe. The fHbp variants expressed on those MnB strains were also prevalent on Western Australian MnB disease causing strains collected during 2000 to 2014. Data were not available for the eastern states.
- Two GLP compliant repeat dose toxicity studies, using the clinical and a related formulation of the vaccine, showed significant increases in fibrinogen concentration in rabbits given relatively high doses of vaccine. Effects of similar magnitude are not expected in patients. A modest pyrogenic response was also noted, which may be of concern if future paediatric use of the vaccine is proposed.
- Trumenba is not considered to pose a genotoxic or carcinogenic hazard.
- There was no evidence for induction of reproductive toxicity in pregnant rabbits by Trumenba. Accordingly, categorisation as Pregnancy Category B1 is considered appropriate.
- There are no nonclinical objections to registration.

The non clinical evaluator also made recommendations relating to the draft PI but these are beyond the scope of the AusPAR.

V. Clinical findings

A summary of the clinical findings is presented in this section. Further details of these clinical findings can be found in Attachment 2.

Introduction

The proposed indication is individuals 10 years and older for active immunisation to prevent invasive meningococcal disease caused by *N. meningitidis* serogroup B.

Dosage forms and strengths

The Trumenba vaccine is a bivalent vaccine presented as a sterile liquid suspension composed of rLP2086 (subfamily A and B proteins formulated at 120 µg/mL per subfamily, in 10 mM histidine buffer, pH 6.0, 150 mM sodium chloride (NaCl) with 0.5 mg/mL aluminium as aluminium phosphate (AlPO4)) provided for injection in prefilled syringes.

Dosage and administration

The primary vaccination schedule consists of 2 doses (0.5 ml each) administered at 0 and 6 months. The schedule for individuals at increased risk of invasive meningococcal disease is 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.

The proposed shelf life and storage condition for Trumenba is 3 years when stored at 2 to 8 °C in a glass prefilled syringe.

Information on the condition being treated

N. meningitidis serogroup B (MnB) is a significant cause of serious endemic meningococcal disease worldwide and can epidemiologically manifest as prolonged outbreaks or as sudden, unpredictable outbreaks. MnB disease is often devastating with sudden onset, fast progression and may result in permanent significant clinical long term sequelae (neurological impairment, hearing loss, renal failure, and/or skin, digit and limb loss) in those that survive. *N. meningitidis* serogroup B (MnB) is a significant cause of serious endemic meningococcal disease worldwide and can epidemiologically manifest as prolonged outbreaks or as sudden, unpredictable outbreaks.

Current treatment options

The main treatment option is antibiotics for meningococcal infection. It still however has a significant mortality and morbidity associated with it despite even early antibiotic therapy. There is one licensed MnB vaccine currently available in Australia (and many other countries). This is now routinely being offered to groups ‘at risk’ for outbreaks in many countries (such as the USA).

Clinical rationale

MnB is now a vaccine preventable disease. There is already one MnB vaccine registered and available in Australia. A recombinant, multicomponent MnB vaccine (4CMnB) was included on the Australian Register of Therapeutic Goods (ARTG) on 14 August 2013. Availability of vaccine supply is an important consideration during endemic use or for outbreak control. Sufficient supply avoids potential vaccine shortages and thus, from a

public health perspective, availability of more than one supplier of broadly protective MnB vaccines is important.

Guidance

As clinical endpoint efficacy studies were not feasible, the sponsor tested, in accordance with the Committee for Medicinal Products for Human Use (CHMP) Scientific Advice EMEA/H/SA/1162/1/2008/111, the vaccine's ability to elicit serum bactericidal activity (SBA), a correlate of protection against invasive meningococcal disease (IMD). The serum bactericidal assay using human complement (hSBA) is a functional serological assay used to measure SBA, and responses in hSBA serve as the surrogate marker of vaccine efficacy.

Contents of the clinical dossier

This application includes data from 15,294 subjects who received at least one dose of bivalent rLP2086, administered either as a single agent or given concomitantly with a licensed vaccine; 6486 subjects in Europe received at least 1 dose of bivalent rLP2086. These participants were enrolled in one of the following 11 studies included in this dossier:

- Two Phase III immunogenicity and safety studies using 4 primary and 10 secondary MnB test strains; Studies B1971009 and B1971016.
- One Phase III study assessing safety only; Study B1971014.
- Five Phase II immunogenicity and safety studies:
  - One Phase II study that examines various 2 and 3 dose schedules and supports the 2 dose (0, 6 month) posology for routine vaccination; Study B1971012.
  - Three Phase II concomitant vaccine Studies B1971010 (Repevax[19]), B1971011 (Gardasil[20]), and B1971015 (Menactra[21] and Adacel[22])).
  - One Phase II study in laboratory workers; Study B1971042.
- 3 early Studies B1971003, B1971004, and B1971005-Stage 1 and Stage 2 (Stage 2 tested persistence of immune response up to 48 months after the last vaccination using the 4 primary test strains. During Stage 2 testing, response for Stage 1 time points was also measured using the 4 primary test strains)).

The clinical module includes reports for all the above studies. It also contains:

- Case report forms with safety data.
- Safety integrated analysis report, immunogenicity integrated analysis report.
- Literature references.

The dossier also included a Clinical Overview, Summaries of Clinical Pharmacology, Clinical Efficacy and Clinical Safety and literature references.

[19] Repevax is a low-dose diphtheria, tetanus, acellular pertussis, and inactivated poliomyelitis virus vaccine (dTaP/IPV)
[20] Gardasil is a human papilloma virus vaccine (HPV)
[21] Menactra is a meningococcal (Groups A, C, Y, and W-135) polysaccharide diphtheria toxoid conjugate vaccine (MCV4)
[22] Adacel is a tetanus, low-dose diphtheria, and low-dose acellular pertussis vaccine (Tdap)

Paediatric data

Seven of the studies submitted in this application include paediatric data including one of the pivotal immunogenicity studies and the Phase III safety study.

Good clinical practice

All clinical studies evaluating the MnB rLP2086 vaccine comply with the Quality Standards of the International Conference on Harmonization (ICH) guidelines,[23], the Food and Drug Administration (FDA) guidelines for Good Clinical Practice (GCP),[24] European Union (EU) Directive 2001/20/EC[25] and the EMA guidelines on clinical evaluation of new vaccines clinical study reports in the submission state the studies complied with CPMP/ICH/135/95 Note for Guidance on Good Clinical Practice.[26]

Pharmacodynamics

In accordance with the EMA Guideline,[27] the pharmacodynamic profile for the Trumenba vaccine was defined by its immunogenicity profile.

Dosage selection for the pivotal studies

Study B1971003 was a Phase I/II, single arm, open label study that recruited a total of 60 Australian adult subjects (aged 18 to ≤ 40 years) who received the final formulation of 120 µg of bivalent rLP2086 given on a 0, 1, 6 month schedule. This population was chosen to establish the appropriate dose in adults before a clinical trial in adolescents could be designed. This study was also designed for serological assay development. An exploratory objective of this study was to assess the immunogenicity of the 120 µg dose formulation of bivalent rLP2086 as measured by hSBA and/or levels of antibody specific to LP2086[28] antigens. Functional antibody responses using hSBA were performed with the following MnB test strains: PMB1745 (A05), which expresses an fHBP variant homologous to one of bivalent rLP2086 antigens, rLP2086-A05, and PMB17 (B02), which expresses an fHBP variant that is heterologous to the other vaccine antigen, rLP2086-B01. Safety was evaluated based on local reactions and systemic events occurring within 7 days after each vaccination and recorded by the subject in an electronic diary (e-diary). Adverse events (AEs), serious adverse events (SAEs), newly diagnosed chronic medical conditions (NDCMCs), were collected at protocol specified time periods.

Study B1971004 was a Phase I study conducted in the US in which 48 subjects (aged 18 to ≤ 40 years) were randomised to an open label, parallel group clinical trial with 3 bivalent rLP2086 dose groups (60 µg, 120 µg, or 200 µg) and a control group. The subjects in the bivalent rLP2086 groups received the final vaccine formulation using a 0, 2, 6 month schedule. The study control group received Tdap[29] vaccine (Adacel) at Month 0 and saline at subsequent injection visits. This trial is the only study in the program with routine assessment of clinical pathology laboratory assays. Immunogenicity of 60, 120, and 200 µg doses of bivalent rLP2086 was assessed by immunoglobulin G (IgG) titres that were elicited by bivalent rLP2086. Safety was evaluated as described for Study B1971003.

[23] http://www.ich.org/products/guidelines/efficacy/article/efficacy-guidelines.html (accessed October 2017)
[24] http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/ (accessed October 2017)
[25] http://ec.europa.eu/health/human-use/clinical-trials/directive/index_en.htm (accessed October 2017)
[26] CPMP/ICH/135/95 Note for Guidance on Good Clinical Practice
[27] EMEA/CHMP/VWP/164653/2005. Committee for Medicinal Products for Human Use CHMP; Guideline on Clinical Evaluation of New Vaccines. 18 October 2006.
[28] LP2086 = lipoprotein fHBP vaccine antigen
[29] Tdap = tetanus, low-dose diphtheria, and low-dose acellular pertussis vaccine

Study B1971005 is a Phase II, randomised, single blind, placebo controlled dose selection study that enrolled 539 European or Australian subjects aged 11 to ≤ 18 years who received bivalent rLP2086 using a 0, 2, 6 month schedule. The control group received saline at each vaccination visit.

Stage 1: Subjects were randomised to 60 µg, 120 µg, or 200 µg bivalent rLP2086, or saline groups and safety and immunogenicity were compared across dosing groups to determine the final vaccine dose (120 µg) that would be used in all subsequent studies. Functional antibody responses, expressed as interpolated hSBA titres, were determined using qualified hSBAs 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). Stage 1 (Vaccination phase) was completed prior to agreement on the Phase III test strains and endpoints, and hence the Phase III endpoints initially were not available for Stage 1 of this study. However, during Stage 2 of Study B1971005, hSBA testing was performed using samples collected at some Stage 1 time points, and results are included in the across study analyses. Safety in Stage 1 was evaluated as described for other Phase II studies.

Stage 2 (persistence of immune response): The persistence stage of the study was designed to evaluate the duration of the MnB-specific immune responses for up to 4 years after the third vaccination with bivalent rLP2086. Only Stage 1 subjects who received bivalent rLP2086 at the dose levels selected for the second stage of the study (120 µg and 200 µg), and saline control recipients, were invited to continue in Stage 2, which was open label. The results for Stage 2 included immunogenicity data from a study visit conducted at 6 months and 1 week after the third vaccination with bivalent rLP2086 during Stage. Immunogenicity of bivalent rLP2086 was measured by validated hSBAs with the 4 primary MnB test strains PMB80 (A22), PMB2001 (A56), PMB2948 (B24), and PMB2707 (B44) using blood samples collected at 6 months + 1 week, and 12, 24, and 48 months after Dose 3. Stage 2 persistence testing using the validated hSBAs and 4 primary test strains was also performed on samples collected at Stage 1 time points (pre immunisation and 1 month post dose 3). In the safety evaluation for Stage 2, SAEs were reported for 7 days following each blood draw, from Visit 8 onward.

Efficacy

Studies providing immunogenicity data

The following studies contributed to the efficacy data:

- Early studies;
  - A Phase I Study (Study B1971004) and a Phase I/II Study (Study B1971003) were conducted in subjects 18 to 40 years of age.
  - A Phase II proof of concept and dose selection, Study B1971005 Stage 1 was conducted in subjects 11 to 18 years of age where the final dose level of 120 µg of bivalent rLP2086 was chosen for all subsequent studies.
  - Study B1971005 Stage 2 also evaluated immunogenicity of bivalent rLP2086 for up to 48 months after the last dose. As part of the Stage 2 evaluation of bactericidal antibody persistence, hSBAs with the 4 primary MnB test strains were performed with sera from essentially all Stage 2 subjects and a subset of sera from Stage 1 subjects (limited serum availability from Stage 1 subjects).
- Phase II studies
  - Phase II study evaluating various 2 and 3 dose vaccination schedules

- § Study B1971012 was conducted in adolescents 11 to < 19 years of age to assess the immunogenicity and safety of rLP2086 when administered in two different 3 dose regimens (0, 1, 6 month or 0. 2, 6 month schedule) and in three different 2 dose regimens (0, 2 month, 0, 4 month, or 0, 6 month schedules).

– Phase II concomitant vaccine studies after the final dose level of 120 µg of bivalent rLP2086 was established, 3 Phase IIa concomitant vaccine administration Studies were initiated in subjects 10 to 18 years of age.[30].

- § Study B1971010; concomitant with Repevax
- § Study B1971011; concomitant with Gardasil
- § Study B1971015; concomitant with Menactrac and Adacel

– Phase II study in laboratory workers, Study B1971042 was initiated in laboratory workers 18 to 65 years of age.

· Phase III studies

After the safety and immunogenicity of bivalent rLP2086 was established, three Phase III studies were conducted:

– B1971009, a lot consistency immunogenicity and safety study in adolescents 10 to 18 years old

– B1971016, an immunogenicity and safety study in young adults 18 to 25 years old

– B1971014, a large scale safety study in adolescents and young adults 10 to 25 years old in which immunogenicity was not evaluated.

For the full clinical evaluation report please see Attachment 2.

Evaluator's conclusions on efficacy

In the major study evaluating several 2 and 3 dose schedules, Study B1971012, the data show that the benefit of bivalent rLP2086 is substantial and is dependent on the vaccine administration schedule. Close administration of the first 2 doses is associated with a lower response than observed with administration of the 2 doses at the greater interval of 6 months where the response is not substantially different from that after 3 doses. This supports the dosing premise that when the risk of disease is low, as it is for endemic disease, vaccination with bivalent rLP2086 administered on a 0, 6 month schedule will provide a protective immune response for a high proportion of vaccinees. During an epidemic, or for those at high risk of disease for biological reasons (for example, due to asplenia or complement deficiency), rapid induction of a protective immune response can be achieved with the first 2 doses given 1 to 2 months apart, and the third dose given at least 4 months later to maximise protection. The vaccine is given in both the 2 and 3 dose schedules in the USA.

The primary immunogenicity objective common to both Phase III studies, to assess the immune response as measured by hSBA performed with 4 primary MnB test strains (PMB80 [A22], PM62001 [A56]), PMB2948 [B24], and PM62707 [B44]), was achieved. The lower limit of the 2-sided 95% Cl for the proportion of subjects in Group 1 (bivalent rLP2086 recipients) with a ≥ 4 fold rise in hSBA titre for each of the 4 primary MnB test strains at 1 month after Vaccination 3 and for the composite hSBA response was greater than the corresponding pre-specified lower bound threshold set for each study.

[30] Clarification; In Study 1015 the subjects were only 10 to 12 years of age.

The co-primary objective of Study B1971009 showed equivalence of bivalent rLP2086 in the 3 lots from the manufacturing process. The 95% Cl for all 3 pairwise geometric mean ratio (GMR) comparisons between lots of bivalent rLP2086 (Lot 1: Lot 2, Lot 2: Lot 3, Lot 1: Lot 3) were within the interval (0.5, 2.0} required to demonstrate equivalence for both test strains PMB80 (A22) and PM62948 (B24). These results support the conclusion that bivalent rLP2086 from 3 lots of the final manufacturing process induces consistent hSBA immune responses to both MnB test strains; hence, the lot consistency objective was also achieved.

In both Phase III studies a high proportion of subjects achieved an hSBA titre ≥ lower limit of quantitation (LLOQ) (that is, hSBA titre equal to 1:8 or 1:16, depending on the strain), and a substantial increase was observed in hSBA geometric mean titres (GMTs) for each the 4 primary test strains, after 2 or 3 doses of bivalent rLP2086 in the evaluable immunogenicity population. In Study B1971009, for example, the proportion of subjects in vaccine Group 1 (bivalent rLP2086 recipients) with hSBA titres ≥ LLOQ ranged from 64.0% to 99.1% after Vaccination 2 and from 87.1% to 99.5% after Vaccination 3. The hSBA GMTs in Group 1 increased substantially from Baseline after the second vaccination and rose again after the third vaccination; hSBA GMTs after Dose 2 and Dose 3, respectively, were 50.4 and 86.8 for PM680 (A22), 131.2 and 222.5 for PM62001 (A56), 14.3 and 24.1 for PMB2948 (B24), and 17.1 and 50.9 for PM62707 (B44). A similar pattern was observed in young adults in Study B1971016.

A secondary objective common to both Phase III studies was to describe the immune response as measured by hSBA performed with 10 secondary MnB test strains expressing rLP2086 subfamily A or B proteins, measured 1 month after the third vaccination with bivalent rLP2086 in the evaluable immunogenicity population and after the second vaccination in the post Vaccination 2 evaluable immunogenicity population (that is, including subjects receiving 2 doses of bivalent rLP2086, irrespective of receipt of a third dose). The majority of subjects in each study achieved hSBA titres ≥ LLOQ and robust GMTs after the second and third vaccinations with bivalent rLP2086 for all secondary MnB test strains, demonstrating a pattern of response similar to that observed for the 4 primary test strains. In Study B1971009, the proportion of subjects in Group 1 (bivalent rLP2086 recipients) with hSBA titres ≥ LLOQ ranged from 61.1% to 100.0% after Vaccination 2 and 75.1% to 98.6% after Vaccination 3; hSBA GMTs for the 10 secondary test strains were substantially higher than Baseline titres after the second and third vaccinations. The results for the 10 secondary strains in Study B1971016 were comparable to those of Study B1971009.

Analyses of the association between the primary strain and the secondary strain responses in both Phase III studies showed that, within the same fHBP subfamily, positive correlations were observed between the primary strain hSBA responses and secondary strain hSBA responses at 1 month after Vaccination 3. The positive predictive value (PPV) analyses, the most reliable and clinically relevant of the analyses of primary-secondary strain associations, were conducted to determine whether immune responses to the primary strains (responses defined as hSBA titres ≥ the assays' LLOQs) were predictive of a more general response to MnB strains. Primary strain responses proved to be highly predictive of secondary strain responses within the same subfamily, at 1 month after both the second and third vaccinations, based on the PPV analysis. For subfamily A strains, PPVs in Study B1971009 ranged from 64.4% to 100.0% after Vaccination 2 and from 75.6% to 99.6% after Vaccination 3. For subfamily B strains, the PPVs ranged from 78.9% to 100.0% after Vaccination 2 and from 85.5% to 99.6% after Vaccination 3. Results were similar for each strain in Study B1971016.

The predictive power of the primary strain responses was also present among subjects negative in hSBAs with primary and secondary strains at Baseline, indicating that Baseline hSBA positivity did not influence the magnitude of the PPVs. Thus, the PPV analysis,

supported by results of the correlation and concordance analyses, provides assurance that the observed immune responses to the primary strains are indicative of broad protection against diverse MnB disease causing strains.

In three Phase II Studies, B1971010, B1971011, and B1971015, the immunogenicity of bivalent rLP2086 has been shown to be unchanged by concomitant administration of other vaccines (dTap-IPV[31], HPV4, or Tdap and MCV4[32] respectively); similarly, the immune responses to the concomitant vaccines were unaffected in a clinically meaningful way when administered with bivalent rLP2086.

Safety

Studies providing safety data

The primary data supporting the safety and tolerability of bivalent rLP2086 are from subjects in the program's 8 randomised controlled Studies (Studies: B1971004, B1971005, B1971009, B1971010, B1971011, B1971014, B1971015 and B1971016). Additional data are from subjects in the 3 uncontrolled Studies (Studies B1971003, B1971012 and B1971042). The overall safety dataset comprises a total of 15,294 subjects who received at least 1 vaccination of bivalent rLP2086 at any dose level and using any dosing schedule; among these, 15,053 received bivalent rLP2086 at the 120 µg dose level, using any schedule.

Safety was assessed on the basis of information regarding solicited local and systemic events as well as unsolicited adverse events. In the core safety dataset (comprising data from the 8 controlled Studies: B1971004, B1971005, B1971009, B1971010, B1971011, B1971014, B1971015 and B1971016, local reactions and systemic events, in general, were reported in a higher proportion of subjects receiving 120 µg of bivalent rLP2086 as compared with saline control.

Patient exposure

In this application includes data from 15,294 subjects who received at least one dose of bivalent rLP2086, administered either as a single agent or given concomitantly with a licensed vaccine. Data are also presented for 5,509 subjects in control groups who received either saline alone, licensed vaccine alone, or saline and a licensed vaccine. These participants were enrolled in one of the following 11 studies (Table 3):

- Two Phase III immunogenicity and safety studies using 4 primary and 10 secondary MnB test strains (Studies B1971009 and B1971016).
- One Phase III study assessing safety only (Study B1971014).
- Five Phase II immunogenicity and safety studies.
  - One Phase II study that examines various 2 and 3 dose schedules and supports the 2 dose (0, 6 months) posology for routine vaccination (Study B1971012).
  - Three Phase II concomitant vaccine Studies B1971010 [Repevax], B1971011 [Gardasil], and B1971015 [Menactra and Adacel].
  - One Phase II study in laboratory workers (Study B1971042).
- 3 early Studies B1971003, B1971004, and B1971005; Stage 1 and Stage 2.

[31] dTap-IPV = low-dose diphtheria, tetanus, and low-dose acellular pertussis vaccine - inactivated poliomyelitis virus vaccine
[32] MCV4 = quadrivalent meningococcal polysaccharide conjugate vaccine

In a breakdown according to age, These 11 studies included:

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

Table 3: Number (%) of vaccinated subjects by study; subjects who received at least 1 dose of bivalent rLP2086 final for formulation (120 µg dose level) or control on a 0, 2, and 6 month schedule; Core Studies

	Dose 1		Dose 2		Dose 3	
	n (%)		n (%)		n (%)	
Study	rLP2086[a]	Control[b]	rLP2086[a]	Control[b]	rLP2086[a]	Control[b]
All vaccinated subjects[c]	13284 (100.0)	5509 (100.0)	12271 (100.0)	5180 (100.0)	11441 (100.0)	4897 (100.0)
B1971004	12 (0.1)	12 (0.2)	12 (0.1)	9 (0.2)	10 (0.1)	7 (0.1)
B1971005	198 (1.5)	121 (2.2)	194 (1.6)	118 (2.3)	191 (1.7)	116 (2.4)
B1971010	374 (2.8)	378 (6.9)	342 (2.8)	359 (6.9)	331 (2.9)	351 (7.2)
B1971011	1982 (14.9)	501 (9.1)	1854 (15.1)	476 (9.2)	1740 (15.2)	452 (9.2)
B1971009	2693 (20.3)	897 (16.3)	2570 (20.9)	860 (16.6)	2462 (21.5)	835 (17.1)
B1971014	3796 (28.6)	1908 (34.6)	3529 (28.8)	1806 (34.9)	3313 (29.0)	1710 (34.9)
B1971015	1758 (13.2)	870 (15.8)	1601 (13.0)	819 (15.8)	1505 (13.2)	777 (15.9)
B1971016	2471 (18.6)	822 (14.9)	2169 (17.7)	733 (14.2)	1889 (16.5)	649 (13.3)

Safety issues with the potential for major regulatory impact

Immunogenicity and immunological events

Among the 8 controlled studies, potential autoimmune conditions among subjects who received 120 µg bivalent rLP2086 on a 0, 2, 6 month schedule were observed in 0.36% (48 of 13,284 vaccinated subjects) compared to 0.34% in controls (19 of the 5,509 subjects). Similarly, the proportion of subjects who reported potential neuroinflammatory conditions was 0.10% (13 of 13,284 subjects) for subjects who were vaccinated with 120 µg bivalent rLP2086 on a 0, 2, 6 month schedule compared to 0.11% (6 of 5,509 subjects) among controls.

Confirmed autoimmune conditions were reported in 0.14% (18 of 13,284 subjects, 95% confidence interval (CI): 0.08%, 0.21%) of subjects receiving 120µg bivalent rLP2086 on a 0, 2, 6 month schedule compared with 0.11% (6 of 5509 subjects, 95% CI: 0.04%, 0.24%) of subjects receiving control vaccine. The difference in proportions between the vaccine groups was 0.03% (95% CI: -0.11%, 0.13%, p = 0.642), supporting the conclusion that there was no significant difference between the 120 µg bivalent rLP2086 group and the control group in the rate of autoimmune disease.

In the core safety dataset, confirmed neuroinflammatory conditions were reported in 0.06% (8 of 13,284 subjects, 95% CI: 0.03%, 0.12%) of subjects receiving 120 µg bivalent rLP2086 compared with 0.07% (4 of 5,509 subjects, 95% CI: 0.02%, 0.19%) of subjects receiving control vaccine. The difference in proportions between vaccine groups was -0.01% (95% CI: -0.13, 0.06, p = 0.760), supporting the conclusion that there was no significant difference between the 120 µg bivalent rLP2086 group and the control group in the rate of neuroinflammatory conditions. The most commonly reported neuroinflammatory condition in this dataset was seventh cranial nerve paralysis (8 of 12 subjects with neuroinflammatory conditions). Six of the cases were reported as Bell's palsy, 1 event was reported as right peripheral facial paralysis, and 1 event was reported as infranuclear facial nerve paralysis. Six of these occurred in patients who received rLP2086 and 3 of these were assessed by the investigator as likely to be related to vaccine.

Safety in special populations

Although pregnancy was an exclusion criterion at enrolment, across all 11 studies, a total of 172 subjects became pregnant during the studies or had partners who became pregnant during the studies: among the 15,294 subjects who received bivalent rLP2086,

pregnancies were reported for 127 subjects (0.83%) (124 subjects who received 120 µg and 3 subjects who received 200 µg); and among the 5,509 subjects who received control vaccine, pregnancies were reported for 45 subjects (0.82%). Information regarding pregnancy outcome was available for 121 of the 172 pregnancies (70.3%). Among the 121 pregnancies with known outcomes, live births were documented for 81 subjects (66.9%), most of which were full term. Fetal loss was reported for 40 (33.1%) of the 121 cases with known outcomes; 21 (52.5%) were elective terminations and 17 (42.5%) were spontaneous abortions. The remainder of foetal loss cases were therapeutic abortion (1 subject who received control vaccine) and stillbirth (1 subject who received bivalent rLP2086). Most pregnancies were distal to study vaccination. Among the 94 pregnancies with an estimated conception date, 67 (71.3%) were distal and 27 (28.7%) were proximal to vaccination. In the core safety dataset, outcome information was available for 116/164 pregnancies. Outcome rates were similar between the bivalent rLP2086 and control groups. Among 85 pregnancies reported in the bivalent rLP2086 group, fetal loss occurred in 26 (30.6%) and live births occurred in 59 (69.4%); in the control group, among the 31 pregnancies reported, fetal loss occurred 12 (38.7%) and live births occurred in 19 (61.3%). In the bivalent rLP2086 group, among the 59 births, 51 (86.4%) were full term and 8 (13.6%) were premature births; and in the control group, all 19 births (100.0%) were full term.

Post marketing data

Bivalent rLP2086 (Trumenba) vaccine was approved in the United States on 29 October 2014 and launched on 17 November 2014. The total estimated unit distribution in the United States for bivalent rLP2086 vaccine from launch through to the 31 October 2015 is approximately 159,320 doses. 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. Cumulatively, a total of 190 cases (597 AEs) were received from spontaneous sources through the cut-off date of 31 October 2015. Of these, 122 cases were medically confirmed. The most frequently reported AEs (> 4% of reports), regardless of System Organ Class (SOC), were as follows: headache, vaccination site pain, pyrexia, chills, pain, fatigue, pain in extremity, nausea, erythema, dizziness, vomiting, malaise, joint range of motion decreased, myalgia, inappropriate schedule of drug administration, vaccination site rash, vaccination site swelling, incomplete course of vaccination, and vaccination site erythema.

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.

Evaluator's conclusions on safety

Local reactions (pain at injection site, redness) and acute systemic events (headache, myalgia, fatigue, fever) were common. Most local reactions and systemic events were mild or moderate in severity and resolved within 1 to 3 days after vaccination. Pain at the injection site was the most frequently reported local reaction, but 0.30% of subjects withdrew from the core studies due to injection site pain. Fatigue, headache, and muscle pain were the most frequently reported systemic events in the 120 µg bivalent rLP2086 group and in the control groups. Fever > 40.0 °C was reported for only 2 subjects who received 120 µg bivalent rLP2086 and for 1 subject who received control vaccine in the core studies. Potentiation (worsening of reactions with increasing doses) of reactogenicity events was not observed with subsequent bivalent rLP2086 doses. The types of unsolicited AEs reported were generally illnesses and conditions common or expected

among healthy individuals of similar age in the general population. Safety data in the overall safety dataset (the core safety dataset plus from the 3 uncontrolled studies: Studies B1971003, B1971012 and B1971042) were consistent with results observed in the core studies.

In addition, the observed frequencies of AEs were generally similar in the group receiving rLP2086 with a concomitant vaccine compared with those in the groups receiving rLP2086 alone or the other vaccine(s) alone.

Analysis of the rates of autoimmune diseases and neuroinflammatory conditions reported among all clinical trials demonstrated a low incidence of autoimmune and neuroinflammatory conditions overall. In addition, among the 8 studies where a control group was available, no significant differences were observed in the proportions of subjects with autoimmune diseases or neuroinflammatory conditions between subjects receiving 120 µg bivalent rLP2086 compared to control. Safety was also evaluated 4 years after vaccination with 3 doses of bivalent rLP2086, and no additional safety signal was detected.

Based on the safety data summarised in this application, bivalent rLP2086 vaccine appears to be safe and well tolerated in the requested population and the ADRs fairly predictable.

First round benefit-risk assessment

First round assessment of benefits

Table 4: First round assessment of benefits

Benefits	Strengths and Uncertainties
Vaccination with bivalent rLP2086 is being proposed for the prevention of invasive disease caused by *N meningitidis* serogroup B in individuals aged 10 years and older based on immunogenicity and safety results from Phase II and Phase III studies conducted in this population. The evaluation of immune response to bivalent rLP2086 in these studies includes measurement of vaccine elicited hSBA responses, the recognised surrogate of meningococcal vaccine efficacy. The hSBA responses to the 10 secondary strains fully support the immunogenicity conclusion from the hSBA responses seen with the 4 primary MnB test strains. Overall, robust response rates were observed for the 14 MnB test strains, based on the proportion of subjects achieving hSBA titres ≥ LLOQ one month after Vaccinations 2 and 3. In each case, the assay LLOQs were hSBA titres equal to either 1:8 or 1:16, which is more stringent than the recognised correlate of protection (hSBA titre ≥ 1:4). In addition to direct coverage measured in the clinical development program using	As approximately 200 fHBP sequences have been identified, it was necessary to design an approach to measure breadth of coverage across these sequences using the accepted correlate for efficacy. Bacterial test strains for hSBAs that expressed fHBP sequences that were heterologous to the vaccine sequences and represented fHBP diversity were selected to test immunogenicity, providing a reflection of the ability of bivalent rLP2086 to induce a protective response against meningococcal strains expressing fHBP. Thus, the Phase III endpoints were designed to be biologically relevant and capable of establishing whether vaccine elicited responses could confer broad protection against MnB strains. Four endpoints demonstrate the vaccine elicited 4 fold hSBA response to each of the 4 primary MnB test strains, and the fifth is a 'composite' endpoint to assess the proportion of study subjects with hSBA responses to all 4 primary MnB test strains combined. The fHBP variants expressed by the 4

representative disease causing strains, bivalent rLP2086 can provide protection against MnB strains expressing new fHBP variants that have caused recent outbreaks. The evaluation of broad protection also can be assessed by additional statistical analyses of responses to primary and secondary test strains. A post-hoc analysis was conducted to assess whether an immune response to one of the 4 primary MnB test strains predicts an immune response to any one of the 10 secondary test strains. This was expressed as the positive predictive value (PPV). 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 the primary strain that expresses an fHBP variant from the same subfamily[33]). These analyses showed that if a subject responded to a primary subfamily A strain, there was a high probability that the subject also responded to a secondary MnB test strain expressing a subfamily A fHBP after the second and third doses of vaccine (range 64.4% to 100% and 75.6% to 99.6%, respectively). The same held true for subfamily B. Importantly, the positive predictive values were similar whether a subject received 2 or 3 doses of bivalent rLP20786. Data from 3 of the Phase II studies have shown that the robust immunogenicity of bivalent rLP2086 is not impacted by concomitant administration with other vaccines. In Studies, B1971010, B1971011, and B1971015, the immune responses to bivalent rLP2086 remained unchanged by concomitant administration of Repevax, Gardasil, or Tdap and MCV4, respectively; similarly, the concomitant vaccines were unaffected in a clinically meaningful way when administered with bivalent rLP2086. In all 3 studies, the non inferiority criteria were met, and primary objectives achieved, for each MnB test strain and each concomitant vaccine antigen, except for HPV-18 (non-inferiority missed by a small margin). Immune responses elicited by bivalent rLP2086 were generally consistent across age groups and reached protective hSBA levels in adults, as well as adolescents.	primary and 10 secondary MnB 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. To supplement the immunogenicity data obtained with use of the 4 primary MnB test strains, and to confirm the broad coverage of MnB isolates elicited by bivalent rLP2086, 10 secondary MnB SBA test strains were selected and developed in qualified hSBAs to evaluate immune responses in serum from subsets of adolescent or young adult subjects vaccinated with bivalent rLP2086 (Study B1971009 and B1971016, respectively). The group of 10 secondary test strains express fHBP variants that are representative of prevalent fHBP variants expressed in disease causing isolates in Europe, and are different from the variants expressed by the primary test strains and heterologous to the vaccine antigens.

[33] Clarification: The PPV analyses were performed to predict the likelihood of responding to a secondary strain in the same subfamily as the primary strain for which a response was elicited. For example for all subjects who responded to a subfamily B primary strain, the PPV analyses assessed the % of individuals that also responded to a specific subfamily B secondary strain.

First round assessment of risks

Table 5: First round assessment of risks

Risks	Strengths and Uncertainties
The major risks of vaccination are AEs, ADRs, SADRs related to the vaccine. The overall safety dataset, which includes a total of 15,294 subjects who received at least 1 vaccination of bivalent rLP2086 at any dose level and using any dosing schedule; among these, 15,053 received bivalent rLP2086 at the 120 µg dose level using any schedule. Most local reactions and systemic events were mild or moderate in severity and resolved within 1 to 3 days after vaccination. Pain at the injection site was the most frequently reported local reaction, but 0.30% of subjects withdrew from the core studies due to injection site pain in the core studies. Fatigue, headache, and muscle pain were the most frequently reported systemic events in the 120 µg bivalent rLP2086 group and in the control groups. Fever > 40.0 °C was reported for only 2 subjects who received 120 µg bivalent rLP2086 and for 1 subject who received control vaccine in the core studies. Potentiation (worsening of reactions with increasing doses) of reactogenicity events was not observed with subsequent bivalent rLP2086 doses. The types of unsolicited AEs reported were generally illnesses and conditions common or expected among healthy individuals of similar age in the general population.	Review and analysis of the rates of autoimmune diseases and neuroinflammatory conditions reported among 11 clinical trials included in this submission demonstrated a low incidence of autoimmune and neuroinflammatory conditions overall. In addition, among the 8 studies where a control group was available, no significant differences were observed in the proportions of subjects with autoimmune diseases or neuroinflammatory conditions between subjects receiving 120 µg bivalent rLP2086 compared to control. Safety was also evaluated up to 4 years after vaccination with 3 doses of bivalent rLP2086, and no additional safety signal was detected.

First round assessment of benefit-risk balance

The benefit-risk balance of bivalent rLP2086 is favourable for individuals receiving the vaccine on a routine 2 dose schedule (0, 6 months), or on a 3 dose schedule (2 doses given at least 1 month apart, followed by a third dose at least 4 months after the second dose) for individuals at increased risk of meningococcal disease.

First round recommendation regarding authorisation

The evaluator recommended registration for the active immunisation of individuals 10 years and older, to prevent invasive meningococcal disease caused by *Neisseria meningitidis* serogroup B.

There was no second round clinical evaluation.

VI. Pharmacovigilance findings

Risk management plan

The sponsor submitted EU-RMP version 1.0 (19 April 2016; DLP 30 November 2015)[34] with ASA versions 1.0 (10 June 2016) and 1.1 (13 February 2017, with the sponsor's post-first round response) in support of this application.

Summary of RMP evaluation[35]

The proposed Summary of Safety Concerns and their associated risk monitoring and mitigation strategies are summarised below:

Table 6: Summary of safety concerns[36]

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
		Routine	Additional	Routine	Additional
Important identified risks	None	–	–	–	–
Important potential risks	Anaphylactic reactions	ü	–	ü	–
Missing information	Safety in pregnancy and lactation	ü	ü	ü	–
	Vaccine effectiveness	ü	ü*	ü	–
	Vaccine Failure	ü	ü*	ü	–
	Bactericidal response in subjects with terminal complement deficiency	ü	–	ü	–

*Indicates the sponsor has committed to conducting additional pharmacovigilance (effectiveness) studies if Trumenba is used as part of a national immunisation program.

Additional Pharmacovigilance activities proposed are:

· B1971052: Observational pregnancy study in the USA to assess pregnancy outcomes

[34] EU-RMP version 1.4 (21 March 2017, was submitted with pre-ACM response

[35] *Routine risk minimisation* activities may be limited to ensuring that suitable warnings are included in the product information or by careful use of labelling and packaging.
Routine pharmacovigilance practices involve the following activities:
- All suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner;
- Reporting to regulatory authorities;
- Continuous monitoring of the safety profiles of approved products including signal detection and updating of labelling;
- Submission of PSURs;
- Meeting other local regulatory agency requirements.

[36] An updated revised table 'Summary of safety concerns' was negotiated prior to registration. Please see Table 12 below or include the updated information.

- Population-based surveillance of the incidence rates of IMD (Invasive Meningococcal Disease, serogroup B) in collaboration with national agencies if bivalent rLP2086 is used as part of a national immunisation program.

Routine risk minimisation is proposed.

New and outstanding recommendations; Round 2

The recommendations made in the round 1 evaluation are reconciled with the sponsor's responses. There are unresolved, outstanding issues including one critical outstanding recommendation and advice to the Delegate, recommended by both RMP and Advisory Committee on Vaccines (ACV), regarding the PI.

Outstanding recommendation

The sponsor must address the important potential risk of off-label use in children younger than 10 years of age in the ASA and propose adequate risk minimisation.

New recommendations; second round

The sponsor must submit the final agreed EU-RMP when it becomes available and update the ASA accordingly. Any changes compared to the EU-RMP evaluated by the TGA should be described separately.

Wording for conditions of registration

Any changes to which the sponsor has agreed should be included in a revised RMP and ASA. However, irrespective of whether or not they are included in the currently available version of the RMP document, the agreed changes become part of the risk management system.

The Trumenba Risk Management Plan cannot be finalised. Risk management for off-label use in children under the age of 10 years is an outstanding issue.

Other advice to the Delegate

The Delegate is requested to consider the advice from ACV with regard to the Product Information and packaging.

VII. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations:

Introduction

Trumenba is a sterile suspension composed of two recombinant lipidated factor H binding protein (fHBP) variants from *N. meningitidis* serogroup B. fHBP can be categorised into two immunologically distinct subfamilies, fHBP subfamily A and subfamily B, Trumenba is composed of fHBP variants from each subfamily (A05 and B01). fHBP is one of many proteins found on the surface of meningococci and contributes to the ability of the bacterium to avoid host defences. The susceptibility of serogroup B meningococci to complement mediated, antibody dependent killing following vaccination with Trumenba is dependent on the ability of elicited antibodies to bind to antigenically diverse fHBP variants and the amount of fHBP expressed on the surface of the invading meningococci.

Overseas regulatory history

Trumenba was initially approved in the United States (US) in October 2014 based on Phase II data under the Accelerated Approval regulations. As a condition of the Accelerated Approval license, the sponsor committed to submit the results of the Phase III studies. The Phase III Studies B1971009, B1971016 and B1971014 have now been submitted to FDA and are included in this dossier.

In June 2017, Trumenba was approved by the EMA for the indications below:

> *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 EMA public assessment report is publically available.[37]

Quality

All the relevant quality evaluations have been completed, and there are no outstanding issues. There are no objections on quality grounds to the approval of Trumenba (Meningococcal group B vaccine). Proposed conditions of registration are detailed in the Quality Summary.

Nonclinical

The submitted studies comply with the requirements of the WHO (2005) vaccine guideline.[11] The primary pharmacology studies showed vaccine activity *in vitro* against contemporary strains of MnB. However, vaccine clinical efficacy was assessed using a panel of MnB strains representative of America, Canada, United Kingdom, and Europe and there was no information on prevalent Australian strains.[38] Two GLP-compliant repeat dose toxicity studies, using the clinical and a related formulation of the vaccine, showed significant increases in fibrinogen concentration in rabbits given relatively high doses of vaccine. Effects of similar magnitude are not expected in patients. A modest pyrogenic response was also noted, which may be of concern if future paediatric use of the vaccine is proposed. Trumenba is not considered to pose a genotoxic or carcinogenic hazard. There was no evidence for induction of reproductive toxicity in pregnant rabbits by Trumenba. Accordingly, categorisation as Pregnancy Category B1 is considered appropriate.

There are no nonclinical objections to registration.

Clinical

The clinical dossier included 11 clinical studies:

· Earlier phase studies (3 studies) using different doses /schedules

[37] http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_Public_assessment_report/human/004051/WC500228997.pdf ;(accessed July 2017)

[38] Clarification: The fHbp variants expressed on those MnB strains were also prevalent on Western Australian MnB disease causing strains collected during 2000 to 2014. Data were not available for the eastern states

  - Studies B1971003, B1971004, and B1971005 (Stage 1 and Stage 2) examined different doses
- Study B1971012 examined various 2 and 3 dose schedules
- Three Phase III Studies, including
  - Two pivotal immunogenicity/safety studies; Studies B1971009 and B1971016
  - One global large scale safety study; Study B1971014
- Three concomitant vaccine studies: Studies B1971010, B1971011, and B1971015
- One study in the US laboratory workers; Study B1971042

The clinical dossier also contains case report forms with safety data, integrated safety analysis report, integrated immunogenicity analysis report, and literature references.

Selection of immunogenicity endpoints for clinical studies

The frequency of meningococcal disease caused by serogroup B (MnB) varies geographically, and could influence the ability to evaluate effectiveness of the vaccine in any given country. Based on the low incidence of MnB disease, placebo controlled clinical efficacy studies for Trumenba were considered unfeasible and were not performed. The sponsor tested, in accordance with the Committee for Medicinal Products for Human Use Scientific Advice,[39] the vaccine's ability to elicit serum bactericidal activity (hSBA), a correlate of protection against invasive meningococcal disease (IMD). The hSBA is a functional serological assay. The responses in hSBA serve as the surrogate marker of vaccine efficacy.

As approximately 200 fHBP sequences have been identified, it was necessary to design an approach to measure breadth of coverage across these sequences using the accepted correlate for efficacy. Bacterial test strains for hSBAs that expressed fHBP sequences that were heterologous to the vaccine sequences and represented fHBP diversity were selected to test immunogenicity, providing a reflection of the ability of bivalent rLP2086 to induce a protective response against meningococcal strains expressing fHBP. The immunogenicity endpoints were designed to determine that bivalent rLP2086 elicits protective bactericidal antibodies that can kill epidemiological diverse MnB disease strains expressing fHBP variants different in sequence from vaccine antigens. The primary immunogenicity endpoints utilised 4 primary hSBA test strains expressing fHBP variants that represent the diversity of fHBP sequences and are heterologous in sequence to the vaccine fHBP antigens. The 4 primary MnB test strains (primary strains) were selected to be representative of strains causing disease in various countries including the EU and the US. To confirm that the hSBA responses to the 4 primary strains reflect broad protection against MnB disease, the assessments were extended to include hSBA analyses with 10 additional secondary test strains in some studies.

For the pivotal studies, four endpoints were used to measure the vaccine elicited 4 fold hSBA response to each of the 4 primary strains, and the fifth endpoint is a 'composite' endpoint to assess the proportion of study subjects with hSBA responses to all 4 primary strains combined. The fHBP variants expressed by the 4 primary and 10 secondary strains represent all 6 major fHBP phylogenetic subgroups, and approximately 77% and 83% of disease causing MnB isolates in Europe and the US, respectively. In addition, an exploratory analysis was conducted with outbreak strains including those that expressed novel fHBP sequences.

[39] Committee for Medicinal Products for Human Use Scientific Advice EMEA/H/SA/1162/1/2008/111 (not publically available)

Earlier phase studies

A number of earlier phase studies assessed the immunogenicity in adults receiving 60 µg, 120 µg, or 200 µg of the vaccine. These data were used to select a dose for later studies. Following these studies, the 120 µg dose was considered appropriate to take forward in subsequent studies. There were also 3 Phase II studies that assessed the concomitant use of bivalent rLP2086 with other licensed vaccines. The persistence of immune responses was assessed in Study B1971005.

Study B1971003 (adults)

Study B1971003 was a Phase I/II open label study, in which 60 subjects (18 to 40 years old) received 120 µg of bivalent rLP2086 on a 0, 1, 6 month schedule. This study was designed for serological assay development. An exploratory objective was to assess the immunogenicity of 120 µg of bivalent rLP2086. Functional antibody responses using hSBA were performed with the following MnB test strains: PMB1745 (A05), which expresses an fHBP variant homologous to one of bivalent rLP2086 antigens, rLP2086-A05, and PMB17 (B02), which expresses an fHBP variant that is heterologous to the other vaccine antigen, rLP2086-B01. Sixty subjects were included in the immunogenicity analyses. The proportions of subjects with hSBA titres ≥ 1:4 for 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.

Study B1971004 (adults)

Study B1971004 was a Phase I, single centre, randomised, open label, active and placebo controlled, and parallel group study in healthy adults. A total of 48 subjects (18 to 40 years old) received the vaccine at either 60 µg, 120 µg, or 200 µg dose levels or the control regimen (Tdap/saline) on a 0, 2, 6 month schedule. The immunogenicity objective was to assess the immunogenicity of the 3 vaccine dose levels as determined by serum IgG binding antibody titres elicited by bivalent rLP2086. The modified intent-to-treat (mITT) population (n = 48) was used for the immunogenicity analyses. Increases in IgG GMTs relative to pre-dose levels were observed for each of the vaccine antigens after administration at 60 µg, 120 µg, or 200 µg dose levels, with a tendency toward higher IgG GMTs with each subsequent dose.

Study B1971005 (adolescents)

Study B1971005 was a Phase II randomised, single blind, placebo controlled study assessing the safety and immunogenicity of bivalent rLP2086 at doses of 60, 120, or 200 µg (0, 2, 6 month schedule) in adolescents (11 to 18 years old). The study was conducted in 2 stages. Stage 1 assessed the vaccine safety and immunogenicity and provided the basis for dose selection. Stage 2 assessed the duration of the immune responses.

Stage 1

Immune responses were evaluated for 60, 120, and 200 µg of bivalent rLP2086 using hSBAs titres obtained with 2 of the 4 primary MnB test strains and additional MnB test strains. The primary endpoint was the proportion of subjects achieving a 4 fold rise in hSBA titre from baseline after Dose 2 and Dose 3 for the MnB test strains, PMB1745 (A05) and PMB17 (B02), in the mITT Population. The mITT population was the primary analysis population and included the following: control (n = 119); 60 µg (n = 22); 120 µg (n = 195); and 200 µg (n = 192). The proportions of subjects achieving a 4 fold rise (hSBA titre) from baseline increased as the dose increased from 60 to 120 µg. However, there was no increase in the proportions when the dose increased from 120 to 200 µg. Hence, 120 µg was chosen as the appropriate dose for adolescent subjects.

Stage 2

Stage 2 evaluated the duration of the immune responses for up to 48 months post the third dose. Subjects who completed Stage 1, and received the vaccine at either; the 120 µg, or 200 µg dose, or saline control recipients, were enrolled into Stage 2. The results for Stage 2 include immunogenicity data starting from a visit at 6 months and 1 week after the third dose during Stage 1. Stage 2 persistence testing was also performed at pre vaccination and 1 month after Dose 3. One of the descriptive immunogenicity endpoints for Stage 2 was the proportion of subjects with hSBA titres ≥ LLOQ at selected time points through 48 months after Dose 3. The LLOQ for the 4 primary strains were an hSBA titre equal to 1:16 for PMB80 (A22) and 1:8 for PMB2001 (A56), PMB2948 (B24), and PMB2707 (B44).

The results showed that the proportion of subjects achieving hSBA titres ≥ LLOQ in the 120 µg group declined following 1 month after Dose 3 then remained stable and ranged from 51% to 69% for PMB80 (A22), PMB2001 (A56) and PMB2948 (B24) from 12 to 48 months after Dose 3. In the control group, the proportion of subjects achieving an hSBA titre ≥ LLOQ ranged from 13% to 36% for these 3 strains over the same timeframe. For PMB2707 (B44), the proportion of subjects achieving hSBA titres ≥ LLOQ in the 120 µg group declined to 20% to 29% from 12 to 48 months after Dose 3. In the control group, the proportion of subjects ranged from 4 to 12% using PMB2707 (B44). Overall, at 48 months post Dose 3 in the 120 µg group, the mean proportion of subjects with hSBA titres ≥ LLOQ was more than 50% (51% to 69%) for three MnB test strains: PMB80 (A22), PMB2001 (A56) and PMB2948 (B24). The persistence of hSBA strain B44 appears to be poor (20.4% at Month 48, see Table 7).

Table 7: Subjects with hBSA titres ≥ LLOQ; Stage 2 ITT population

Strain (Variant) Sampling Time Point	Vaccine Group (as Randomized) Control N[a]	Control n[b] (%)	Control (95% CI)[c]	rLP2086 Vaccine 120 µg N[a]	rLP2086 Vaccine 120 µg n[b] (%)	rLP2086 Vaccine 120 µg (95% CI)[c]
PMB80 (A22)						
Predose 1	78	19 (24.4)	(16.1, 35.1)	146	33 (22.6)	(16.5, 30.1)
1-Month postdose 3	80	23 (28.8)	(19.9, 39.6)	150	143 (95.3)	(90.5, 97.8)
6 Months 1 week after last dose in Stage 1	79	16 (20.3)	(12.8, 30.5)	161	97 (60.2)	(52.5, 67.5)
12 Months after last dose in Stage 1	76	22 (28.9)	(19.9, 40.1)	155	84 (54.2)	(46.3, 61.9)
24 Months after last dose in Stage 1	74	23 (31.1)	(21.6, 42.5)	153	82 (53.6)	(45.7, 61.3)
48 Months after last dose in Stage 1	67	23 (34.3)	(24.0, 46.4)	134	79 (59.0)	(50.4, 67.0)
PMB2001 (A56)						
Predose 1	21	5 (23.8)	(10.3, 46.0)	44	10 (22.7)	(12.7, 37.3)
1-Month postdose 3	23	8 (34.8)	(18.4, 55.7)	48	48 (100.0)	(85.5, 99.9)
6 Months 1 week after last dose in Stage 1	23	5 (21.7)	(9.3, 42.8)	47	42 (89.4)	(76.9, 95.5)
12 Months after last dose in Stage 1	23	6 (26.1)	(12.2, 47.2)	48	33 (68.8)	(54.4, 80.2)
24 Months after last dose in Stage 1	22	8 (36.4)	(19.3, 57.7)	49	26 (53.1)	(39.2, 66.5)
48 Months after last dose in Stage 1	23	8 (34.8)	(18.4, 55.7)	47	24 (51.1)	(37.1, 64.9)
PMB2948 (B24)						
Predose 1	80	7 (8.8)	(4.2, 17.2)	148	13 (8.8)	(5.2, 14.5)
1-Month postdose 3	79	12 (15.2)	(8.8, 24.9)	149	139 (93.3)	(88.0, 96.4)
6 Months 1 week after last dose in Stage 1	80	11 (13.8)	(7.8, 23.1)	163	93 (57.1)	(49.3, 64.4)
12 Months after last dose in Stage 1	78	10 (12.8)	(7.0, 22.2)	150	82 (54.7)	(46.6, 62.4)
24 Months after last dose in Stage 1	74	12 (16.2)	(9.4, 26.4)	152	82 (53.9)	(46.0, 61.7)
48 Months after last dose in Stage 1	68	16 (23.5)	(14.9, 35.0)	128	73 (57.0)	(48.3, 65.3)
PMB2707 (B44)						
Predose 1	25	0 (0.0)	(0.0, 24.7)	49	1 (2.0)	(0.3, 13.1)
1-Month postdose 3	25	0 (0.0)	(0.0, 24.7)	47	45 (95.7)	(84.5, 98.9)
6 Months 1 week after last dose in Stage 1	25	0 (0.0)	(0.0, 24.7)	49	18 (36.7)	(24.5, 50.9)
12 Months after last dose in Stage 1	25	1 (4.0)	(0.6, 23.5)	48	14 (29.2)	(18.1, 43.4)
24 Months after last dose in Stage 1	25	1 (4.0)	(0.6, 23.5)	49	11 (22.4)	(12.9, 36.2)
48 Months after last dose in Stage 1	25	3 (12.0)	(3.9, 31.3)	49	10 (20.4)	(11.3, 33.9)

Abbreviations: hSBA = serum bactericidal assay using human complement; LLOQ = lower limit of quantitation.
Note: All testing was performed with the validated hSBA.
Note: Testing using the validated assay for type A56 and B44 was only done for a subset of 75 subjects (25 subjects from the control group and 50 subjects for 120 µg group).
Note: LLOQ = 1:16 for A22; 1:8 for A56, B24 and B44.
Note: For all Stage 2 subjects, the last dose in Stage 1 was Dose 3.
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. Confidence intervals (CIs) are based on a generalized linear model with vaccine group and sampling time as fixed effects and a logit function.

Study B1971012 (adolescents)

This Phase II randomised study assessed various 2 and 3 dose schedules using primary MnB test strains. A total of 1,713 subjects (11 to18 years) were randomly assigned to receive 120 µg of the vaccine in 5 groups in a 3:3:3:2:1 ratio:

- Group 1 (0, 1, 6 month schedule)
- Group 2 (0, 2, 6 month schedule)
- Group 3 (0, 6 month schedule)
- Group 4 (0, 2 month schedule)
- Group 5 (2, 6 month schedule, same as 0, 4 month schedule).

The co-primary objectives were to assess the hSBA with the 4 primary strains measured 1 month after Dose 3, among the two 3 dose groups (Group 1 and 2). The primary endpoint was the proportion of subjects with hSBA responses ≥ LLOQ for each of the 4 primary strains in the evaluable immunogenicity population. The co-primary objectives were achieved if the 97.5% lower bound confidence interval (LCI) for the response rate was > 50% for each of the 4 primary strains for either 3 dose regimen. The LLOQ for each strain was 1:8 for the primary analysis. A post-hoc analysis was performed using a LLOQ = 1:16 for the strains expressing fHBP variant A22 to address feedback from Center for Biologics Evaluation and Research (CBER) indicating that the higher LLOQ should be used. The results with an LLOQ = 1:16 for A22 are presented here.

The evaluable immunogenicity population included 365 subjects in Group 1, 360 in Group 2, 371 in Group 3, 241 in Group 4, and 113 in Group 5. With the LLOQ of 1:16 for the hSBA with PMB80 (A22), the proportions in Group 1 achieving an hSBA titre ≥ LLOQ after 3 doses on the 0, 1, 6 month schedule were 91.4% for PMB80 (A22), 99.4% for PMB2001 (A56), 89.0% for PMB2948 (B24), and 88.5% for PMB2707 (B44).

Table 8: Proportion of subjects achieving hBSA titre ≥ LLOQ; for each primary MnB test strain at 1 month after the last bivalent rLP2086 dose; evaluable immunogenicity population (Study B197102)

	Vaccine Group (as Randomized)														
	Group 1 0,1,6-Schedule					Group 2 0,2,6-Schedule					Group 3 0,6-Schedule				
Primary MnB Test Strain	N[a]	n[b]	%	(97.5% CI)[c]	p-Value[d]	N[a]	n[b]	%	(97.5% CI)[c]	p-Value[d]	N[a]	n[b]	%	(97.5% CI)[c]	p-Value[d]
PMB80 (A22)	360	329	91.4	(87.5, 94.4)	<.001	357	339	95.0	(91.7, 97.2)	<.001	369	344	93.2	(89.7, 95.8)	<.001
PMB2001 (A56)	362	360	99.4	(97.8, 100.0)	<.001	359	355	98.9	(96.9, 99.8)	<.001	370	364	98.4	(96.2, 99.5)	<.001
PMB2948 (B24)	354	315	89.0	(84.7, 92.4)	<.001	354	313	88.4	(84.1, 91.9)	<.001	359	291	81.1	(76.0, 85.5)	<.001
PMB2707 (B44)	356	315	88.5	(84.1, 92.0)	<.001	352	303	86.1	(81.4, 90.0)	<.001	356	276	77.5	(72.2, 82.3)	<.001

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

Note: LLOQ = 16 for PMB80 (A22); 8 for PMB2001 (A56), PMB2948 (B24), and PMB2707 (B44).

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

b. n = Number of subjects with observed hSBA titer ≥ LLOQ for the given primary MnB test strain. For Group 1 and Group 2 subjects, hSBA titer was measured 1 month after the third vaccination with bivalent rLP2086. For Group 3 subjects, hSBA titer was measured 1 month after the second vaccination with bivalent rLP2086.

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

d. Response rates are compared with 50% (ie, lower bound of 97.5% CI threshold is greater than 50% on the LLOQ response rates), using 1-sided exact test based on binomial distribution. p-Values <0.0125 are considered significant.

The corresponding values in Group 1 at 1 month after 2 doses (0, 1) were 62.3% for PMB80 (A22), 89.1% for PMB2001 (A56), 50.6% for PMB2948 (B24), and 35.4% for PMB2707 (B44).

In Group 2, at 1 month after 3 doses (0, 2, 6 months), the proportions of subjects with hSBA titres ≥ LLOQ were 95.0% for PMB80 (A22), 98.9% for PMB2001 (A56), 88.4% for PMB2948 (B24), and 86.1% for PMB2707 (B44).

At 1 month after 2 doses (0, 2 months), the corresponding proportions were 88.1%, 97.9%, 70.3%, and 61.9%. In Groups 1 and 2, the 97.5% LCI for the proportion of subjects achieving hSBA titres ≥ LLOQ was greater than 50% with use of each primary test strain, and thus the study met the co-primary objectives.

In Group 1 and 2, hSBA response 1 month after the 1st dose was not determined. However, hSBA response at this time point was determined for Group 5; the proportions of subjects achieving an hSBA titre ≥ LLOQ 1 month after 1st dose were 55.9% for PMB80 (A22), 67.6% for PMB2001 (A56), 56.9% for PMB2948 (B24), and 23.8% for PMB2707 (B44).

The secondary objective was to assess the immune response with the 4 primary strains measured 1 month after Dose 2 in Group 3 (0, 6 month schedule). The proportion of subjects with an hSBA titre ≥ LLOQ after 2 doses in Group 3 was 93.2% for PMB80 [A22], 98.4% for PMB2001 [A56], 81.1% for PMB2948 [B24], and 77.5% for PMB2707 [B44]. These observed point estimates in Group 3 were similar to those of Group 1 and 2. This objective was achieved as all p-values for the hSBA response rates for each of the 4 primary strains in Group 3 were < 0.0125.

The same analysis was performed for Group 4 (0, 2 month schedule) and Group 5 (0, 4 month schedule); the proportions of subjects with an hSBA titre ≥ LLOQ at 1 month after the second dose for the 4 primary test strains were as follows for Group 4 and 5, respectively: 90.8% and 91.0% for PMB80 (A22); 100.0% and 99.1% for PMB2001 (A56); 73.0% and 69.1% for PMB2948 (B24); and 70.1% and 73.0% for PMB2707 (B44).

The proportion of responders at ≥ LLOQ was higher in Group 3 subjects who received 2 doses on a 0, 6 month schedule than in Group 4 or Group 5 subjects receiving vaccinations on a 0, 2 month or 0, 4-month schedule, respectively. The proportions of responders were higher after 2 doses spaced 6 months apart in Group 3 than after the second dose in Group 1 (0, 1 month schedule) and Group 2 (0, 2 month schedule).

The results from this study showed that the benefit of this vaccine is dependent on the vaccine schedule. Close administration of the first 2 doses is associated with a lower response than that with administration of the 2 doses at the greater interval of 6 months where the response is not substantially different from that after 3 doses. This supports the dosing premise that when the risk of disease is low, vaccination administered on a 0, 6 month schedule will provide a protective immune response for a high proportion of vaccinees. During an epidemic, or for those at high risk (for example, due to asplenia or complement deficiency), rapid induction of a protective immune response can be achieved with the first 2 doses given 1 to 2 months apart, and the third dose given at least 4 months later to maximise protection. The vaccine is given in both the 2 and 3 dose schedules in the USA. See Attachment 2 for the results of additional secondary endpoints analysis.

Pivotal Phase III studies

The Phase III program consists of 3 studies. Study B1971009, assessed the vaccine immune responses in adolescents (10 to < 19 years) while Study B1971016 assessed the immune responses in adults (18 to < 26 years). Study B1971009 also assessed the lot consistency. Study B1971014 was a safety study in a large population (10 to < 26 years) to identify uncommon safety events.

Study B1971009 (adolescents 10 to < 19 years)

This was a Phase III, randomised, active controlled, observer blinded, multicentre trial in which subjects received 1 of 3 lots of the bivalent rLP2086 (refer to as MnB vaccine or the vaccine) or the active control (hepatitis A virus (HAV) vaccine /saline). The study assessed the immunogenicity, safety, and lot consistency of 3 lots of 120 µg MnB vaccine given at 0, 2, and 6 months. The first primary objective was to assess the hSBA with 4 primary MnB test strains measured 1 month after the third dose. The co-primary objective was to show that the hSBA induced by 3 lots of the vaccine are equivalent as measured by hSBA with 2 primary test strains one month after the third dose.

Subjects were randomised into 1 of 4 groups in a 5:2:2:3 ratio, (Lot 1: Lot 2: Lot 3: HAV/saline). Subjects in Groups 1, 2, and 3 received 1 dose of the vaccine (lots 1, 2, or 3, respectively) at Visits 1, 2, and 4; Subjects in Group 4 received 1 dose of HAV at Visit 1, 1 dose of saline at Visit 2, and 1 dose of HAV at Visit 4, according to the design.

The 5 co-primary endpoints were the proportion of subjects in Group 1 achieving at least a 4 fold rise in hSBA for each of the 4 primary MnB test strains and the proportion of subjects achieving a composite response at 1 month after third dose.

The second primary objective was to show that the immune responses induced by 3 lots of the vaccine were equivalent with 2 primary strains. The primary endpoints were hSBA GMTs for each of the 2 primary strains, PMB80 (A22) and PMB2948 (B24), at 1 month post third dose for subjects in Groups 1, 2, and 3. Secondary objectives were to describe the immune response with 10 secondary test strains, measured 1 month post third dose and to describe the immune response with 4 primary strains, measured 1 month after the second dose.

The evaluable immunogenicity population was the primary analysis population for immunogenicity data. The primary analysis at 1 month post third dose was based on the evaluable immunogenicity population for the 5 co-primary endpoints (composite hSBA response and 4 fold increase from baseline for each of the 4 primary strains) in Group 1. The 95% CIs were presented along with the response rate. The objectives were achieved if the lower limit (LL) of 95% CIs at Visit 5 were greater than the thresholds specified for each of the 5 co-primary endpoints in Group 1. The first primary objective would be achieved if the LL of the 95% CI at one month after the third dose was greater than the lower bound threshold specified for each of the 5 co-primary endpoints in Group 1. The criteria of lower bound threshold (LL of 95% CI for the response rate) for the 5 co-primary endpoints was agreed between the sponsor and the regulatory authorities and was based on the exploratory post Dose 3 data from Study B1971012. The lot consistency objective would be achieved if the 2-sided 95% CIs on the hSBA GMT ratio between any 2 of the 3 lots for both PMB80 (A22) and PMB2948 (B24) were within the interval (0.5, 2.0) 1 month post Dose 3, after the primary immunogenicity objective was achieved. A total of 3,596 subjects were randomised and 3,590 were vaccinated. A total of 3,059 (85.1%) subjects were included in the evaluable immunogenicity population.

Results for the primary efficacy outcome

For the evaluable immunogenicity population, the proportion of subjects achieving a 4 fold rise in hSBA titre in Group 1 was as shown in Table 9.

Table 9: Primary immunogenicity Analysis-Subjects achieving 4 fold increase in hSBA and composite response at 1 month post dose 3 for primary strains (Evaluable immunogenicity population)

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

The LL of the 2-sided 95% CI was greater than the corresponding pre-specified LL threshold for each of the 4 primary MnB strains and for the composite response; thus, the first primary objective (immunogenicity) was met.

With lot to lot consistency outcome, the 95% CI for all pairwise GMRs between lots were within the interval (0.5, 2.0), for both test strains PMB80 (A22) and PMB2948 (B24). Therefore, the lot consistency objective was met. The results of other efficacy outcomes are discussed in the CER.

Study B1971016 (adults ≥ 18 to < 26 years)

Study B1971016 was a Phase III, randomised, placebo controlled, observer blinded, multicentre study to assess the vaccine safety and immunogenicity when administered as a 3 dose regimen in healthy young adults (≥ 18 to < 26 years). Approximately 3,300 subjects were to be randomly assigned to 1 of 2 groups in a 3:1 ratio (Group 1: Group 2). Group 1 received the vaccine at Month 0 (Day 1), Months 2 and 6. Group 2 received saline at Month 0 prior to first dose, Month 2, and Month 6. The primary objective was to assess the hSBA response with 4 primary MnB test strains, measured 1 month after the third dose.

The first primary objective was to assess the hSBA with 4 primary MnB test strains, measured 1 month after the third dose. Five co-primary endpoints were defined for the primary immunogenicity objective based upon results for hSBAs performed with the 4 primary test strains for Group 1 subjects. One of the 5 co-primary endpoints was the composite endpoint defined as the proportion of subjects with an hSBA titre ≥ LLOQ for all primary MnB test strains combined, 1 month after the third dose. The secondary objectives were to describe the hSBA performed with 10 secondary MnB test strains measured 1 month post Dose 3 and to describe the hSBA with 4 primary MnB test strains, measured 1 month post Dose 2.

Subjects 18 to < 26 years old were randomised to Group 1 or 2 in a 3:1 ratio. A total of 2,305 subjects were included in the evaluable immunogenicity population (Group 1 (rLP2086), n = 1723, Group 2 (saline), n = 582). The statistical methodology for the primary outcome was based on the use of the 2-sided 95% CI. The first primary objective would be achieved if the LL of the 95% CI at one month post Dose 3 was greater than the threshold specified above. The study objective would be achieved if the LL of the 95% CIs at 1 month after third dose were greater than the threshold specified for each of the 5 co-primary endpoints in Group 1 (See Table 10). The success criteria of this study were slightly different from the criteria used in the adolescent Study (B1971009) to account for the older age of subjects in this study. The sponsor and regulatory authorities agreed upon the success criteria (LL of the 95% CI for the response rate) for the 5 co-primary endpoints based on exploratory data from Study B1971003 and Studies B1971005 and B1971012.

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; evaluable immunogenicity population (Study B1971016)

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

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

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

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

a. For hSBA titer fold rise ≥4 from baseline, N = number of subjects with valid and determinate hSBA titers for the given strain at both the specified time point and baseline. For composite hSBA response (hSBA ≥ LLOQ for all 4 primary strains), N = number of subjects with valid and determinate hSBA results on all 4 strains at the given time point.

b. For hSBA titer fold rise ≥4 from baseline, n = number of subjects who achieved hSBA titer fold rise ≥4 from baseline for the given strain. For composite hSBA response (hSBA ≥ LLOQ for all 4 primary strains), n = number of subjects with observed hSBA titer ≥ LLOQ for all 4 primary strains at the given time point.

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

d. If the lower bound of the 95% CI is greater than the corresponding threshold, the immunogenicity objective with respect to that endpoint is achieved. The primary study objective requires this criterion to be met for all 5 coprimary endpoints.

e. Baseline is defined as the blood draw prior to Vaccination 1.

Source: Program ID: Study B1971016/CP HSBA_FR4_THRES.SAS. File ID: 4_2_IMM_FR4THRES_EVL.HTM. Runtime ID: 20JUL2015 16:05. Date of reporting dataset creation: 17JUN2015.

A total of 3,304 subjects were randomised, and 2,480 subjects were included in Group 1 (bivalent rLP2086) while 824 subjects were included in Group 2 (saline). Of the 3,304 randomised subjects, 2,474 (74.88%) subjects completed the Vaccination Phase: 3,293 (99.67%) received Vaccination 1; 2,902 (87.83%) received Vaccination 2; and 2,538 (76.82%) received Vaccination 3. A total of 2770 (83.84%) subjects completed the 6 month follow-up, and 2,419 (73.21%) subjects completed the study. Among 3,293 vaccinated subjects, 1,359 (41.27%) were male and 1,934 (58.73%) were female. The majority of subjects were White. The mean age at vaccination was 21.48 years. Percentages by sex and race/ethnicity and mean age at vaccination were similar in each group.

Results for the primary efficacy outcome

For the evaluable immunogenicity population in Group 1, the proportion of subjects achieving a ≥ 4 fold increase in hSBA titre from baseline for each of the 4 primary test strains after 3 doses of 120 µg was as shown in Table 11.

Table 11: Primary immunogenicity analysis; Subjects achieving 4 fold increase in hSBA and composite response at 1 month post Dose 3 for primary strains (Evaluable immunogenicity population)

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

The LL of the 2-sided 95% CI was greater than the pre-specified threshold for each of the 4 primary MnB strains and for the composite response; thus, the primary objective was met. The results for other efficacy outcomes are discussed in detail in Attachment 2.

Other efficacy studies

Studies of concomitant use with other vaccines

In the three Phase II studies, Studies B1971010, B1971011, and B1971015, the immunogenicity of bivalent rLP2086 has been shown to be unchanged by concomitant administration of other vaccines (dTap-IPV, Gardasil, or Tdap and Menactra respectively); similarly, the immune responses to the concomitant vaccines were unaffected in a clinically meaningful way when administered with bivalent rLP2086. Please see Attachment 2 for details of the results from these studies.

Study B1971042 (Laboratory workers 18 to ≤ 65 years of age)

Study B1971042 was a Phase II, single arm, open label, descriptive study of bivalent rLP2086 in laboratory workers 18 to ≤ 65 years of age. The study assessed the safety and immunogenicity of 120 µg bivalent rLP2086 given administered on a 0, 2, 6 month schedule. The objective was to describe the hSBA response with 4 primary strains at 1 month after the third dose of the vaccine.

A total of 13 enrolled subjects, aged 24 to 62 years, were included. Five subjects were ≤ 40 years and 8 subjects were > 40 years of age. Of the 13 subjects vaccinated, 6 subjects were included in the evaluable immunogenicity population. At 1 month after Dose 3, 6 of 6 subjects had an hSBA titre ≥ LLOQ for PMB80 (A22) and PMB2948 (B24), 5 of 5 subjects had an hSBA titre ≥ LLOQ for PMB2001 (A56), and 3 of 6 subjects had an hSBA titre ≥ LLOQ for PMB2707 (B44).

When phase 3 primary endpoints were assessed, 5 of 6 subjects achieved an hSBA titre fold rise ≥ 4 from baseline to 1 month after Dose 3 for PMB80 (A22), 5 of 5 subjects for PMB2001 (A56), 4 of 6 subjects for PMB2948 (B24), and 3 of 6 subjects for PMB2707 (B44). Three of 5 subjects achieved a composite hSBA response (hSBA ≥ LLOQ for all 4 primary strains combined).

While the number of subjects is limited, these data in an older population demonstrate that a protective immune response can be elicited after 3 doses of bivalent rLP2086 in adults, as measured by a 4 fold rise in hSBA titres from baseline and composite response as well as the proportion of subjects with hSBA titres ≥ LLOQ.

Post hoc analysis of positive predictive values for the Phase III studies

The positive predictive value (PPV) analyses were conducted to determine whether immune responses to the primary strains were predictive of a more general response to

MnB strains. The analyses of both pivotal studies showed that primary strain responses are highly predictive of secondary strain responses within the same subfamily. The predictive power of the primary strain responses was also present among subjects negative in hSBAs with primary and secondary strains at baseline, indicating that baseline hSBA positivity did not influence the magnitude of the PPVs. The PPV analysis, supported by results of the correlation and concordance analyses, provides assurance that the observed immune responses to the primary strains are indicative of broad protection against diverse MnB disease causing strains.

Safety

Studies providing evaluable safety data

The primary data supporting the safety of the vaccine are from subjects in the 8 randomised controlled studies (Studies B1971004, B1971005, B1971009, B1971010, B1971011, B1971014, B1971015, and B1971016). Additional data are from the 3 uncontrolled studies (Studies B1971003, B1971012, and B1971042). This application includes 11 studies and a total of 15,294 subjects who received at least one dose of bivalent rLP2086, administered either as a single agent or given concomitantly with a licensed vaccine, 14,153 subjects who received 2 or more doses. Data are also presented for 5,509 subjects in control groups who received either saline alone, licensed vaccine alone, or saline and a licensed vaccine. A total of 12,268 subjects received 3 doses of 120 µg of bivalent rLP2086.

Study B1971014 was a Phase III, randomized, active controlled, observer blinded, multicentre trial assessing the safety and tolerability of bivalent rLP2086 in healthy subjects age 10 to < 26 years. Subjects were randomized in a 2:1 ratio (bivalent rLP2086: control) to receive 120 µg bivalent rLP2086 at 0, 2, and 6 months or control vaccine (HAV at 0 and 6 months, saline at 2 months). The primary objectives were to evaluate the safety of bivalent rLP2086 compared to a control. Detailed safety results of this study are discussed in detail in Attachment 2.

Adverse events

Local reactions and acute systemic events were common. Most of them were mild or moderate in severity and resolved within 1 to 3 days post vaccination. Pain at the injection site was the most frequently reported local reaction, but only 0.30% of subjects withdrew from the core studies due to injection site pain. Fatigue, headache, and muscle pain were the most frequently reported systemic events. Fever > 40.0 °C was reported for only 2 subjects who received 120 µg dose and for 1 subject who received control vaccine in the core studies. Potentiation (worsening of reactions with increasing doses) of reactogenicity events with subsequent vaccinations was rarely observed. The types of unsolicited AEs reported were generally illnesses and conditions common or expected among healthy individuals of similar age in the general population. In addition, the observed frequencies of AEs were generally similar in the group received rLP2086 vaccine with a concomitant vaccine compared with those in the groups receiving rLP2086 alone or the other vaccine(s) alone.

Deaths and other serious adverse events (SAEs)

In the 8 controlled studies, the percentages of subjects experiencing SAEs was similar in the 120 µg group and the control group during the Vaccination Phase (1.15% versus 1.34%) and throughout the studies (1.60% versus 1.92%), as well as during the period before Dose 3 (0.98% versus 1.25%) and after Dose 3 (0.74% versus 0.86%). SAEs considered related to study vaccine were reported for 5 subjects (0.04%) who received the 120 µg dose and for 2 subjects (0.04%) who received control vaccine. Among the 13,284 subjects who received the 120 µg dose, 5 subjects (0.04%) died, while there were no deaths among the 5,509 subjects who received control vaccine. Among the subjects

who died, 3 died as a result of road traffic accidents, 1 subject died due to a gunshot wound, and 1 subject committed suicide. None of the deaths were considered related to study vaccine.

Discontinuations due to adverse events

Withdrawal due to local reactions: Among the 13,284 subjects who received 120 µg dose in the 8 controlled studies, 46 subjects (0.35%) were withdrawn due to local reactions; and among the 5,509 subjects who received control vaccine, 2 (0.04%) were withdrawn due to local reactions.

Withdrawal due to systemic events: in the core safety dataset, systemic events resulted in withdrawal of 31 subjects (0.23%) who received 120 µg dose and 2 subjects (0.04%) who received control vaccine. Among subjects receiving the 120 µg dose, the systemic events most frequently leading to withdrawal were headache and pyrexia. Among subjects who received control vaccine, 1 subject was withdrawn due to chills and 1 subject was withdrawn due to headache, fatigue, pyrexia, chills, myalgia, and arthralgia.

Immunological events and neuroinflammatory conditions

Among the 8 controlled studies, potential autoimmune conditions among subjects who received 120 µg dose on a 0, 2, 6 month schedule were observed in 0.36% compared to 0.34% in controls. Similarly, the proportion of subjects who reported potential neuroinflammatory conditions was 0.10% for subjects who received 120 µg dose on a 0, 2, 6 month schedule compared to 0.11% among controls. Confirmed autoimmune conditions were reported in 0.14% (95% CI: 0.08%, 0.21%) of subjects receiving 120 µg dose on a 0, 2, 6 month schedule compared with 0.11% (95% CI: 0.04%, 0.24%) of subjects receiving control vaccine. The difference in proportions was 0.03% (95% CI: -0.11%, 0.13%, p = 0.642), supporting the conclusion that there was no significant difference between the 120 µg bivalent rLP2086 group and the control group in the rate of autoimmune disease.

In the core safety dataset, confirmed neuroinflammatory conditions were reported in 0.06% (95% CI: 0.03%, 0.12%) of subjects receiving 120 µg dose compared with 0.07% (95% CI: 0.02%, 0.19%) of subjects receiving control vaccine. The difference in proportions was -0.01% (95% CI: -0.13, 0.06, p = 0.760), supporting the conclusion that there was no significant difference between the 120 µg bivalent rLP2086 group and the control group in the rate of neuroinflammatory conditions. The most commonly reported neuroinflammatory condition was seventh cranial nerve paralysis (8 of 12 subjects with neuroinflammatory conditions).

Analysis of the rates of autoimmune diseases and neuro inflammatory conditions reported among all clinical trials demonstrated a low incidence of autoimmune and neuro inflammatory conditions overall. In addition, among the 8 studies where a control group was available, no significant differences were observed in the proportions of subjects with autoimmune diseases or neuro-inflammatory conditions between subjects receiving 120 µg bivalent rLP2086 compared to control. Safety was also evaluated 4 years after vaccination with 3 doses of bivalent rLP2086, and no additional safety signal was detected.

Post marketing experience

Bivalent rLP2086 vaccine was launched in the US on 17 November 2014. The total estimated unit distribution in the US from launch through to 31 October 2015 is approximately 159,320 doses. The safety database contains cases of 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 SAEs reported from clinical studies, regardless of causality. Cumulatively, a total of 190 cases (597 AEs) were received from spontaneous sources through the cut-off date of 31 October 2015. Of these, 122 cases were medically confirmed. The most frequently reported AEs were as follows: headache, vaccination site pain,

pyrexia, chills, pain, fatigue, pain in extremity, nausea, erythema, dizziness, vomiting, malaise, joint range of motion decreased, myalgia, inappropriate schedule of drug administration, vaccination site rash, vaccination site swelling, incomplete course of vaccination, and vaccination site erythema. 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.

Risk management plan

The sponsor submitted EU-RMP version 1.0 (19 April 2016; DLP 30 November2015) with ASA versions 1.0 (10 June 2016) and 1.1 (13 February 2017, with S31 response) in support of this application. The RMP evaluation report (TRIM D17-301281) is included for ACV information. ACV advice was discussed in the RMP Evaluation Report.

The proposed Summary of Safety Concerns and their associated risk monitoring and mitigation strategies are summarised in Table 6 above.

- Additional Pharmacovigilance activities proposed are:
  - Study B1971052: Observational pregnancy study in the USA to assess pregnancy outcomes
  - Population-based surveillance of the incidence rates of IMD (Invasive Meningococcal Disease, serogroup B) in collaboration with national agencies if bivalent rLP2086 is used as part of a national immunisation program.
- Routine risk minimisation is proposed.

There are two outstanding RMP issues:

1. The sponsor must address the important potential risk of off-label use in children younger than 10 years of age in the ASA and propose adequate risk minimisation.
2. The sponsor must submit the final agreed EU-RMP when it becomes available and update the ASA accordingly. Any changes compared to the EU-RMP evaluated by the TGA should be described separately.

The RMP evaluator suggested the following wording as conditions of registration

Any changes to which the sponsor has agreed should be included in a revised RMP and ASA. However, irrespective of whether or not they are included in the currently available version of the RMP document, the agreed changes become part of the risk management system.

The RMP evaluator commented that the Trumenba risk Management Plan cannot be finalised. Risk management for off-label use in children under the age of 10 years is an outstanding issue.

Risk-benefit analysis

Delegate's summary and discussion

N. meningitidis serogroup B (MnB) is a significant cause of serious endemic meningococcal disease worldwide and can manifest as prolonged outbreaks or as sudden, unpredictable outbreaks. MnB disease is often devastating with sudden onset, fast progression and may result in permanent long term sequelae in those that survive. The main treatment option is antibiotics. It still however has a significant mortality and morbidity associated with it despite antibiotic therapy. There is one licensed MnB vaccine, Bexsero, which was included on the ARTG in 2013. Availability of vaccine supply is an important consideration

during endemic use or for outbreak control. Sufficient supply avoids potential shortages and thus, from a public health perspective, availability of more than one MnB vaccines is important. Invasive meningococcal disease mainly affects infants aged 3 to 12 months, followed by teenagers. However, during epidemics, incidence rates can also rise among older children and young adults.

In this application, a total of 11 studies were provided, including two pivotal Phase III studies evaluating immunogenicity. The primary objective of both Phase III studies, to assess the immune response with 4 primary MnB test strains, was achieved. Study B1971009 also showed the equivalence of the 3 lots of the vaccine. A secondary objective common to both Phase III studies was to describe the hSBA with 10 secondary MnB test strains at 1 month post Dose 3 and 1 month post Dose 2. The majority of subjects achieved hSBA titres ≥ LLOQ and there were robust GMTs after the second and third dose for all secondary strains, demonstrating a pattern of response similar to that for the 4 primary strains.

The two dose schedule

The immune responses to several two dose schedules, including the 0, 6 month schedule, were evaluated in healthy subjects (11 to18 years) in Study B1191012. The results from this study showed that the close administration of the first 2 doses (0, 2 and 0, 4 month schedules) is associated with a lower hSBA response than that with administration of the 2 doses at the greater interval (the 0, 6 month schedule). Study B1191012 also showed that while the responses elicited by the third dose are higher than the response following the first 2 doses given at 0, and 1 month or 0 and 2 months, the response after the 3 dose schedules are not substantially higher than the response following 2 dose schedule given at 0 and 6 months. This provides supporting argument for routine vaccination with 2 doses at 0 and 6 months in adolescents/adults and for 3 doses (0, 1-2 and 6 months) administered to individuals with increased risk of invasive meningococcal disease where 2 doses of vaccine need to be administered more rapidly to afford protection.

Antibody persistence data

Antibody persistence was evaluated in Stage 2 of Study B1971005. Data is limited as groups are small. The results showed that the proportion of subjects achieving hSBA titres ≥ LLOQ in the 120 µg group declined following 1 month after Dose 3; then remained stable and ranged from 51% to 69% for PMB80 (A22), PMB2001 (A56) and PMB2948 (B24) from 12 months to 48 months after Dose 3. In the control group, the proportion of subjects achieving an hSBA titre ≥ LLOQ ranged from 13% to 36% for these 3 strains over the same timeframe. For PMB2707 (B44), the proportion of subjects achieving hSBA titres ≥ LLOQ in the 120 µg group declined to 20% to 29% from 12 months to 48 months after Dose 3.

Overall, at 48 months post Dose 3 in the 120 µg group, the proportions of subjects with hSBA titres ≥ LLOQ was still > 50% (ranging from 51% to 69%) for three MnB test strains: PMB80 (A22), PMB2001 (A56) and PMB2948 (B24). The immune persistence for strain B44 declined with20.4% subjects maintaining hSBA titre ≥ LLOQ at 48 Months post Dose 3.

Concomitant use with other vaccines

The data from three Phase II studies (Studies B1971010, B1971011, and B1971015) have shown that the immunogenicity of bivalent rLP2086 is not impacted by concomitant administration with other vaccines (Repevax, Gardasil, or Tdap and MCV4). Similarly, the immune responses to the concomitant vaccines were unaffected in a clinical meaningful way when administered with bivalent rLP2086.

Data in older adults

Study B1971042 was the only study in which older subjects were included. In total 13 subjects aged 24 to 62 years were included and 8 subjects were > 40 years

(no subjects > 65 years). The available data in the limited number of older adults indicate that the safety and immunogenicity are acceptable and similar to that seen in younger adults. It is known that the immune response may decrease with age, however, the impact is unlikely to be of significant degree and the benefit/risk balance of vaccinating older adults is unlikely to be unfavourable. The incidence of invasive meningococcal serogroup B disease is low in older adults. However, in an outbreak situation, adults and elderly would need to be vaccinated and protected.

Overall safety data

The overall safety dataset includes a total of 15,294 subjects who received at least 1 vaccination at any dose level and using any dosing schedule; among these, 15,053 received the vaccine at the 120 µg dose using any schedule. Most local reactions and systemic events were mild or moderate in severity and resolved within 1 to 3 days. Pain at the injection site was the most frequently reported local reaction, and 0.30% of subjects withdrew from the core studies due to injection site pain. Fatigue, headache, and muscle pain were the most frequently reported systemic events in the 120 µg group and in the control groups. Fever > 40.0 °C was reported for only 2 subjects who received 120 µg dose and for 1 subject who received control vaccine in the core studies. Potentiation (worsening of reactions with increasing doses) of reactogenicity events was not observed with subsequent bivalent rLP2086 doses. The types of unsolicited AEs reported were generally illnesses and conditions common or expected among healthy individuals of similar age in the general population. Review and analysis of the rates of autoimmune diseases and neuroinflammatory conditions reported among 11 clinical trials showed a low incidence of autoimmune and neuroinflammatory conditions. In addition, among the 8 controlled studies, no significant differences were observed in the proportions of subjects with autoimmune diseases or neuroinflammatory conditions between subjects receiving 120 µg bivalent rLP2086 compared to control. Safety was also evaluated up to 4 years after 3 doses of bivalent rLP2086, and no additional safety signal was detected.

Uncertainty about the vaccine effectiveness

The efficacy of this vaccine has not been assessed in the submitted clinical trials. Although the IMD is a rare disease, in view of the significant impact of the deadly disease, vaccination against the disease is considered beneficial when the strains in the vaccine match the strain circulating in Australia.[40] The sponsor should monitor the vaccine effectiveness and vaccine failure rate when it is feasible to do so.

Risk of potential off-label use

The RMP evaluator raises the issue regarding the risk of potential off-label use of Trumenba in children < 10 years of age. The ACV (Advisory Committee on Vaccines) considers that the packaging should clearly state the lower age limit in order to distinguish this vaccine from other vaccines, and recommends that the lower age limit should be more prominent in the PI and CMI, and the educational activities for healthcare worker should be considered. ACV noted that another meningococcal serogroup B vaccine, Bexsero, is registered for individuals from 2 months of age and older, and this could affect the public health contexts for the use of Trumenba. ACV advises the TGA to obtain the relevant data relating to the safety of Trumenba in children < 12 months old. A brief summary of Study B1971008 was submitted following the TGA request. Study B1971008 was a Phase I/II study conducted in infants. A total of 46 infants (aged 45 to 86 days) received 1 dose of the final formulation of rLP2086. After 22 subjects received the 20 µg dose and 10 subjects received the 60 µg dose, the fever rate were 63.6% in the 20 µg dose level and 90% in the 60 µg dose level. Study B1971008 was terminated 90% of infants < 12 months

[40] Note: The vaccine was assessed using a panel of MnB strains expressing fHBP variants prevalent on Western Australian MnB disease causing strains; data are not available for the eastern states.

of age who were vaccinated with a reduced dosage formulation had fever which was deemed not acceptable in this population.

In the response to the RMP evaluation report, the sponsor states that the age groups for which Trumenba is indicated are clearly communicated in the proposed product label indications section, and further information, particular to experience in children < 10 years of age is communicated in the precautions section. If Trumenba is licensed in Australia, the Australian Technical Advisory Group on Immunisation (ATAGI) will review available data and provide clear recommendations on the use of Trumenba to be included in the Australian Immunisation Handbook. Administration information with regard to age will also be communicated by the Australian Department of Health (Immunise Australia Program). The sponsor further states that they regularly monitor and review reports of off-label use as part of routine post marketing pharmacovigilance and safety signal detection activities and discusses off-label use experience in the periodic safety update report (PSUR). If these pharmacovigilance activities indicate that off-label use may require additional risk mitigation measures beyond communication via the product label, the sponsor will act accordingly. The sponsor is currently conducting 2 ongoing studies that are evaluating the safety and immunogenicity of bivalent rLP2086 in children < 10 years of age (Study B1971017, 24 months to < 10 years of age; and Study B1971035, 12 to < 24 months of age). The safety data from each study are carefully monitored and routinely reviewed as a standard requirement. To date vaccinations are completed in Study B1971017 and are near completion in Study B1971035; although these studies are still blinded, the subjects have tolerated their injections well and no new safety issues have been identified.

Delegate's considerations

- Indication

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

- No efficacy studies were conducted. Serum bactericidal assay using human complement (hSBA) and the responses in hSBA were used as the surrogate marker for vaccine efficacy.
- The selection of factor H binding protein (fHBP) variants in the vaccine was not justified against the prevalent variants in Australia.
- The data in older adults are limited.
- RMP evaluation: Risk management for off-label use in children under the age of 10 years is an outstanding issue.
- The delegate supports the regulatory approval of Trumenba. The wording of the indication, the content of the PI, and the detailed RMP requirements will be further discussed at the August 2017 ACV meeting.
- The condition of registration should include:

  Any changes to which the sponsor has agreed should be included in a revised RMP and ASA. However, irrespective of whether or not they are included in the currently available version of the RMP document, the agreed changes become part of the risk management system.

The final approval is subject to satisfactory resolutions of any issues relating to the Product Information (PI) and the Risk Management Plan (RMP/ASA).

Proposed action

The Delegate had no reason to say, at this time, that the application should not be approved.

The wording of the indication, the content of the Product Information, and the RMP requirements will be discussed at the ACV meeting. The condition of registration should include:

Any changes to which the sponsor has agreed should be included in a revised RMP and ASA. However, irrespective of whether or not they are included in the currently available version of the RMP document, the agreed changes become part of the risk management system.

The final approval is subject to satisfactory resolutions of any issues relating to the Product Information (PI) and the Risk Management Plan (RMP/ASA).

Request for ACV advice

The committee is requested to provide advice on the following specific issues:

1. The selection of fHBP variants in this vaccine was not justified against the prevalent variants in Australia; the committee is request to comment on the use of this vaccine in the Australia context.
2. The committee is requested to advice whether the submitted data are adequate to support the proposed indication?
3. The committee is requested to advice on whether the submitted data support the proposed two dose and three dose schedules?
4. The committee is requested to advise on whether the PI statements in the Indication and Precaution sections regarding the age limit (> 10 years of age) are considered adequate in addressing the potential off-label use of this vaccine in children < 10 years of age?

The committee is (also) requested to provide advice on any other issues that it thinks may be relevant to a decision on whether or not to approve this application

Response from sponsor

Please note a PSUR for Trumenba has not been released in the EU as yet. This has not been included on the EMA list as yet and the sponsor is waiting on its inclusion in the list of European Union Reference Dates in order to establish the data-lock point. The company does have a PSUR in PBRER format covering the period 29 October 2014 through 28 April 2016. However this information has either been included in the dossier that the TGA has evaluated and has been used in the latest company reference document update which the proposed PI is aligned with.

Trumenba is currently under evaluation in Canada and has not been submitted in New Zealand therefore corresponding PI documents are not available.

Indication

The sponsor agrees with the proposed indication in the Delegate's overview:

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

Sponsor's response to the issues raised by the delegate for the ACV

The Delegate has sought the advice of the ACV on 5 main issues addressed below:

1. Justification of the selection of fHBP variants in the vaccine against the prevalent variants in Australia

Trumenba was designed to induce a broadly protective response against *N. meningitidis* group B (MnB) strains that express factor H binding protein. To date, over 95% of MnB strains tested express fHBP on their cell surface (VR-VTR-10183).[41] Strains representing diverse fHBP variants were tested with both preclinical and clinical immune serum early in the program to confirm that Trumenba is able to elicit antibodies that can kill MnB isolates in serum bactericidal assays using human complement (hSBAs), regardless of the specific fHBP variant expressed.

Extensive epidemiological evaluations of circulating disease strains, collected in a prospective prevalence based manner were conducted in collaboration with public health laboratories in Europe and the United States to understand the global distribution and sequence diversity of fHBP variants. This collection, referred to as the Extended MnB SBA strain pool, includes 1,814 invasive MnB disease isolates from 2000 to 2006 (VR-VTR-10183).[42, 43] Based on amino acid sequence similarity, fHBP variants segregate into 2 distinct subfamilies, designated A and B. Within the respective subfamilies, fHBP pairwise amino acid sequence identity is > 83%, but there is only 60% to 75% identity when comparing variants across subfamilies. While a total of 198 unique fHBP variants were identified, nearly 80% of the isolates express one of 11 prevalent variants. Comparison of the Extended MnB SBA strain pool with the genotypes of contemporary invasive disease isolates from North America and Europe revealed that the fHBP subfamily distribution and composition of prevalent fHBP variants has remained much the same (VR-VTR-10147, VR-VTR-10181, VR-VTR-10258).

Strains representing diverse fHBP variants were tested with both preclinical and clinical immune serum to confirm that Trumenba can induce antibodies that can kill MnB isolates in serum bactericidal assays using human complement (hSBAs), regardless of the specific fHBP variant expressed. Considering the diversity of fHBP, and given that only a limited number of MnB strains can be evaluated in Phase II/III clinical studies, the sponsor used an unbiased approach to select 4 primary hSBA test strains to support licensure. These strains express fHBP variants that:

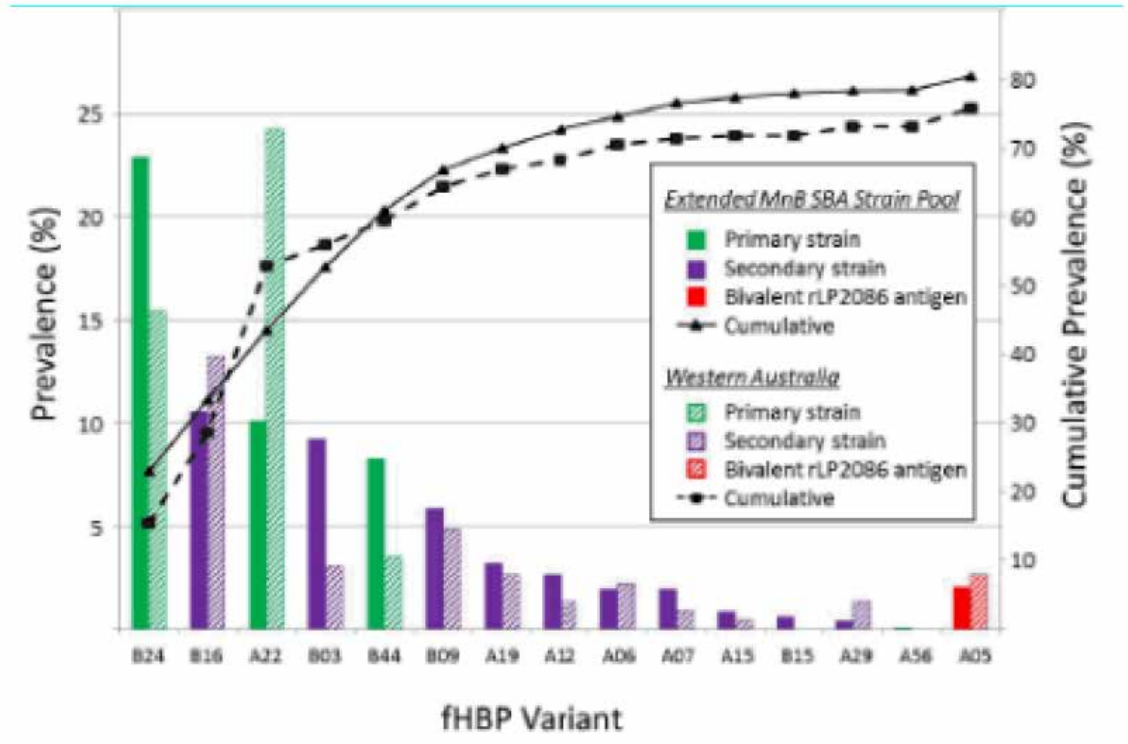
- are different from the vaccine antigens,
- include both fHBP subfamily A and B variants, and
- are representative of the fHBP and clonal complex diversity of strains in the Extended MnB SBA strain pool (VR-VTR-10156).

Ten secondary hSBA test strains, selected using similar criteria, have provided supportive evidence of the breadth of the protective response elicited by immunisation with bivalent rLP2086 (VR-VTR-10240). Together, the 4 primary and 10 secondary test strains express fHBP variants that are heterologous to the vaccine antigens and epidemiologically relevant in both the Extended MnB SBA strain pool and more contemporary collections of MnB disease causing isolates. The fHBP variants expressed by the 14 test strains represent the phylogenetic diversity of fHBP and, together with the bivalent rLP2086 vaccine antigens, collectively account for approximately 80% of disease isolates in the Extended MnB SBA strain pool (Figure 1).

[41] VR-VTR-10183 = Vaccine Research - Vaccine Technical Report. - 10183
[42] Murphy E, et al. Sequence diversity of the factor H binding protein vaccine candidate in epidemiologically relevant strains of serogroup B Neisseria meningitidis. *J Infect Dis* 2009; 200: 379-89.
[43] Hoiseth SK, et al. A multi-country evaluation of Neisseria meningitidis serogroup B factor H-binding proteins and implications for vaccine coverage in different age groups. *Pediatr Infect Dis J* 2013; 32: 1096-1101.

Mowlaboccus and colleagues have provided the most recent and comprehensive analysis of IMD isolates from Australia.[44] The authors describe the epidemiology of 278 IMD isolates from Western Australia, representing 62% of the notified cases from 2000 to 2014. MnB accounted for 82% of the total (227/278) and whole genome sequence data was recorded for each of these isolates. A total of 46 unique fHBP variants were identified among the 227 MnB strains and the eleven most prevalent of these variants represent 78% (178/227) of the total. These same 11 fHBP variants are expressed by 76% (1378/1814) of strains in the Extended MnB SBA strain pool, demonstrating that the most prevalent variants in the Extended MnB SBA strain pool are also the most prevalent in Western Australia. Finally, 76% (172/227) of the MnB strains described by Mowlaboccus and colleagues express fHBP variants corresponding to either the bivalent rLP2086 vaccine antigen (A05), or the variants expressed by the 4 primary and 10 secondary hSBA test strains (Figure 1). Thus, the variants expressed by the hSBA test strains used to provide the critical immunological support for licensure of bivalent rLP2086 are indeed representative of prevalent fHBP variants associated with the disease causing MnB isolates circulating in Western Australia from 2000 to 2014.

Figure 1: Comparative prevalence of the fHBP variants corresponding to the bivalent rLP2086 vaccine antigens and variants expressed by the 4 primary and 10 secondary hSBA strains among MnB isolates from the Extended MnB SBA strain pool (n = 1814) [441] and the strain collection from Western Australia (n = 227).[44]



2. The submitted data are adequate to support the proposed indication

Immunogenicity studies

The clinical development program for Trumenba establishes a safety and immunogenicity database appropriate and sufficient for registration.

The Phase III program consisted of 3 studies. Study B1971009 assessed the immune responses in adolescents (10 to < 19 years) and lot consistency. Study B1971016 assessed

[44] Mowlaboccus S, et al. Temporal Changes in BEXSERO Antigen Sequence Type Associated with Genetic Lineages of Neisseria meningitidis over a 15-Year Period in Western Australia. PLoS One. 2016; 11:e0158315.

the immune responses in adults (18 to < 26 years). Study B1971014 was a safety study in a large population (10 to < 26 years).

Robust functional and broadly protective immune responses were observed in individuals receiving Trumenba in a 2 dose schedule (0 and 6 months) in Phase II Study B1971012, and in a 3 dose schedule (0, 2, and 6 months and 0, 1, and 6 months) in the Phase III program. In these studies, the immune responses were measured by hSBAs that used *N. meningitidis* serogroup B (MnB) strains (4 primary or 10 secondary) that were prospectively selected to represent the diversity of the target antigen, fHBP. Each primary and secondary strain expressed fHBPs that were heterologous to the vaccine fHBP variants. Additional exploratory analysis with outbreak strains has further exemplified the ability of Trumenba to induce broadly protective responses (VR-VTR-10151 and VR- VTR-10287).[45] [46] In addition, a consistent favourable safety and reactogenicity profile supports the use of Trumenba to prevent invasive MnB disease in individuals 10 years of age and older. Clinical studies also demonstrated that Trumenba may be co-administered with MCV4, Tdap, HPV4, and Tdap-IPV vaccines.

The benefit-risk ratio of Trumenba is favourable for individuals receiving the vaccine on a routine 2 dose schedule (0, 6 months), or on a 3 dose schedule (2 doses given at least 1 month apart, followed by a third dose at least 4 months after the second dose) for individuals at increased risk of meningococcal disease.

Efficacy studies

Based on the low incidence of MnB disease, placebo controlled clinical efficacy studies for Trumenba were considered unfeasible and were not performed. In accordance with the Committee for Medicinal Products for Human Use Scientific Advice[39], the sponsor tested the ability of the vaccine to elicit serum bactericidal activity, the recognised and accepted correlate of protection, against invasive meningococcal disease (IMD).[47] [48] [49] The hSBA is a functional serological assay. The responses as measured by hSBA serve as the surrogate marker of vaccine efficacy.

3. Data in older adults are limited

While there are limited data in older adults, the sponsor agrees with the Delegate that these data indicate that the safety and immunogenicity of the vaccine are acceptable and similar to that seen in younger adults and that the impact of a potential decreased immune response with age is unlikely to negatively affect Trumenba's favourable benefit-risk balance, especially when utilised in an outbreak situation.

4. Dosage schedule

The sponsor agrees with the Delegate that results from Study B1971012 showed that the close administration of the first 2 doses (0, 2 and 0, 4 month schedules) is associated with a lower hSBA response than that seen with administration of the 2 doses at the greater interval (the 0, 6 month schedule). Study B1971012 also showed that while the responses elicited by the 3 dose schedule are higher than the response following the first 2 doses

[45] Harris SL, et al. Neisseria meningitidis serogroup B vaccine, bivalent rLP2086, induces broad serum bactericidal activity against diverse invasive disease strains including outbreak strains. *Pediatr Infect Dis J* 2017; 36: 216-223.
[46] Taha MK, et al. Bactericidal activity of sera from adolescents vaccinated with bivalent rLP2086 against meningococcal serogroup B outbreak strains from France. *Vaccine* 2017; 35: 1530-1537.
[47] Holst J, et al. Serum bactericidal activity correlates with the vaccine efficacy of outer membrane vesicle vaccines against Neisseria meningitidis serogroup B disease. *Vaccine* 2003; 21:734-737.
[48] Borrow R, et al. Neisseria meningitidis group B correlates of protection and assay standardization–International Meeting Report Emory University, Atlanta, Georgia, United States, 16–17 March 2005. *Vaccine* 2006; 24: 5093-5107.
[49] Frasch CE, et al Bactericidal antibody is the immunologic surrogate of protection against meningococcal disease. *Vaccine* 2009;27S:B112-6.

given at 0 and 1 month or 0 and 2 months, the responses after the 3 dose schedule are not substantially higher than the response following the 2 dose schedule given at 0 and 6 months. These data support the proposal for routine vaccination with 2 doses at 0 and 6 months in adolescents/adults and for 3 doses (0, 1-2, and 6 months) administered to individuals with increased risk of invasive meningococcal disease, when 2 doses of vaccine need to be administered more rapidly to afford protection. The sponsor concludes that data from Study B1971012 support the proposed 2 dose and 3 dose schedules.

5. Suitability of Product Information in addressing the potential off-label use of Trumenba in children < 10 years of age

In regard to addressing the potential risk of off-label use in children less than 10 years of age in the PI, the sponsor proposes to add further information to the paediatric population precaution in order to communicate specifically the potential for fever if Trumenba is administered off-label to infants, which comprise the population most susceptible to such a reaction. The proposed text is as follows: 'In a clinical study, 90% of infants less than 12 months of age who were vaccinated with a reduced dosage formulation had fever.' (For detailed information concerning the safety results from Study 1008, in which this observation was made, please see, the sponsor's comments on the PI (provided), 'The risk of harm in off-label use in children under 10 year of age').

In regard to children aged 12 months to < 10 years, the sponsor is currently conducting a study evaluating the safety and immunogenicity of bivalent rLP2086 in toddlers 12 to < 24 months of age (Study B1971035). The safety data from this study are carefully monitored and routinely reviewed. Vaccinations have been completed and subjects have tolerated their injections well and no new safety issues have been identified. In addition, final safety data have recently become available for Study B1971017, which was conducted in children from 24 months to < 10 years of age. The results show that bivalent rLP2086 was well tolerated in these subjects, and no new safety issues were identified. A summary of data from Study B1971017 is available upon request.

This risk minimisation, in addition to the clearly stated age indication in the PI and the lower age of use prominently placed on the product packaging, will effectively convey that Trumenba should not be administered to children less than 10 years of age.

6. Risk Management Plan (RMP) requirements

The sponsor must submit the final EU RMP and update the ASA accordingly. Any changes compared to the EU RMP evaluated by the TGA should be described.

In this response, the sponsor is submitting the EMA-approved EU RMP (version 1.4), including tracked changes showing the final language as it has changed from the initially proposed version submitted to the EMA and TGA at the filing of the original applications. An updated proposed ASA will be submitted by the sponsor following finalisation of the Australia PI.

7. The Sponsor must address the important potential risk of off-label use in children younger than 10 years of age in the ASA and propose adequate risk minimisation measures and consider the advice with regard to the PI and packaging.

Risk of off-label use in children < 10 years of age

In response to the RMP Evaluator's comment that 'Off-label use in children under 10 years of age' should be included as an important potential risk in the summary of safety concerns in the Australia-Specific Annex (ASA) to the RMP, the sponsor proposes a modification to the risk language to more directly address the evaluator's concern regarding the potential for fever and febrile convulsions in the age group most at risk for such events. Safety data available from studies of bivalent rLP2086 in infants and toddlers show that the important potential risk is specifically applicable to infants less than 1 year of age.

The risk of fever in infants was identified during review of data from an ongoing study in which a reduced dosage formulation of bivalent rLP2086 was administered to infants at 2, 4, 6, and 12 months of age (Study B1971008). These results led to termination of the trial, as the vaccine was deemed not acceptable in infants less than 1 year old.

In contrast, observations from 2 clinical studies conducted in children in the age range of 12 months to < 10 years confirm that bivalent rLP2086 is well tolerated in this age group. The sponsor is currently conducting a study evaluating the safety and immunogenicity of bivalent rLP2086 in toddlers 12 to < 24 months of age (Study B1971035). The safety data from this study are carefully monitored and routinely reviewed. Vaccinations have been completed and subjects have tolerated their injections well and no new safety issues have been identified. In addition, final safety data have recently become available for Study B1971017, which was conducted in children from 24 months to < 10 years of age. The results from this study show that bivalent rLP2086 was well tolerated in these subjects, and no new safety issues were identified. A summary of data from Study B1971017 is available upon request.

Based on these data, the sponsor proposes that the important potential risk should more appropriately be worded to address 'Off-label use in infants < 12 months of age.'

Risk minimisation measures; PI and packaging

The sponsor agrees that it is important for the PI, Consumer Medical Information (CMI), and product packaging to clearly communicate the lower age limit for use of Trumenba. This information will be clearly stated in the labelling and will be prominently placed on the product packaging. In addition, the sponsor agrees to reinforce the PI as a risk minimization tool against off-label use by including the following safety information from the infant experience in Study B1971008: 'In a clinical study, 90% of infants less than 12 months of age who were vaccinated with a reduced dosage formulation had fever.'

The sponsor considers that the planned routine risk minimization, comprising clear language in the PI to reinforce the approved age indication and communicate the potential risk of fever with off-label use in infants < 12 months of age, as well as the lower age of use prominently placed on the product packaging, will effectively convey that Trumenba should not be administered to children younger than 10 years of age. Therefore, the sponsor considers that additional educational activities for prescribers and those administering the vaccine to mitigate the potential risk of off-label use in infants < 12 months of age will not be necessary.

RMP PI requests

Responses to the specific PI requests from the RMP evaluation concerning premedication with paracetamol as prophylaxis for AE's, increased prominence of precautions regarding off-label use in the under 10 age group, inclusion of a precaution regarding use in infants < 12 months, a statement on the lack of clinical evidence in the > 40 age group, and the format of the presentation of data for adverse effects are contained in the accompanying document 'sponsor's comments on PI' [not included].

Advisory Committee Considerations

The ACV taking into account the submitted evidence of efficacy, safety and quality, agreed with the Delegate and considered Trumenba meningococcal group B vaccine to have an overall positive benefit-risk profile for the indication:

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

and for dosing schedules, summarised as:

- The primary vaccination schedule consists of 2 doses (0.5 ml each) administered at 0 and 6 months
- The schedule for individuals at increased risk of invasive meningococcal disease is 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.

Each 0.5 mL dose contains: *N. meningitidis* serogroup B recombinant lipidated factor H binding protein subfamily A 60 µg factor H binding protein subfamily B 60 µg.

In making this recommendation the ACV:

- Considered that the vaccine would be likely to provide protection for a large proportion of meningococcal group B strains in Australia.
- Advised that the data are adequate to support use in those > 10 years of age.
- Noted that post-market surveillance was important to detect any possible vaccine failures.
- Advised that the data supported the 2 or 3 dose schedule but further clarification in the PI was necessary in order to better define who should receive the 2 or 3 dose schedule.
- Noted that Bexsero and Trumenba are not interchangeable as they have different dosing schedules as well as different doses depending on age.
- Advised that further risk mitigation is needed to prevent use in children less than 10 years of age.

Proposed PI / Consumer Medicine Information (CMI) amendments

The committee emphasised that the PI and CMI should provide sufficient information to allow prescribers and consumers to make a determination of the risks and benefits of the vaccine. (See also Specific Advice 3 and 4)

Specific Advice

The ACV advised the following in response to the Delegate's specific questions on the submission:

1. ***The selection of fHBP variants in this vaccine was not justified against the prevalent variants in Australia; the committee is requested to comment on the use of this vaccine in the Australia context.***

The ACV noted that Trumenba contained 2 lipidated factor H (LPH) binding protein subfamilies, A and B, which is different from the currently available meningococcal group B vaccine, Bexsero (multicomponent Meningococcal group B vaccine).

The ACV considered the sponsor's pre-ACV response, which provided information regarding recent and comprehensive analysis of invasive meningococcal disease (IMD) isolates from Australia.[50] In this analysis, 76% (172/227) of the MnB strains expressed fHBP variants corresponding to either the bivalent rLP2086 vaccine antigen (A05), or the variants expressed by the 4 primary and 10 secondary hSBA test strains. The analysis concluded that the variants expressed by the hSBA test strains used to provide the critical immunological support for licensure of bivalent rLP2086 are representative of prevalent fHBP variants associated with the disease causing MnB isolates circulating in Western Australia from 2000 to 2014.

[50] Mowlaboccus S, et al. Temporal Changes in Bexsero Antigen Sequence Type Associated with Genetic Lineages of Neisseria meningitidis over a 15-Year Period in Western Australia. PLoS One. 2016; 11(6):e0158315.

The ACV concluded that whilst Trumenba would not protect against every strain of meningococcus in Australia, it would provide protection for a large proportion of serogroup B strains, the proportion of which may be comparable to that covered by Bexsero. The ACV considered that it is important to monitor for any potential vaccine failures (that is meningococcal serogroup B disease in someone vaccinated with Trumenba) with post-market surveillance.

2. Whether the submitted data are adequate to support the proposed indication?

The ACV noted that there were limitations to the data presented in support of registration such as the reliance on surrogate immunologic assays to support immunogenicity rather than efficacy data based on clinical endpoints, reliance on test strains for serum bactericidal assay (SBA) and limited data on use in patients older than 26 years of age. However, despite these limitations, the ACV advised that the submitted data are adequate to support the proposed indication.

3. Whether the submitted data support the proposed two dose and three dose schedules?

The ACV considered that it was difficult to compare 2 and 3 dose studies which had complex multiple immunogenicity results.

The ACV noted that the pivotal Phase III studies present predominantly the 3 dose immunogenicity results. The ACV noted that the 3 dose schedule will provide a rapid antibody response following the first 2 doses (at 0, 1 month or 0, 2 months) and this 3 dose schedule would benefit the population who is at increased risk of the invasive disease and needs immediate protection.

The data indicate that both schedules provide protection but scheduling is based on the clinical scenario.

The ACV was of the view that the scenario for choosing the scheduling is reflected in the USA Advisory Committee on Immunization Practices (ACIP) and noted that there is a comment in the US PI as follows: *'The choice of dosing schedule may depend on the risk of exposure and the patient's susceptibility to meningococcal serogroup B disease.'* The ACV advised that similar wording could be included in the Australian PI or alternatively the PI should highlight that clinical guidelines should be followed prior to the administration of the vaccine with regards to the dosing schedule in order to better define who should receive the 2 or 3 dose schedule.

4. Whether the statements in the Indication and Precaution sections of the PI regarding the age limit (> 10 years of age) are considered adequate in addressing the potential off-label use of this vaccine in children < 10 years of age?

The ACV noted that a study in infants using a reduced dose formulation had been stopped early due to high rates of fever. The ACV considered that if Trumenba is administered inadvertently to children less than 1 years of age, a febrile reaction would be highly likely, based on the study in infants.

The ACV noted that the clinical program in children has resumed with studies including children from 1 to less than 10 years of age. The sponsor's pre-ACV response stated that final safety data have recently become available for Study B1971017, which was conducted in children from 24 months to < 10 years of age and the results show that bivalent rLP2086 was well tolerated in these subjects, and no new safety issues were identified. The ACV considered that the sponsor should submit the summary of data from Study B1971017 to the TGA, as these data would provide additional information on use in children less than 10 years of age which at some stage could be included in the PI, to provide information in the event that off-label or inadvertent use in this group occurs.

The ACV advised that further risk mitigation is needed to prevent use in children less than 10 years of age such as improved wording in the PI and agreed that the packaging should highlight that Trumenba should only be given to children over 10 years of age. In addition, educational activities for healthcare professionals should be considered.

The ACV noted that the sponsor in its pre-ACV response has committed to communicate the risk of fever with off-label use in infants < 12 months of age by clearer language in the PI and highlight the lower age of use prominently placed on the product packaging. Both will be reviewed by the TGA prior to registration.

The ACV noted that the two meningococcal B vaccines are not interchangeable as they have different dosing schedules as well as different doses depending on age. This should be highlighted in the PIs of both the vaccines and in clinical guidelines for immunisation providers.

Post ACV negotiations

Update to RMP

Prior to agreement to registration the Delegate negotiated an update to the RMP table summary of safety concerns see Table 12 below.

Table 12: Revised summary of safety concerns from revised ASA

Summary of safety concerns (ASA v1.2)		Pharmacovigilance		Risk Minimisation	
		Routine	Additional	Routine	Additional
Important identified risks	None	–	–	–	–
Important potential risks	Safety of off-label use in children younger than 10 years of age	ü	–	ü	–
Missing information	Use in pregnancy and lactation	ü	ü	ü	–
	Use in individuals 40 years and older				
	Use in immunocompromised individuals (e.g. with terminal complement deficiency or asplenia)	ü	ü	ü	-
	Vaccine effectiveness	ü	ü*	ü	–
	Vaccine Failure	ü	ü*	ü	–

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Trumenba (Neisseria meningitidis serogroup B recombinant lipidated- factor H binding protein subfamily A, Neisseria meningitidis serogroup B recombinant lipidated- factor H binding protein subfamily B) for suspension for injection, indicated for:

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

Specific conditions of registration applying to these goods

- The EU-RMP version 1.4 dated 21 March 2017 (DLP 30 November 2015), with Australian Specific Annex version 1.1 dated February 2017, to be revised to the satisfaction of the TGA, must be implemented. The revised Australian Specific Annex should include 'safety of off-label use in children younger than 10 years of age' as an important potential risk and a Dear Healthcare Professional Letter to mitigate the risk of interchanging Trumenba with other meningococcal group B vaccines.
- The company will submit a Category 3 application to transition the In Vivo Potency assay conducted on Trumenba Drug Product to a release test when appropriate GMP clearance for the testing sites is received.
- Batch Release: It is a condition of registration that all independent batches of Trumenba imported into Australia are not released for sale until samples and the manufacturer's release data have been assessed and you have received notification from the Laboratories Branch, TGA that there is no objection to you releasing the product to the Australian market.

  For each independent batch of the product imported into Australia, the Sponsor must supply the following:

  - A completed Request for Release Form.
  - Complete summary protocols for manufacture and QC, including all steps in production.
  - At least 5 doses of each first consignment of product lot with the Australian approved labels, PI and packaging. 3 doses of any further consignment of already released product with the Australian approved labels, PI and packaging. (Number to be confirmed)
  - Certificate of Release from regulatory agency acting for the country of origin such as an OMCL (if available).
  - Pfizer will provide the European Release Protocol including the IVP assay results in the Summary Manufacturing Protocol.
  - Any reagents, reference material and standards required to undertake testing, as requested by Laboratories Branch, TGA.

  Distribution of each shipment of each batch of vaccine is conditional upon fulfilment of these conditions and receipt of a notification letter from the Laboratories Branch.

Attachment 1. Product Information

The PI for Trumenba approved with the submission which is described in this AusPAR is at Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>

Attachment 2. Extract from the Clinical Evaluation Report

Therapeutic Goods Administration

PO Box 100 Woden ACT 2606 Australia
Email: info@tga.gov.au Phone: 1800 020 653 Fax: 02 6232 8605
https://www.tga.gov.au