NEISSERIA MENINGITIDIS SEROGROUP B BIVALENT RECOMBINANT LIPOPROTEIN RISK MANAGEMENT PLAN

RMP Version number: 9.0

Data lock point for this RMP:

Clinical Trial database	31 March 2024
Post-Authorization exposure	28 October 2024

Date of final sign off: 17 January 2025

Rationale for submitting an updated RMP: to propose removal of Missing Information "Use in co-administration with MMR and pneumococcal vaccines" and the associated additional PV activity (study C3511006). Trumenba is indicated for individuals 10 years of age and older and therefore, does not include the paediatric age group in which MMR and pneumococcal vaccines are routinely administered. In the majority of EU countries, MMR and pneumococcal vaccines are not included in the national immunization schedules as a general recommendation for individuals 10 years of age and older. Furthermore, no safety signals have been identified from 7 years of post-marketing data and no unknown risks of a clinical significance would be anticipated as the risks associated with the vaccines, primarily those of reactogenicity-type events, are known and well described.

Summary of significant changes in this RMP:

RMP Part/Module	Major Change(s)
PART I. PRODUCT OVERVIEW	No changes.
PART II SAFETY SPECIFICATION	
Module SI. Epidemiology of the Indications and Target Population	No changes.
Module SII Non-Clinical Part of the Safety Specification	No changes.
Module SIII. Clinical Trial Exposure	No changes as all studies were already completed at the existing DLP (31 March 2024).
Module SIV. Populations Not Studied in Clinical Trials	No changes.
Module SV. Post-Authorisation Experience	Post-authorization exposure updated at the DLP of 28 October 2024.
Module SVI. Additional EU Requirements for the Safety Specification	No changes.
Module SVII. Identified and Potential Risks	Update of Module SVII.2 to reflect proposal to remove the Missing Information of "Use in co-administration with MMR and pneumococcal vaccines" and the rationale for this action.
Module SVIII. Summary of the Safety Concerns	Removal of the Missing Information "Use in co-administration with MMR and pneumococcal vaccines"

RMP Part/Module	Major Change(s)
PART III. PHARMACOVIGILANCE PLAN (INCLUDING POST AUTHORISATION SAFETY STUDIES)	C3511006 removed from planned PV activities. B1971060 removed as completed PV activity.
PART IV. PLANS FOR POST AUTHORISATION EFFICACY STUDIES	Removal of completed study B1971057.
PART V. RISK MINIMISATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMISATION ACTIVITIES)	Updated to remove the Missing Information "Use in co-administration with MMR and pneumococcal vaccines" and to remove associated routine risk minimisation measure and additional PV activity (C3511006).
PART VI. SUMMARY OF THE RISK MANAGEMENT PLAN	Updated to reflect changes made in the other Parts and Modules of the RMP.
PART VII. ANNEXES TO THE RISK MANAGEMENT PLAN	Annex 2: Study C3511006 removed. Annex 3: Study C3511006 removed. Annex 8: Changes to reflect the updated information in the RMP Part I to Part VI.

Other RMP versions: Not applicable

Details of the currently approved RMP:

RMP Version Number	Approved with Procedure	Date of Approval (Opinion Date)
8.0	EMEA/H/C/004051/II/0053	16 January 2025

QPPV name[1:] Barbara De Bernardi

QPPV oversight declaration: The content of this RMP has been reviewed and approved by the marketing authorisation holder´s QPPV. The electronic signature is available on file.

[1] QPPV name will not be redacted in case of an access to documents request; see HMA/EMA Guidance document on the identification of commercially confidential information and personal data within the structure of the marketing-authorisation application; available on EMA website http://www.ema.europa.eu

LIST OF ABBREVIATIONS

ATC	Anatomical Therapeutic Chemical (drug classification system)
CFR	Case Fatality Rate
CHMP	Committee for Medicinal Products for Human Use
CT	Clinical Trial
ECDC	European Centre for Disease Prevention and Control
EDP	Exposure During Pregnancy
EEA	European Economic Area
EMA/EMEA	European Medicines Agency
EPAR	European Public Assessment Report
EU	European Union
fHbp	Factor H Binding Protein
HAV	Hepatitis A virus
HCP	Health Care Professional
IM	Intramuscular
IMD	Invasive Meningococcal Disease
IMS	Intercontinental Marketing Services
INN	Inventory non-proprietary name
IV	Intravenous
MA	Marketing Authorisation
MAA	Marketing Authorisation Application
MAH	Marketing Authorisation Holder
MenABCWY	Meningococcal polysaccharide groups A, B, C, W-135, and Y
MMR	Measles-Mumps-Rubella Vaccine
MnB	*Neisseria meningitidis* serogroup B
N. meningitidis	*Neisseria meningitidis*
NA	Not applicable
NDTI	National Disease and Therapeutic Index
NMTA	National Medical and Treatment Audit
PDCO	Paediatric Committee
PL	Package Leaflet
PSUR	Periodic Safety Update Report
rLP2086	Recombinant Lipoprotein 2086
RMMs	Risk minimisation measure(s)
RMP	Risk Management Plan
ROW	Rest of World
SmPC	Summary of Product Characteristics
US	United States
WHO	World Health Organisation

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PART I. PRODUCT(S) OVERVIEW

Active substance(s) (INN or common name)	*Neisseria meningitidis* Serogroup B fHbp subfamily A and B
Pharmacotherapeutic group(s) (ATC Code)	Meningococcal group b vaccine (recombinant, adsorbed) (J07AH09)
Marketing Authorisation Holder Applicant	Pfizer Europe MA EEIG (Belgium)
Medicinal products to which this RMP refers	1
Invented name(s) in the EEA	Trumenba
Marketing authorisation procedure	Centralised
Brief description of the product:	Chemical class: *N. meningitidis* Serogroup B fHbp subfamily A and B (Bivalent rLP2086, herein after referred to as bivalent rLP2086) is white liquid suspension composed of 2 recombinant lipidated factor H binding protein (fHbp) variants from *N. meningitidis* serogroup B, 1 from fHbp subfamily A and 1 from subfamily B.
	Summary of mode of action: Immunisation with bivalent rLP2086, which contains one fHbp variant each from subfamily A and B, is intended to stimulate the production of bactericidal antibodies that recognize fHbp expressed by meningococci
	Important information about its composition: The proteins are individually produced in *Escherichia coli*. The recombinant proteins are extracted from the production strains and purified. Each 0.5 mL dose contains 60 µg of each fHbp variant (total of 120 µg of protein), sodium chloride, histidine, water for injections, aluminium phosphate, and polysorbate 80 (PS80).
Hyperlink to the Product Information:	Please refer to Module 1.3.1 of this submission.
Indication(s) in the EEA	Bivalent rLP2086 is indicated for active immunisation of individuals 10 years and older to prevent invasive meningococcal disease (IMD) caused by *N. meningitidis* serogroup B.
Dosage in the EEA	**Primary series** 2 doses (0.5 mL each) administered at a 6-month interval. 3 doses: 2 doses (0.5 mL each) administered at least 1 month apart, followed by a third dose at least 4 months after the second dose. **Booster dose** A booster dose should be considered following either dosing regimen for individuals at continued risk of invasive meningococcal disease.

Pharmaceutical form(s) and strengths	Bivalent rLP2086 is a white liquid suspension for injection. 1 dose (0.5 mL) contains: - *N. meningitidis* serogroup B fHbp protein subfamily A: 60 micrograms. - *N. meningitidis* serogroup B fHbp protein subfamily B: 60 micrograms. Excipients: Sodium chloride, histidine, polysorbate 80 (E433), water for injections.
Is/will the product be subject to additional monitoring in the EU?	No

ATC = Anatomical Therapeutic Chemical; *E. coli* = *Escherichia coli*; EEA = European Economic Area; EU = European union; fHbp = Factor H Binding Protein; IMD = Invasive Meningococcal Disease; mL = Milliliter; mM = millimoles; *N. meningitidis* = *Neisseria meningitidis*; PS80 = Polysorbate 80; rLP2086 = Recombinant Lipoprotein 2086; RMP = Risk management Plan.

PART II. SAFETY SPECIFICATION

Module SI. Epidemiology of the Indication(s) and Target Population (s)

Indication:

The approved indication for bivalent rLP2086 is for active immunization to prevent invasive meningococcal disease caused by *Neisseria meningitidis* (*N. meningitidis*) serogroup B in individuals aged 10 and older.

Incidence:

The World Health Organization (WHO) has identified twelve serogroups of *N. meningitidis* based on immunologic differences in their polysaccharide capsule[1]. Five of these serogroups (A, B, C, W, and Y) are responsible for the vast majority of invasive disease worldwide[2]. Serogroup B accounts for approximately 62% of the cases in Europe[3]. Unencapsulated strains can be found in the nasopharynx in asymptomatic carriers but rarely cause invasive meningococcal disease (IMD)[2].

For the most recent report published in 2024 based on 2022 reporting, 28 EU member states and 2 European Economic Area (EEA) countries provided case information to the European Centre for Disease Prevention and Control (ECDC)[3]. Most countries reported data from comprehensive, passive surveillance systems with national coverage. Belgium reported data from a sentinel surveillance system. Bulgaria and Croatia reported aggregated data in 2022. The United Kingdom (UK) contributed surveillance data up to 2019. No data were reported by the UK for 2020 or 2021 due to its withdrawal from the EU on 31 January 2020. The UK data that were reported up to 2019 are not included in the analysis of trends. Only laboratory-confirmed cases of IMD are considered for presentation[3]. For this review, estimates of incidence were derived from the ECDC system unless otherwise noted.

While the overall reported notification rate declined from 0.5 per 100,000 (N=2456) in 2018 to 0.3 per 100,000 (N=1149) in 2022[3], there was a doubling of reported confirmed cases between 2021 and 2022 (612 vs 1149 per 100,000). Four countries (France, Germany, Poland and Spain) accounted for 60% of all confirmed cases. Cyprus and Liechtenstein reported zero cases. Notification rates ranged from <0.1 cases (Bulgaria, Greece) to 0.6 cases per 100 000 population (Ireland, Luxembourg). The incidence in France, Lithuania and Slovakia reached 0.5 cases per 100 000 population, the second highest notification rate reported in 2022 after Ireland and Luxemburg.

Prevalence:

Meningococcal disease is an acute infectious disease. Because of the short (acute) duration of disease, incidence is equivalent to prevalence; and as a result, there are no epidemiologic studies reporting the prevalence of meningococcal disease.

Demographics of the population in the authorised indication – age, gender, racial and/or ethnic origin and risk factors for the disease:

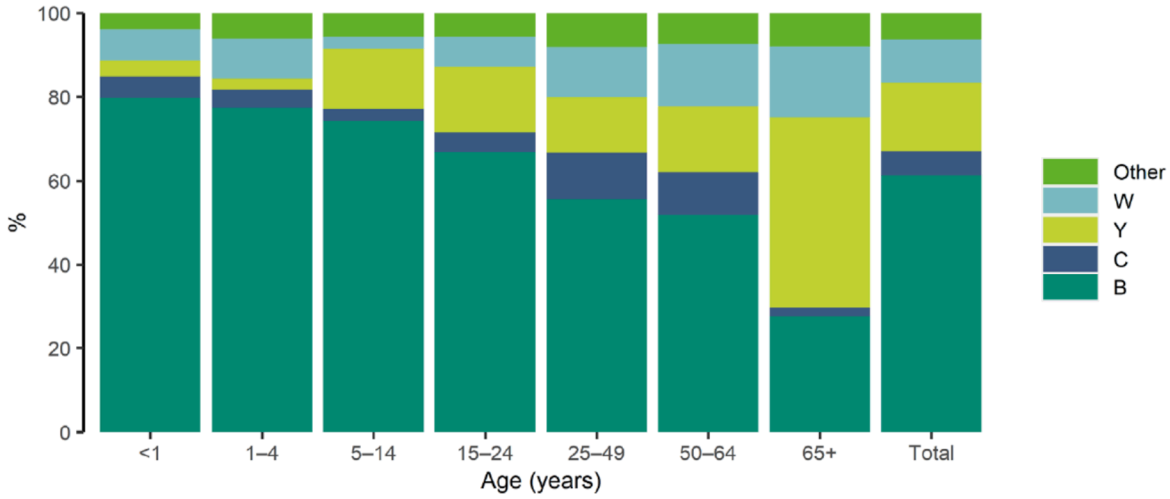
Age and Meningococcal Group distribution

In 2022, notification rates were greatest among children <1 year of age (4.3 per 100,000) and children aged 1-4 years (0.8 per 100,000).[3] Another peak occurred among adolescents and young adults ages 15-24 (0.6 per 100,000).[3] Notification rates for other age groups were: 5-14 years (0.2 per 100,000), and 65 years and older (0.2 per 100,000). Notification rates were higher in males compared to females: 0.3 versus 0.2 confirmed cases per 100,000 population. The overall male-to-female ratio of IMD cases was 1.18:1.

Out of 1149 confirmed IMD cases reported in 2022, 991 (86%) had a documented serogroup Sixty-two percent was due to serogroup B followed by serogroups Y (16%), W (10%) and C (6%). A total of 14% did not have a serogroup designation. Serogroup B was predominant in all age groups aged below 65-year-olds (Figure 1). In total, serogroup B accounted for 80% of cases aged less than one year. Serogroup Y was mostly documented in those aged 65 years and above, causing 46% of cases in this age group. Serogroup W was most common in the 65 years and above age group, causing 17% of cases, and was the second most common serotype identified in this age group. In other age groups, the proportion fluctuated between 6.6% (15–24-year-olds) and 14.8% (50–64-year-olds). Serogroup C was the third serogroup reported in <1 year (5%) and in 1–4-year-olds (4.3%), age groups where serogroup B was dominant. In 25–49-year-old and in 50–64-year-olds, the proportion of serogroup C was respectively 11% and 10% and it was the serogroup less commonly reported in these age groups.

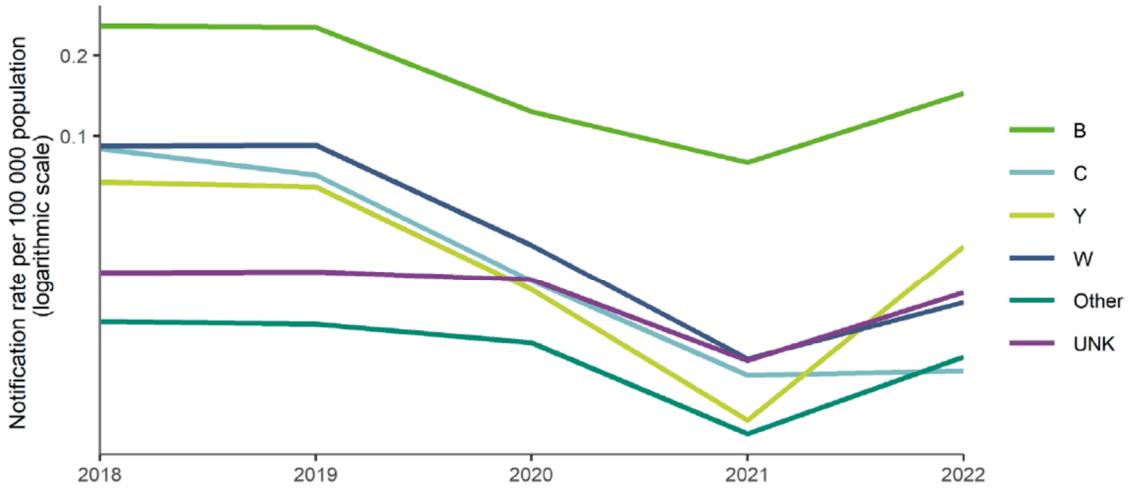
As seen in Figure 2 there has been an overall increase in notification rates for serogroups B, W, and Y in 2022 compared to 2021, while serogroup C has continued to decrease. There was a sharp rise in notification rates for serogroup Y in 2022 compared to 2021 and it was the second highest serogroup overall in 2022 (0.04 cases per 100,000 population).

Figure 1. Serogroup Distribution of Confirmed Cases of IMD by Age Group, EU/EEA, 2022[3]



'Other' refers to all cases reported as serogroup A, X, Z, 29E, non-groupable or 'other'.

Figure 2. Notificaiton Rates of Confirmed Cases of IMD by Serogroup and Year, EU/EEA, 2018-2022[3]



Source: country reports from Austria, Belgium, Czechia, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Luxembourg, the Netherlands, Norway, Poland, Portugal, Slovakia, Slovenia, Spain, and Sweden.

Meningococcal Disease Outbreaks

Table 1 shows outbreaks of *N. meningitidis* serogroup B were reported in Europe as identified from the literature within the last 18 years. Among several studies, the risks identified for carriage or invasive MnB disease included living in confined quarters,

attending crowded social venues, recent or concomitant upper respiratory tract infection or influenza, greater social deprivation, and older age.[4,5]

Table 1. Outbreaks of Neisseria Meningitidis Serogroup B in Europe, 2006-2022.

Author	Year	Region, Country	Cases (n)	Deaths (CFR)	Epidemiological Link between Cases
ECDC Weekly Bulletin Week 50, 11-17 Dec, 2022[6]	2022	Strasbourg, France	4	1 (25.0%)	Night club
Jacquinet[7] 2018	2018	Wallonia, Belgium	3	0 (0.0%)	Nursery school
Tzanakaki[8] 2006	2003	Athens, Greece	3	0 (0.0%)	Kindergarten classroom
Tzanakaki[8] 2006	2003	Athens, Greece	2	0 (0.0%)	High school
Stewart 2013[9]	2010	West Midlands, England	2	0 (0.0%)	Nursery school
O'Connor 2015[4]	2010-2013	Ireland	8	0 (0.0%)	Family cluster
Acheson 2012[10]	2011	England	4	0 (0.0%)	Family cluster
Chatt 2014[11]	2013	Warwickshire, England	5	0 (0.0%)	Nursery school, close contacts
Public Health England, 2017[12]	2017	Surrey, England	3	1 (33.3%)	University

N=number; CFR=case fatality rate

Carriage

Recent studies estimate that carriage prevalence peaks during late adolescence in Europe and Americas, and early adolescence in Africa.[13, 14]. Based on a systematic review and meta-analysis of 21 studies of sero-specific meningococcal carriage by age group (all ages in Africa, 18–24-year olds in the Americas, and 11–17 and 18–24-year olds in Europe), the overall carriage prevalence varied markedly by age group and region[14]. Capsular groups W, X, Y and 'other' (non-ABCWXY, including non-groupable) were the most prevalent in Africa, and 5–17-year-olds had higher carriage prevalence than other age groups. 'Other' serogroups (11.5%, 95% CI 1.6% to 16.1%) were the most common among 18–24-year-olds from the Americas. In Europe, 18–24-year-old were carriers more frequently than 11–17-year-olds, and groups B (5.0%, 95% CI 3.0% to 7.5%), Y (3.9%, 95% CI 1.3% to 7.8%) and 'other' (6.4%, 95% CI 3.1% to 10.8%) were the most commonly carried in the older age group.

Risk Factors for the Disease

Predicting a healthy individual person's risk of IMD is difficult. Humans are the only known reservoir for *N. meningitidis*. While approximately 10% of the population carry the bacterium in their nasopharynx, most remain well. Though infants have the highest risk of disease, carriage of *N. meningitidis* is infrequent in infants. Carriage rates increase through childhood to peak in late adolescence and decline in older adults.[13,15, 16, 17, 18, 19] A meta-analysis

estimated carriage prevalence of 4.5% in infants, 7.7% in 10-year olds, peaking at 23.7% in 19-year olds and subsequently declining in adults (50 years old) to 7.8%[19]. Because the highest rates of carriage are observed in adolescents and young adults, often notable among individuals living in university and college dormitories and military barracks, these groups represent important targets for implementation of a preventive vaccination strategy[15, 20, 21]. Other risk factors for the disease include ethnicity, socioeconomic status, complement deficiencies, and asplenia[2, 22].

The main existing treatment and preventive options for IMD:

Treatment for invasive meningococcal disease includes antibiotic therapy to which the organism is susceptible. Because there is a high degree of morbidity and mortality and the course of disease is often very rapid, prevention of invasive MnB disease is a more effective strategy. Chemoprophylaxis, while highly effective for prevention of MnB disease among close contacts of individual patients, is not a sufficient or practical public health measure to prevent IMD in the general healthy EU population or during large outbreaks. Availability of preventive vaccines is therefore necessary. In Europe, there are licensed meningococcal conjugate vaccines for the prevention of disease due to serogroup C alone or serogroups A, C, W, and Y. There are two approved vaccines for the prevention of disease caused by serogroup B: 4CMenB and bivalent rLP2086.

Natural history of the indicated condition in the untreated population, including mortality and morbidity:

Regardless of age, MnB disease can be dramatic, often with sudden onset, even in otherwise healthy individuals. Patients may initially present with a nonspecific febrile illness characterised by headache and drowsiness but then progress to severe illness within 24 hours. Early stages of meningococcal disease are therefore difficult to diagnose, especially if the disease occurs in the absence of a known outbreak. The median time from the onset of disease to presentation of an adolescent patient to a general practitioner is approximately 19 hours[19]. This is important because IMD is most often manifested by meningitis and/or septicaemia, which can cause precipitous disease in 24 to 48 hours and be fatal within 48 hours or result in permanent significant clinical sequelae in those who survive[20].
In 2015 the overall case fatality ratio (CFR) for laboratory confirmed meningococcal disease in the EU/EEA was 9.0% (N=259) [23]. The CFR is also observed to vary by serogroup, with the highest among cases of serogroup W (14%, N=43/301), followed by serogroup C (11%, N=40/355), serogroup Y (10%, N=26/267), and serogroup B (8%, N=121/1,602).

Also, different patterns have been observed for various countries. The CFR for serogroup B in Sweden was 11% between 1995-2004, which was similar to the CFR for serogroup C in Sweden (12%) but higher than serogroup B CFRs reported for other European countries such as Ireland (3.6%), Poland (4.3%) and England and Wales (5.1%).[11, 21, 24, 25]

In addition to the risk of mortality, a further concern involves the high risk of complications among survivors with 11%-19% experiencing long-term sequelae including neurologic disability, limb amputation and hearing loss.[26, 27]

Important co-morbidities:

The complement system is particularly important in host defence against meningococcal disease. The risk of meningococcal disease is estimated to be approximately 5000 times greater in persons with inherited late complement component deficiency than in complement sufficient persons.[28]

The incidence of specific complement component deficiencies in the general population as well as in select ethnic subgroups is not known. Similarly, data on the prevalence of complement deficiencies at the population level are lacking. However, it is recognised to be a rare condition and an overall prevalence in the general population of approximately 0.03% has been suggested for inherited defects affecting individual complement proteins. The limited data available also suggest that the prevalence of this condition may vary by ethnic background. C7 and C8β deficiencies appear to occur mainly in Caucasians, C6 and C8α-γ deficiencies to be more common in blacks, and C5 deficiency occurs about equally in the two races.[29] This is supported by a study conducted in the south eastern US where C6 deficiency was found to be more common amongst blacks than whites, with a frequency of ~1 in 1600 black individuals.[30] A further study suggests that persons of Moroccan Jewish ancestry may be at a higher risk of C7 deficiency.[31] C9 deficiency is rare in Caucasian populations but is reported to be more common among Japanese people occurring in 0.045-0.104% of normal blood donors.[32]

Module SII. Non-Clinical Part of the Safety Specification

Table 2. Key Safety Findings and Relevance to Human Usage

Key Safety findings from Non-clinical Studies	Relevance to Human Usage
Toxicity including: Single and repeat-dose toxicity Injection site irritation (oedema and/or erythema) and increase in temperature occurred after administration of vehicle or bivalent rLP2086. Additionally, increases in fibrinogen, total globulins, and creatine kinase were observed following administration of bivalent rLP2086. All findings are consistent with the expected response to vaccine administration in rabbits.	Findings indicative of local reactogenicity were observed in CTs with adults, adolescents, and toddlers administered bivalent rLP2086.
Reproductive toxicity: The vaccine did not affect mating, female fertility, or embryo/foetal viability, growth and/or development of F_1 foetuses and pups. Effects on male fertility were not evaluated.	There are no adequate and well-controlled studies in pregnant women. Animal reproduction studies are not always predictive of human response.
Developmental toxicity: No findings.	
Nephrotoxicity: No findings.	
Hepatotoxicity: No findings.	
Genotoxicity: NA	
Carcinogenicity: NA.	
General safety pharmacology: NA	
Nervous system: NA	
Mechanisms for drug interactions: NA	
Other toxicity-related information or data: NA	

CT = Clinical Trial; NA = Not Applicable; rLP2086 = Recombinant Lipoprotein 2086.

Module SIII. Clinical Trial Exposure

Cumulatively, through 31 March 2024, more than 23,000 subjects have participated in the bivalent rLP2086 clinical development program and in the MenABCWY clinical development program which utilized bivalent rLP2086.

Population for analysis of clinical trials data in this RMP includes 19 completed studies, of which 2 were MenABCWY studies (C3511001 and C3511002).

- Bivalent rLP2086 studies:

  6 studies in adolescents (age range, 10 to <19 years):
  B1971005, B1971009, B1971010, B1971011, B1971012, B1971015;

  4 studies in adults:
  B1971003 (≥18 years to ≤40 years), B1971004 (≥18 years to ≤40 years),
  B1971016 (≥18 years to <26 years), B1971042 (≥18 years to ≤65 years);

  3 studies in adolescents and young adults (10 to <26 years):
  B1971014, B1971033, and B1971057;

  1 study in adolescents, young adults and adults (10 to < 26 years and ≥ 26 years):
  B1971060;

  1 study in children (2 to <10 years)
  B1971017;

  1 study in toddlers (1 to <2 years)
  B1971035;

  1 study in infants (< 1 year)
  B1971008

- MenABCWY studies:

  1 study in adolescents and young adults (10 to <26 years)
  C3511001;

  1 study in infants (< 1 year)
  C3511002

Tables from Table 3 to Table 7 present the exposure from all the Trumenba studies (including study B1971060). Table 8 and Table 9 present exposure for immunocompromised participants from study B1971060.

Table 3. Exposure to Bivalent rLP2086 by Age Group and Dose

Age Group		
Dose		
Exposure (No. of Doses Received)	**No. of Subjects Exposed to Bivalent rLP2086**	**Total No. of Vaccine Doses**
Subjects 6 weeks to <24 months		
Bivalent rLP2086 20 µg		
1 Dose	22	22
2 Dose	0	0
3 Dose	0	0
Booster dose	0	0
Total	22	22
Bivalent rLP2086 60 µg		
1 Dose	25	25
2 Doses	37	74
3 Doses	44	132
Booster Dose	24	24
Total	106	255
Bivalent rLP2086 120 µg		
1 Dose	8	8
2 Doses	53	106
3 Doses	212	636
Booster Dose	11	11
Total	273	761
Subjects 24 months to <10 years		
Bivalent rLP2086 120 µg		
1 Dose	3	3
2 Doses	4	8
3 Doses	287	861
Booster Dose	0	0
Total	294	872
Subjects 10 to <18 years		
Bivalent rLP2086 60 µg		
1 Dose	0	0
2 Doses	1	2
3 Doses	20	60
Booster Dose	0	0
Total	21	62
Bivalent rLP2086 120 µg		
1 Dose	695	695
2 Doses	2017	4034

Table 3. Exposure to Bivalent rLP2086 by Age Group and Dose

Age Group		
Dose		
Exposure (No. of Doses Received)	**No. of Subjects Exposed to Bivalent rLP2086**	**Total No. of Vaccine Doses**
3 Doses	8348	25044
Booster Dose	135	135
Total	11060	29908
Bivalent rLP2086 200 µg		
1 Dose	5	5
2 Doses	6	12
3 Doses	174	522
Booster Dose	0	0
Total	185	539
Subjects 18 to <26 years		
Bivalent rLP2086 60 µg		
1 Dose	1	1
2 Doses	0	0
3 Doses	5	15
Booster Dose	0	0
Total	6	16
Bivalent rLP2086 120 µg		
1 Dose	634	634
2 Doses	1165	2330
3 Doses	3876	11628
Booster Dose	245	245
Total	5675	14837
Bivalent rLP2086 200 µg		
1 Dose	2	2
2 Doses	0	0
3 Doses	13	39
Booster Dose	0	0
Total	15	41
Subjects ≥26 years		
Bivalent rLP2086 60 µg		
1 Dose	1	1
2 Doses	2	4
3 Doses	4	12
Booster Dose	0	0
Total	7	17

Table 3. Exposure to Bivalent rLP2086 by Age Group and Dose

Age Group		
Dose		
Exposure (No. of Doses Received)	**No. of Subjects Exposed to Bivalent rLP2086**	**Total No. of Vaccine Doses**
Bivalent rLP2086 120 µg		
1 Dose	8	8
2 Doses	27	54
3 Doses	44	132
Booster Dose	17	17
Total	79	211
Bivalent rLP2086 200 µg		
1 Dose	0	0
2 Doses	2	4
3 Doses	5	15
Booster Dose	0	0
Total	7	19

Abbreviation: HAV = hepatitis A virus.
Note: Studies B1971003, B1971004, B1971005, B1971008, B1971009, B1971010, B1971011, B1971012, B1971014, B1971015, B1971016, B1971017, B1971033, B1971035, B1971042, and B1971057 Stage 1 and Stage 2, B1971060, C3511001 (Bivalent rLP2086 arms only) and C3511002 (Bivalent rLP2086 arms only) are summarized in this table.
Note: Subjects [redacted] (from Study B1971009) received HAV vaccine at Vaccination 1 and bivalent rLP2086 other than as randomized at Vaccinations 2 or 3 and are not included in this table.
Note: Primary series data is displayed according to the age at time of first primary series vaccination. The Booster dose data is displayed according to the age at the time of the booster vaccination. The booster vaccination is approximately 48 months after the last dose of the primary series.
Note: Subjects from Study B1971033 who received bivalent rLP2086 in the primary series were also eligible to receive booster dose. The "No. of Subjects Exposed to Bivalent rLP2086" will only be counted once in total. The "Total No. of Vaccine Doses" column corresponds to how many subjects received at least one dose of bivalent rLP2086 vaccine, regardless of whether 1, 2, 3 or booster dose was received.
Note: Primary series data is displayed according to the age at time of first primary series vaccination. The Booster dose data is displayed according to the age at the time of the booster vaccination.
Note: 172 subjects less than 1 year of age derive from the 2 infant studies B1971008 and C3511002.
Note: Prior to version 8.0, infant exposure data were not included in the RMP because the Trumenba SmPC did not present data arising from infants. Now that data arising from infants are being included in the Trumenba SmPC, infant exposure data from studies B1971008 and C3511002 is presented in this RMP.
Note: Data cutoffs for all of the included studies were March 31, 2024 or earlier, based on studies completion.
[redacted] Source Data: adsl Output File: ./nda1_caps/B197_RMP_Mar2024/exp_rmp_age_dose Date of Generation: 13MAY2024 (10:20)

Table 4. Exposure to Bivalent rLP2086 by Dose (Totals)

Dose		
Exposure (No. of Doses Received)	**No. of Subjects Exposed to Bivalent rLP2086**	**Total No. of Vaccine Doses**
Bivalent rLP2086 20 µg		
1 Dose	22	22

Table 4. Exposure to Bivalent rLP2086 by Dose (Totals)

Dose		
Exposure (No. of Doses Received)	**No. of Subjects Exposed to Bivalent rLP2086**	**Total No. of Vaccine Doses**
2 Doses	0	0
3 Doses	0	0
Booster dose	0	0
Total	22	22
Bivalent rLP2086 60 µg		
1 Dose	27	27
2 Doses	40	80
3 Doses	73	219
Booster Dose	24	24
Total	140	350
Bivalent rLP2086 120 µg		
1 Dose	1348	1348
2 Doses	3266	6532
3 Doses	12767	38301
Booster Dose	408	408
Total	17381	46589
Bivalent rLP2086 200 µg		
1 Dose	7	7
2 Doses	8	16
3 Doses	192	576
Booster Dose	0	0
Total	207	599

Abbreviation: HAV = hepatitis A virus.
Note: Studies B1971003, B1971004, B1971005, B1971008, B1971009, B1971010, B1971011, B1971012, B1971014, B1971015, B1971016, B1971017, B1971033, B1971035, B1971042, and B1971057 Stage 1 and Stage 2, B1971060, C3511001 (Bivalent rLP2086 arms only) and C3511002 (Bivalent rLP2086 arms only) are summarized in this table.
Note: Subjects [redacted] (from Study B1971009) received HAV vaccine at Vaccination 1 and bivalent rLP2086 other than as randomized at Vaccinations 2 or 3 and are not included in this table.
Note: Subjects from Study B1971033 who received bivalent rLP2086 in the primary series were also eligible to receive booster dose. The "No. of Subjects Exposed to Bivalent rLP2086" will only be counted once in total. The "Total No. of Vaccine Doses " column corresponds to how many subjects received at least one dose of bivalent rLP2086 vaccine, regardless of whether 1, 2, 3 or booster dose was received.
Note: Prior to version 8.0, infant exposure data were not included in the RMP because the Trumenba SmPC did not present data arising from infants. Now that data arising from infants are being included in the Trumenba SmPC, infant exposure data from studies B1971008 and C3511002 is presented in this RMP.
Note: Data cutoffs for all of the included studies were March 31, 2024 or earlier, based on studies completion. [redacted] Source Data: adsl Output File: ./nda1_caps/B197_RMP_Mar2024/exp_rmp Date of Generation: 09MAY2024 (09:22)

Table 5. Exposure to Bivalent rLP2086 by Dose, Age Group, and Gender

Dose	Number of Subjects Exposed to Bivalent rLP2086		Total Number of Vaccine Doses	
Age Group	**Male**	**Female**	**Male**	**Female**
Bivalent rLP2086 20 µg				
≥6 weeks to <10 years	10	12	10	12
6 weeks to <24 Months	10	12	10	12
≥24 Months to <10 years	0	0	0	0
Total	10	12	10	12
Bivalent rLP2086 60 µg				
≥6 weeks to <10 years	53	53	125	130
6 weeks to <24 Months	53	53	125	130
≥24 Months to <10 years	0	0	0	0
≥10 to ≤25 Years	14	13	42	36
10 to 18 Years	11	11	33	32
10 to 14 Years	9	7	27	20
15 to 18 Years	2	4	6	12
≥19 to ≤25 Years	3	2	9	4
≥26 Years	3	4	5	12
Total	70	70	172	178
Bivalent rLP2086 120 µg				
≥6 weeks to <10 years	282	285	811	822
6 weeks to <24 Months	134	139	375	386
≥24 Months to <10 years	148	146	436	436
≥10 to ≤25 Years	8370	8365	22463	22282
10 to 18 Years	6457	5775	17515	15551
10 to 14 Years	3990	3498	10835	9482
15 to 18 Years	2467	2277	6680	6069
≥19 to ≤25 Years	1913	2590	4948	6731
≥26 Years	27	52	69	142
Total	8679	8702	23343	23246
Bivalent rLP2086 200 µg				
≥6 weeks to <10 years	0	0	0	0
6 weeks to <24 Months	0	0	0	0
≥24 Months to <10 years	0	0	0	0
≥10 to ≤25 Years	94	106	270	310
10 to 18 Years	92	102	264	300
10 to 14 Years	54	61	157	178
15 to 18 Years	38	41	107	122
≥19 to ≤25 Years	2	4	6	10
≥26 Years	1	6	3	16
Total	95	112	273	326

Table 5. Exposure to Bivalent rLP2086 by Dose, Age Group, and Gender

Dose	Number of Subjects Exposed to Bivalent rLP2086		Total Number of Vaccine Doses	
Age Group	Male	Female	Male	Female

Abbreviation: HAV = hepatitis A virus.
Note: Studies B1971003, B1971004, B1971005, B1971008, B1971009, B1971010, B1971011, B1971012, B1971014, B1971015, B1971016, B1971017, B1971033, B1971035, B1971042, and B1971057 Stage 1 and Stage 2, B1971060, C3511001 (Bivalent rLP2086 arms only) and C3511002 (Bivalent rLP2086 arms only) are summarized in this table.
Note: Subjects [redacted] (from Study B1971009) received HAV vaccine at Vaccination 1 and bivalent rLP2086 other than as randomized at Vaccinations 2 or 3 and are not included in this table.
Note: Subjects from Study B1971033 who received bivalent rLP2086 in the primary series were also eligible to receive booster dose. The "No. of Subjects Exposed to Bivalent rLP2086" will only be counted once in total. The "Total No. of Vaccine Doses" column corresponds to how many subjects received at least one dose of bivalent rLP2086 vaccine, regardless of whether 1, 2, 3 or booster dose was received.
Note: Primary series data is displayed according to the age at time of first primary series vaccination. The Booster dose data is displayed according to the age at the time of the booster vaccination.
Note: For the Bivalent rLP2086 20 µg dose category, there were no participants in age groups ≥10 to ≤25 and ≥26.
Note: 172 subjects less than 1 year of age derive from the 2 infant studies B1971008 and C3511002.
Note: Prior to version 8.0, infant exposure data were not included in the RMP because the Trumenba SmPC did not present data arising from infants. Now that data arising from infants are being included in the Trumenba SmPC, infant exposure data from studies B1971008 and C3511002 is presented in this RMP.
Note: Data cutoffs for all of the included studies were March 31, 2024 or earlier, based on studies completion.
[redacted] Source Data: adsl Output File: ./nda1_caps/B197_RMP_Mar2024/exp_rmp_age_sex Date of Generation: 13MAY2024 (10:22)

Table 6. Exposure to Bivalent rLP2086 by Age Group, Dose, and Race

Age Group		
Dose		
Race	Number of Subjects Exposed to Bivalent rLP2086	Total Number of Vaccine Doses
Subjects 6 weeks to <24 months		
Bivalent rLP2086 20 µg		
White	22	22
Black	0	0
Asian	0	0
Other	0	0
Total	22	22
Bivalent rLP2086 60 µg		
White	98	231
Black	1	3
Asian	5	15
Other	2	6
Total	106	255

Table 6. Exposure to Bivalent rLP2086 by Age Group, Dose, and Race

Age Group		
Dose		
Race	**Number of Subjects Exposed to Bivalent rLP2086**	**Total Number of Vaccine Doses**
Bivalent rLP2086 120 µg		
White	262	730
Black	0	0
Asian	2	6
Other	9	25
Total	273	761
Subjects 24 months to <10 years		
Bivalent rLP2086 120 µg		
White	291	863
Black	0	0
Asian	0	0
Other	3	9
Total	294	872
Subjects 10 to <18 years		
Bivalent rLP2086 60 µg		
White	17	50
Black	0	0
Asian	1	3
Other	3	9
Total	21	62
Bivalent rLP2086 120 µg		
White	9692	26335
Black	886	2339
Asian	102	273
Other	380	961
Total	11060	29908
Bivalent rLP2086 200 µg		
White	182	530
Black	1	3
Asian	1	3
Other	1	3
Total	185	539
Subjects 18 to <26 years		
Bivalent rLP2086 60 µg		
White	5	13

Table 6. Exposure to Bivalent rLP2086 by Age Group, Dose, and Race

Age Group		
Dose		
Race	**Number of Subjects Exposed to Bivalent rLP2086**	**Total Number of Vaccine Doses**
Black	1	3
Asian	0	0
Other	0	0
Total	6	16
Bivalent rLP2086 120 µg		
White	4674	12505
Black	809	1865
Asian	101	253
Other	91	214
Total	5675	14837
Bivalent rLP2086 200 µg		
White	14	38
Black	1	3
Asian	0	0
Other	0	0
Total	15	41
Subjects ≥26 years		
Bivalent rLP2086 60 µg		
White	6	14
Black	1	3
Asian	0	0
Other	0	0
Total	7	17
Bivalent rLP2086 120 µg		
White	75	201
Black	0	2
Asian	4	8
Other	0	0
Total	79	211
Bivalent rLP2086 200 µg		
White	4	11
Black	3	8
Asian	0	0
Other	0	0
Total	7	19

Table 6. Exposure to Bivalent rLP2086 by Age Group, Dose, and Race

Age Group		
Dose		
Race	Number of Subjects Exposed to Bivalent rLP2086	Total Number of Vaccine Doses

Abbreviation: HAV = hepatitis A virus.
Note: Studies B1971003, B1971004, B1971005, B1971008, B1971009, B1971010, B1971011, B1971012, B1971014, B1971015, B1971016, B1971017, B1971033, B1971035, B1971042, and B1971057 Stage 1 and Stage 2, B1971060, C3511001 (Bivalent rLP2086 arms only) and C3511002 (Bivalent rLP2086 arms only) are summarized in this table.
Note: Subjects [redacted] (from Study B1971009) received HAV vaccine at Vaccination 1 and bivalent rLP2086 other than as randomized at Vaccinations 2 or 3 and are not included in this table.
Note: Subjects from Study B1971033 who received bivalent rLP2086 in the primary series were also eligible to receive booster dose. The "No. of Subjects Exposed to Bivalent rLP2086" will only be counted once in total. The "Total No. of Vaccine Doses" column corresponds to how many subjects received at least one dose of bivalent rLP2086 vaccine, regardless of whether 1, 2, 3 or booster dose was received
Note: Primary series data is displayed according to the age at time of first primary series vaccination. The Booster dose data is displayed according to the age at the time of the booster vaccination.
Note: 172 subjects less than 1 year of age derive from the 2 infant studies B1971008 and C3511002.
Note: Prior to version 8.0, infant exposure data were not included in the RMP because the Trumenba SmPC did not present data arising from infants. Now that data arising from infants are being included in the Trumenba SmPC, infant exposure data from studies B1971008 and C3511002 is presented in this RMP.
Note: Data cutoffs for all of the included studies were March 31, 2024 or earlier, based on studies completion. [redacted] Source Data: adsl Output File: ./nda1_caps/B197_RMP_Mar2024/exp_rmp_age_race Date of Generation: 13MAY2024 (10:24)

Table 7. Exposure to Bivalent rLP2086 by Dose and Race (Totals)

Dose		
Race	Number of Subjects Exposed to Bivalent rLP2086	Total Number of Vaccine Doses
Bivalent rLP2086 20 µg		
White	22	22
Black	0	0
Asian	0	0
Other	0	0
Total	22	22
Bivalent rLP2086 60 µg		
White	126	308
Black	3	9
Asian	6	18
Other	5	15
Total	140	350
Bivalent rLP2086 120 µg		

Table 7. Exposure to Bivalent rLP2086 by Dose and Race (Totals)

White	14994	40634
Black	1695	4206
Asian	209	540
Other	483	1209
Total	17381	46589
Bivalent rLP2086 200 µg		
White	200	579
Black	5	14
Asian	1	3
Other	1	3
Total	207	599

Abbreviation: HAV = hepatitis A virus.
Note: Studies B1971003, B1971004, B1971005, B1971008, B1971009, B1971010, B1971011, B1971012, B1971014, B1971015, B1971016, B1971017, B1971033, B1971035, B1971042, and B1971057 Stage 1 and Stage 2, B1971060, C3511001 (Bivalent rLP2086 arms only) and C3511002 (Bivalent rLP2086 arms only) are summarized in this table.
Note: Subjects [redacted] (from Study B1971009) received HAV vaccine at Vaccination 1 and bivalent rLP2086 other than as randomized at Vaccinations 2 or 3 and are not included in this table.
Note: Subjects from Study B1971033 who received bivalent rLP2086 in the primary series were also eligible to receive booster dose. The "No. of Subjects Exposed to Bivalent rLP2086" will only be counted once in total. The "Total No. of Vaccine Doses" column corresponds to how many subjects received at least one dose of bivalent rLP2086 vaccine, regardless of whether 1, 2, 3 or booster dose was received.
Note: Prior to version 8.0, infant exposure data were not included in the RMP because the Trumenba SmPC did not present data arising from infants. Now that data arising from infants are being included in the Trumenba SmPC, infant exposure data from studies B1971008 and C3511002 is presented in this RMP.
Note: Data cutoffs for all of the included studies were March 31, 2024 or earlier, based on studies completion.
[redacted] Source Data: adsl Output File: ./nda1_caps/B197_RMP_Mar2024/exp_rmp_race Date of Generation: 09MAY2024 (09:32)

Table 8. Exposure to Bivalent rLP2086 by Dose (Totals) – B1971060

Dose Exposure (No. of Doses Received)	No. of Subjects Exposed to Bivalent rLP2086	Total No. of Vaccine Doses
Bivalent rLP2086 120 µg		
1 Dose	6	6
2 Doses	47	94
Total	53	100

Note: The "No. of Subjects Exposed to Bivalent rLP2086" will only be counted once in total. The "Total No. of Vaccine Doses" column corresponds to how many subjects received at least one dose of bivalent rLP2086 vaccine, regardless of whether 1 or 2 was received.
Note: The data cutoff date for B1971060 is 03NOV2023.
[redacted] Source Data: adsl Output File: ./nda1_caps/B197_RMP_Mar2024/exp_rmp_b1060 Date of Generation: 23APR2024 (13:30)

Table 9. Exposure to Bivalent rLP2086 by Dose, Age Group and Gender – B1971060

	No. of Subjects Exposed to Bivalent rLP2086		Total No. of Vaccine Doses	
Dose Age Group	**Male**	**Female**	**Male**	**Female**
Bivalent rLP2086 120 µg				
≥10 to ≤25 Years	16	11	30	20
10 to 18 Years	5	6	9	10
10 to 14 Years	2	2	3	4
15 to 18 Years	3	4	6	6
≥19 to ≤25 Years	11	5	21	10
≥26 Years	14	12	26	24
Total	30	23	56	44

Note: The "No. of Subjects Exposed to Bivalent rLP2086" will only be counted once in total. The "Total No. of Vaccine Doses" column corresponds to how many subjects received at least one dose of bivalent rLP2086 vaccine, regardless of whether 1 or 2 dose was received.
Note: The data cutoff date for B1971060 is 03NOV2023.
[redacted] Source Data: adsl Output File: ./nda1_caps/B197_RMP_Mar2024/exp_rmp_age_sex_b1060 Date of Generation: 26APR2024 (10:06)

Module SIV. Populations Not Studied in Clinical Trials

SIV.1. Exclusion Criteria in Pivotal Clinical Studies Within the Development Programme

Subjects Aged 10 Years and Older

Adolescents and adults included in the studies of bivalent rLP2086 were determined to be healthy by medical history, physical examination, and by the judgment of the investigator.

Across studies, ages ranged from 10 to less than 65 years. Subjects were excluded from these studies according to the general criteria listed in the table below.

Criteria	Reason for Exclusion	Missing Information (Yes/No)	Rationale (if not included as Missing Information)
Previous vaccination with any meningococcal serogroup B vaccine.	To avoid confounding the assessment of immune response in the study population.	No	Minimal potential impact on target population
A known or suspected defect of the immune system that would prevent an immune response to the vaccine, such as subjects with congenital or acquired defects in B cell function, those receiving chronic systemic (oral, IV, or IM) corticosteroid therapy, or those receiving immunosuppressive therapy.	To avoid confounding the assessment of immune response in the study population.	No	Based on the completion of study B1971060, in subjects at increased risk of meningococcal disease due to anatomic asplenia, or functional asplenia (eg, sickle cell anemia), or complement deficiencies, this information is no longer missing for Trumenba. Information concerning this exclusion criterion is provided in the SmPC Section 4.4 *Special warnings and precautions for use*.
History of microbiologically proven disease caused by *N. meningitidis* or *N. gonorrhoeae*.	To avoid confounding the assessment of immunogenicity endpoints in the study population.	No	No impact on the safety of the target population
Receipt of any blood products, including immunoglobulin within 6 months before the first study vaccination.	To avoid confounding the assessment of immune response in the study population.	No	No impact on the safety of the target population.
Current chronic use of systemic antibiotics.	To avoid confounding the assessment of immunogenicity endpoints in the study population.	No	No impact on the safety of the target population.

Criteria	Reason for Exclusion	Missing Information (Yes/No)	Rationale (if not included as Missing Information)
Other severe acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgement of the investigator, would make the subject inappropriate for entry into this study.	To ensure the safety of the study population.	No	No impact on the safety of the target population.
Significant neurological disorder or history of seizure (excluding simple febrile seizure).	To ensure the safety of the study population.	No	No impact on the safety of the target population.
Any neuro-inflammatory or autoimmune condition.	To ensure the safety of the study population.	No	No impact on the safety of the target population.
Pregnant women.	To ensure the safety of the study population.	No	Based on the available clinical data and the accumulated post-marketing safety experience, no different safety profile in pregnant women is anticipated. Information concerning this exclusion criterion is provided in the SmPC Section 4.6 *Fertility, pregnancy and lactation*.
Bleeding diathesis or condition associated with prolonged bleeding time that would contraindicate IM injection.	To ensure the safety of the study population.	No	Information concerning this criterion is provided in the SmPC Section 4.4, *Special warnings and precautions for use*.

HCP = Health Care Professional; IV = Intravenous; IM = Intramuscular; *N. gonorrhoeae = Neisseria gonorrhoeae; N. meningitidis = Neisseria meningitidis*; rLP2086 = Recombinant Lipoprotein 2086; SmPC = Summary of Product Characteristics.

SIV.2. Limitations to Detect Adverse Reactions in Clinical Trial Development Programmes

Table 10. Limitations of Adverse Reaction Detection

Ability to Detect Adverse Reactions	Limitation of Trial Programme	Discussion of Implications for Target Population
That are rare (<0.01%)	Approximately 18,000 individuals have been exposed to bivalent rLP2086 over the entire CT programme.	ARs with a frequency greater than 1 in 10,000 could be detected if there were no background incidence of ARs, such that we would expect to see 1 to 2 cases among the over 17,000 exposed.

AR = Adverse Reaction; CT = Clinical Trial; bivalent rLP2086 = Recombinant Lipoprotein 2086.

SIV.3. Limitations in Respect to Populations Typically Under-Represented in Clinical Trial Development Programmes

Table 11. Exposure of Special Populations Included or not in Clinical Trial Development Programmes

Type of special population	Exposure
Pregnant women	There are no data on use of bivalent rLP2086 vaccine in pregnant women. The potential risk for pregnant women is unknown. Nevertheless, vaccination should not be withheld when there is a clear risk of exposure to meningococcal infection. All studies required a negative pregnancy test prior to each vaccination for female subjects. Women who were pregnant were excluded from participation. Both maternal and paternal exposure were considered reportable if a study subject or study subject's partner became pregnant or was found to be pregnant during the study following administration of study vaccine. Across the 11 clinical studies completed in individuals 10 years and older, 172 subjects became pregnant during the studies or had sexual partners who became pregnant during the studies: among the 15294 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 5509 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. Foetal 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 was therapeutic abortion (1 subject who received control vaccine) and stillbirth (1 subject who received bivalent rLP2086).
Breast-feeding women	It is unknown whether bivalent rLP2086 is excreted in human milk. Bivalent rLP2086 should only be used during breast-feeding when the possible advantages outweigh the potential risks. Women who were breast-feeding were excluded from participation.
Patients with Hepatic Impairment	Bivalent rLP2086 has not been studied in patients with hepatic impairment.
Patients with Renal Impairment	Bivalent rLP2086 has not been studied in patients with renal impairment.
Patients with Other Relevant Co-Morbidity	The use of bivalent rLP2086 in individuals with the impairment of the immune system has not been studied. Individuals with terminal complement deficiency were not excluded from study participation in Europe; however, no subject with diagnosed terminal complement deficiency was enrolled in CTs. Immunocompromised individuals, including individuals receiving immunosuppressant therapy, may have a diminished immune response to Trumenba.
Subpopulations Carrying Known and Relevant Polymorphisms	Individuals with inherited disorders of the complement system were not excluded from study participation in Europe; however, no subject diagnosed with inherited complement deficiency was enrolled in CTs.

Table 11. Exposure of Special Populations Included or not in Clinical Trial Development Programmes

Type of special population	Exposure
Children (below 10 years of age)	The use of bivalent rLP2086 in individuals below 10 years of age has been evaluated in 2 clinical trials, B1971017 (2 to <10 years) and B1971035 (1 to <2 years). These studies are part of the paediatric investigational plan approved by the EU Paediatric Committee (EU-PDCO). Study B1971017 evaluated the immunogenicity, safety and tolerability of 3 doses of bivalent rLP2086 at 120-µg dose administered to healthy subjects aged ≥24 months to <10 years. The clinical study report was submitted as part of the procedure CHMP/752098/2017 on 01 September 2017. Study B1971035 evaluated the immunogenicity, safety, and tolerability of 3 doses of bivalent rLP2086 at 60- µg or 120-µg dose when administered to healthy toddlers aged 12 to <18 months or 18 to<24 months (Stage 1). The clinical study report for immunogenicity data through 1 month after 3rd dose and safety data through 6 months after 3rd dose has been submitted. Stage 2 of this study was originally designed to collect data on immune persistence for up to 4 years in children between the ages of 12 to <24 months when they received their first dose in the 3-dose primary series. The MAH updated the B1971035 protocol to remove the persistence bleeds at 36 and 48 months following completion of the primary series and replaced these with a pre-booster bleed followed by a booster vaccination of 120 µg rLP2086 during the same visit at approximately 24 months after completion of the primary series, a 1-month post-booster blood draw and a 6 months post-booster safety telephone call. The final Stage 2 CSR to add persistence and booster data will be submitted to the EMA on 27 August 2021 as a type II label variation. In addition, limited data on the use of bivalent rLP2086 in individuals below 10 years of age are available from 2 terminated clinical trials, B1971008 (<1 year) and C3511002 (<1 year). Study B1971008 intended to evaluate the safety and immunogenicity of doses of 20 µg–200 µg in infants 2 months of age during a sentinel phase. Those dose levels not eliminated by the end of the sentinel phase would proceed into a full enrolment phase. The Sponsor decided to terminate the study due to the relatively high frequency of fever observed in the 2 initial cohorts of the sentinel phase. No immunogenicity data were collected. Study C3511002 intended to describe the safety, tolerability, and immunogenicity of MenABCWY in healthy infants, beginning with infants 6 months of age and progressing to infants 2 months of age. The study was designed to be conducted in 3 stages, the first of which (open-label sentinel-cohort stage) included cohorts of 2-month-old participants receiving 60 µg or 120 µg rLP2086. The Sponsor decided to terminate the study after "fever requiring invasive investigations" was identified as a special safety concern following a review of 2 serious adverse events reported from this study in 2-month-old infants. The available safety and immunogenicity data were included in the final CSR which was submitted to the EMA on 14 March 2023. Please refer to Exposure tables in Module SIII for exposure information regarding these studies.

Table 11. Exposure of Special Populations Included or not in Clinical Trial Development Programmes

Type of special population	Exposure
Adults (40 to less than 65 years old)	In study B1971042, bivalent rLP2086 was studied in adults, between the ages of 24-62 years of age who were at increased risk for meningococcal disease due to occupational exposure to MnB. A total of 13 subjects were enrolled. Nine (9) subjects in the study were 40 years of age or older. Although the number of individuals over the age of 40 years is limited, the safety profile observed in older subjects in clinical studies is consistent with that seen in younger individuals (10 through 40 years). In addition, immunogenicity results among older individuals demonstrated the ability of the vaccine to elicit immune responses in this population. Because the clinical manifestations of IMD are equally serious across all age groups, accessibility to bivalent rLP2086 vaccine will allow prescribers to weigh expected safety and efficacy for use in older patients in an increased risk setting.
Elderly (≥65 years old)	Currently, there are no clinical data available in adults 65 years of age and older for bivalent rLP2086, however the safety of bivalent rLP2086 is not expected to differ from that observed in younger age groups evaluated in the CT programme; therefore, the use of the vaccine should be considered in a benefit risk context for elderly patients.

CT = Clinical Trial; EU-PDCO = European Union Paediatric Committee; IMD = Invasive Meningococcal Disease; MnB = *Neisseria meningitidis* serogroup B; *N. meningitidis* = *Neisseria meningitidis*; rLP2086= Recombinant Lipoprotein 2086.

Module SV. Post-Authorisation Experience

SV.1. Post-Authorisation Exposure

SV.1.1. Method Used to Calculate Exposure

Due to various dosage regimens and country-specific vaccination schedules, it is not possible to determine with certainty the number of individuals who received bivalent rLP2086 during the period of this review. Estimated worldwide units' distribution may serve as a reasonable indicator of patient exposure.

SV.1.2. Exposure

The estimated cumulative worldwide unit distribution for bivalent rLP2086 from launch through 28 October 2024 is approximately 9,721,088 doses.

Estimated cumulative exposure by gender, age group, and region based on or extrapolated from Pfizer internal sales data and factored, as applicable, by data from IQVIA (formerly IMS) Health Prescribing Insights Medical from launch through 28 October 2024, is summarized in Table 12, Table 13 and Table 14. Beginning with the release of 1Q22 data, IQVIA medical data moved from NDTI (National Disease and Therapeutic Index, used to capture data in the US) to NMTA (National Medical and Treatment Audit, used to capture data in the US and Puerto Rico). Due to the change in methodology, for these two countries a trend break in data for indication, formulation, region, gender, age and dose is observed. For patient age information, the NMTA audit does not allow for flexible age customizations which had been previously present in NDTI and ROW audits. Consequently, stratification is provided for US/PR.

Table 12. Cumulative Estimated Exposure Worldwide (excluding US and PR) for Bivalent rLP2086 (Thousands of Doses)

Total	Sex (% of Rx)		Age (years, % of Rx)					
	M	F	0-16	17-25	26-39	40-65	>65	Age Unspecified
1,640,984	42.5%	57.5%	93.5%	3.2%	0.4%	2.0%	0.8%	0.1%
	697,418	943,566	1,534,320	52,511	6,564[a]	32,820[a]	13,128	1,641

a. Changes in the age distribution of doses distributed are resultant of percentage allocations across the age cohorts. As data are collated from the external sources there are resultant changes in the age cohort percentages. This can then affect the doses attributable to those age cohorts over time.

M= Male; F= Female; Rx = prescription; rLP2086= Recombinant Lipoprotein 2086; US= United States; PR= Puerto Rico; gap vs. total due to % of unknown sex and age attribution.

Table 13. Cumulative Estimated Exposure in US and PR for Bivalent rLP2086 (Thousands of Doses)

Total	Sex (% of Rx)		Age (years, % of Rx)					
	M	F	0-15	16-30	31-50	51-65	>65	Age Unspecified
8,080,104	48.7%	51.3%	2.4%	96.3%	0.4%	0.3%	0.6%	0.0%
	3,935,011	4,145,093	193,922	7,781,140	32,320	24,240	48,481	-

M= Male; F= Female; Rx = prescription; rLP2086= Recombinant Lipoprotein 2086; US=United States; PR=Puerto Rico

Table 14. Cumulative Estimated Exposure for Bivalent rLP2086 Vaccine (Thousands of Doses) by Region Worldwide

Region/Country/Other	% of Doses[a]	Total
US	83%	8,080,104
Western EU	14%	1,388,847
Central and Eastern Europe	2%	217,795
Canada	0%	23,866
Australia/New Zealand	0%	1,684
Latin America	0%	2,163
Asia (excl. Japan)	0%	6,329
Africa/Middle East	0%	300
Total	**100%**	**9,721,088**

a. Numbers in the table are rounded and therefore percentages < 1% are showing as zero.
EU=Europe; rLP2086= Recombinant Lipoprotein 2086; US = United States.

Module SVI. Additional EU Requirements for the Safety Specification

Potential for misuse for illegal purposes

No potential for drug abuse or dependence with bivalent rLP2086 is expected.

Module SVII. Identified and Potential Risks

SVII.1. Identification of Safety Concerns in the Initial RMP Submission

Please refer to the initial RMP (version 1.0, April 2016) (EMEA/H/C/0004051).

SVII.1.1. Risks not Considered Important for Inclusion in the List of Safety Concerns in the RMP

Not applicable.

SVII.1.2. Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Not applicable.

SVII.2. New Safety Concerns and Reclassification with a Submission of an Updated RMP

There are no new safety concerns identified for the use of Trumenba indicated in individuals 10 years of age and older since the RMP version 6.0 (procedure no. EMEA/H/C/004051/R/0036 – submitted on 10 August 2021 and approved by the EMA on 24 February 2022).

The MAH proposes to remove the safety concern of "Use in co-administration with MMR and pneumococcal vaccines", previously included in the RMP as Missing Information.

The rationale for removal is presented below:

Use in co-administration with MMR and pneumococcal vaccines

The MAH considers that Trumenba is indicated for individuals 10 years of age and older and therefore, does not include the paediatric age group in which MMR and pneumococcal vaccines are routinely administered. In the majority of EU countries, MMR and pneumococcal vaccines are not included in the national immunization schedules as a general recommendation for individuals 10 years of age and older. Furthermore, no safety signals have been identified from 7 years of post-marketing data and no unknown risks of a clinical significance would be anticipated as the risks associated with the vaccines, primarily those of reactogenicity-type events, are known and well described.

SVII.3. Details of Important Identified, Important Potential Risks, and Missing Information

SVII.3.1. Presentation of Important Identified Risks and Important Potential Risks

Important Identified Risks:

None.

Important Potential Risks:

None.

SVII.3.2. Presentation of the Missing Information

None.

Module SVIII. Summary of the Safety Concerns

There are no important identified/potential risks or missing information for Trumenba.

Table 15. Summary of Safety Concerns

Important identified risks	None
Important potential risks	None
Missing Information	None.

PART III. PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORISATION SAFETY STUDIES)

III.1. Routine Pharmacovigilance Activities

Routine pharmacovigilance activities beyond Adverse Drug Reactions reporting and signal detection:

Specific adverse reaction follow-up questionnaires for safety concern:

Routine pharmacovigilance activity is conducted for spontaneous reports of exposure during pregnancy, aligned with the European Medicines Agency (EMA) Committee for Medicinal Products for Human Use (CHMP), Guideline on the exposure to medicinal products during pregnancy: need for post-authorisation data (May 2006). Pfizer pursues follow-up information in all reported cases of exposure during pregnancy using an Exposure During Pregnancy (EDP) Follow-Up Questionnaire (Annex 4). The range of information requested includes demographic information, current and past pregnancy and obstetrical information, details on drug use by the pregnant female (including the Pfizer product, non-Pfizer products, and illicit drugs), and delivery details. Information is also requested about the neonate, including measurements after birth, the presence of congenital or developmental abnormalities, illnesses, hospitalisation, and breastfeeding information. Relevant paternal health and exposure information is also queried.

Other forms of routine pharmacovigilance activities for safety concerns:

If bivalent rLP2086 is used as part of a national immunisation programme or in a large outbreak situation the MAH will review and summarize, in the PSUR, national surveillance data for invasive meningococcal disease, as available.

III.2. Additional Pharmacovigilance Activities

There are no ongoing or planned category 1 - 3 studies for bivalent rLP2086. Completed additional pharmacovigilance activities are detailed in Annex 2.

III.3. Summary Table of Additional Pharmacovigilance Activities

As stated in Part III.2, there are no ongoing or planned category 1 – 3 safety studies for bivalent rLP2086.

PART IV. PLANS FOR POST AUTHORISATION EFFICACY STUDIES

There are no planned or ongoing post-authorisation efficacy studies which are specific obligations and/or conditions of the MAA.

PART V. RISK MINIMISATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMISATION ACTIVITIES)

RISK MINIMISATION PLAN

V.1. Routine Risk Minimisation Measures

The EU SmPC and package leaflet (PL) give essential information to healthcare professionals and vaccine recipients on how Trumenba should be used, allowing for a safe use.

V.2. Additional Risk Minimisation Measures

No additional risk minimisation measures (RRMs) are proposed.

V.3. Summary of Risk Minimisation Measures

Routine risk minimisation actions include the use of the SmPC and PL to address the safe use of the vaccine. There are no additional RMMs proposed.

PART VI. SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of risk management plan for Trumenba (bivalent rLP2086)

This is a summary of the risk management plan (RMP) for Trumenba. The RMP details important risks of Trumenba, how these risks can be minimised, and how more information will be obtained about Trumenba's risks and uncertainties (Missing Information).

Trumenba's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Trumenba should be used.

This summary of the RMP for Trumenba should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all of which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Trumenba's RMP.

I. The Medicine and What It Is Used For

Trumenba is a vaccine to prevent invasive meningococcal disease, caused by *Neisseria meningitidis* serogroup B, for use in people 10 years and older (see SmPC for the full indication). It contains *Neisseria meningitidis* serogroup B fHbp subfamily A (60 micrograms) and *Neisseria meningitidis* serogroup B fHbp subfamily B (60 micrograms) as active substances and it is a white suspension for injection, provided in a pre-filled syringe.

Further information about the evaluation of Trumenba's benefits can be found in Trumenba's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Summary_for_the_public/human/004051/WC500228998.pdf

II. Risks Associated with the Medicine and Activities to Minimise or Further Characterise the Risks

Important risks of Trumenba, together with measures to minimise such risks and the proposed studies for learning more about Trumenba's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

Specific Information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to vaccine recipients and healthcare professionals;

Important advice on the medicine's packaging;

The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;

The medicine's legal status — the way a medicine is supplied to the public (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In addition to these measures, information about adverse events is collected continuously and regularly analysed, including PSUR assessment so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

II.A. List of Important Risks and Missing Information

Important risks of Trumenba are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Trumenba. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing Information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine).

There are no important identified or potential risks nor Missing Information for Trumenba.

II.B. Summary of Important Risks and Missing Information

There are no identified or potential risks that are considered important nor Missing Information for Trumenba.

II.C. Post-Authorisation Development Plan

II.C.1. Studies which are Conditions of the Marketing Authorisation

There are no planned or ongoing post-authorisation studies which are specific obligations and/or conditions of the MAA.

II.C.2. Other Studies in Post-Authorisation Development Plan

There are no post-authorisation studies required for Trumenba.

PART VII. ANNEXES TO THE RISK MANAGEMENT PLAN

Annex 2 – Tabulated summary of planned, on-going, and completed pharmacovigilance study programme

Annex 3 - Protocols for proposed, on-going, and completed studies in the pharmacovigilance plan

Annex 4 - Specific Adverse Drug Reaction Follow-Up Forms

Annex 5 - Protocols for proposed and on-going studies in RMP Part IV

Annex 6 - Details of Proposed Additional Risk Minimisation Activities (if applicable)

Annex 7 - Other Supporting Data (Including Referenced Material)

Annex 8 – Summary of Changes to the Risk Management Plan over Time

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ANNEX 4. SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

EXPOSURE DURING PREGNANCY FOLLOW-UP QUESTIONNAIRE

EDP FU Questionnaire

**Merge this questionnaire with the appropriate Basic FU or Drug/Vaccine/Medical Device FU Questionnaire, and any other applicable questionnaires.*

Exposure During Pregnancy

1. According to the information provided, exposure to a product may have occurred during pregnancy or around the time of conception. Please confirm and complete all questions to the best of your ability and knowledge.

☐ Yes ☐ No ☐ Unknown

Maternal Obstetrical History

1. Occupation

_____

2. Was the mother previously pregnant?

☐ Yes ☐ No ☐ Unknown

If Yes, how many times:_____

3. Number of other children

_____

4. Outcome of previous pregnancies (e.g., live birth, miscarriage, elective termination, late fetal death, ectopic pregnancy, molar pregnancy)

_____

5. Did the mother experience previous pregnancy complications?

☐ Yes ☐ No ☐ Unknown

If yes, please specify_____

6. Did the mother experience previous fetal/neonatal abnormalities?

☐ Yes ☐ No ☐ Unknown

If yes, please specify_____

7. Does the mother have a history of sub-fertility?

☐ Yes ☐ No ☐ Unknown

If yes, please specify_____

8. Was the mother treated for infertility?
☐ Yes ☐ No ☐ Unknown

If yes, please specify_____

9. Mother's Relevant History (i.e., risk factors including environmental or occupational exposures (e.g., AIDS, toxins)).

10. Does the mother have a family history of congenital abnormality/ genetic diseases, and/or consanguinity (or any family relation or lineage) between parents?
☐ Yes ☐ No ☐ Unknown

If yes, please specify_____

11. Results of serology tests (e.g., rubella, toxoplasmosis, etc.)

Maternal Information

1. Ante-natal check-up (e.g., fetal ultrasound, serum markers, etc.). Please specify dates in dd-Mmm-YYYY format and check-up results for this pregnancy.
_____

2. First day of last menstrual period (dd-Mmm-yyyy)
_____

3. Number of fetuses for this pregnancy
_____

4. Estimated delivery date for this pregnancy (dd-Mmm-yyyy)
_____

5. Gestational period at time of initial suspect drug exposure

_____ ☐ Trimester ☐ Month

6. Did the mother smoke during this pregnancy?

☐ Yes ☐ No ☐ Unknown

If Yes, frequency:_____

7. Did the mother drink alcohol during this pregnancy?

☐ Yes ☐ No ☐ Unknown

If Yes, frequency:_____

8. Did the mother use illicit drugs during this pregnancy?

☐ Yes ☐ No ☐ Unknown

If Yes, frequency:_____

9. Did the mother experience any problems before delivery?

☐ Yes ☐ No ☐ Unknown

If yes, please specify_____

10. Did the mother experience any problems during delivery (including delivery complications, fetal distress, amniotic fluid abnormal, abnormal placenta)?

☐ Yes ☐ No ☐ Unknown

If yes, please specify_____

11. Did the mother experience any problems after delivery?

☐ Yes ☐ No ☐ Unknown

If yes, please specify_____

12. Mode of delivery

☐ Vaginal ☐ Cesarean ☐ Unknown

13. Outcome of this pregnancy

- ☐ Full term live birth
- ☐ Premature live birth
- ☐ Post-mature live birth
- ☐ Stillbirth
- ☐ Late foetal death
- ☐ Ectopic pregnancy
- ☐ Molar pregnancy
- ☐ Spontaneous abortion/miscarriage
- ☐ Induced/elective abortion
- ☐ Unknown

14. Date of outcome of this pregnancy (dd-Mmm-yyyy)

_____

Neonatal Information

1. Sex (at birth)

☐ Male ☐ Female

2. Weight at birth (number and unit)

_____ ☐ kg ☐ lbs & oz

3. Length at birth (number and unit)

_____

4. Head circumference at birth (number and unit)

_____

5. Apgar score at 1 min

_____

6. Apgar score at 5 min

_____

7. Gestational age at birth in weeks

_____

8. Outcome of Fetus/Infant

- ☐ Healthy newborn
- ☐ Congenital malformation/anomaly (specify below)
- ☐ Other neonatal problem/abnormality (include dysmaturity, neonatal illness, hospitalization, drug therapies) (specify below)
- ☐ Intrauterine death
- ☐ Neonatal death
- ☐ Outcome pending (not born yet)
- ☐ Perinatal complications (specify below)
- ☐ Post-perinatal complications (specify below)
- ☐ Unknown

Please specify:

Paternal Information

1. Father's Age

_____ ☐ Years ☐ Months ☐ Days

Age Group:

☐ Adolescent (12-17 Years) ☐ Adult (18-64 Years) ☐ Elderly (65 or older)

2. Occupation

_____

3. Father's Relevant History (i.e., risk factors including environmental or occupational exposures (e.g., AIDS, toxins)).

4. Were any drugs (e.g., over-the-counter, medical prescription) taken by the father during the mother's pregnancy or around the time of conception?

☐ Yes ☐ No ☐ Unknown

If yes, please specify:_____

5. Did the father smoke during the mother's pregnancy or around the time of conception?

☐ Yes ☐ No ☐ Unknown

If Yes, frequency:_____

6. Did the father drink alcohol during the mother's pregnancy or around the time of conception?

☐ Yes ☐ No ☐ Unknown

If Yes, frequency:_____

7. Did the father use illicit drugs during the mother's pregnancy or around the time of conception?

☐ Yes ☐ No ☐ Unknown

If Yes, frequency:_____

8. Does the father have a family history of congenital abnormality/ genetic diseases, and/or consanguinity (or any family relation or lineage) between parents?

☐ Yes ☐ No ☐ Unknown

If yes, please specify:_____

ANNEX 6. DETAILS OF PROPOSED ADDITIONAL RISK MINIMISATION ACTIVITIES (IF APPLICABLE)

No additional risk minimization measures have been undertaken.