MODULE 1

1.8 - Information Relating to Pharmacovigilance

1.8.2

EU Risk Management Plan for
VacPertagen suspension for injection in pre-filled syringe
Recombinant acellular pertussis vaccine adsorbed

RMP version to be assessed as part of this application:

RMP Version number: 1.0
Data lock point for this RMP: 31 Aug 2025
Date of final sign-off: 6 Nov 2025

Rationale for submitting an updated RMP: Not applicable

Summary of significant changes in this RMP: Not applicable

Other RMP versions under evaluation: Not applicable
Details of the currently approved RMP: Not applicable

QPPV name: Dr. Nicole Niemeier-Siegl

[redacted]

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Abbreviations / Acronyms

ACIP	Advisory Committee on Immunisation Practices
ACTRN	Australian New Zealand Clinical Trials Registry number
ADR	Adverse Drug Reaction
AE	Adverse Event
AEFI	Adverse Event Following Immunisation
aP/aP_{gen}	Acellular Pertussis vaccine containing genetically detoxified Pertussis Toxin
CDC	Centers for Disease Control and Prevention, USA
CHO	Chinese Hamster Ovary cell
CI	Confidence Interval
cPT	Chemically detoxified Pertussis Toxin
DSMC	Data and Safety Monitoring Committee
DTaP	Diphtheria toxoid, Tetanus toxoid, acellular Pertussis vaccine
$DTaP_{gen}$	Diphtheria toxoid, Tetanus toxoid, recombinant acellular Pertussis vaccine
DTwP	Diphtheria toxoid, Tetanus toxoid, whole-cell Pertussis vaccine
DT	Diphtheria Toxoid
EC	Ethics Committee
EEA	European Economic Area
EMA	European Medicines Agency
EU	European Union
FHA	Filamentous Haemagglutinin
FIM	Fimbriae
GCP	Good Clinical Practice
GVP	Good Pharmacovigilance Practices
HIV	Human Immunodeficiency Virus
ICH	International Council for Harmonisation of Technical Requirements of Pharmaceuticals for Human Use
ICSR	Individual case safety report
IgG	Immunoglobulin G
IM / i.m.	Intramuscular
INN	International Non-proprietary Name
IRB	Institutional Review Board
IU	International Unit
Lf	Limit of flocculation
NCT	National Clinical Trial
NIAID	National Institute of Allergy and Infectious Diseases
NRA	National Regulatory Authority
PCR	Polymerase Chain Reaction
PertADO	Pertagen in Adolescents
Ph. Eur.	European Pharmacopoeia
PIDST	Pediatric Infectious Disease Society of Thailand
PRN	Pertactin

PSUR	Product Safety Update Report
PT	Pertussis Toxin
PT_{gen}	Genetically detoxified Pertussis Toxin
PV	Pharmacovigilance
PW	Pregnant Women
q.s.	as much as suffices (from Latin quantum satis or quantum sufficit)
RMP	Risk Management Plan
rPT	Recombinant Pertussis Toxin
SAE	Serious Adverse Event
SmPC	Summary of Product Characteristics
TCTR	Thai Clinical Trials Registry
Td	Tetanus toxoid, Diphtheria toxoid (reduced dose)
TdaP	Tetanus toxoid, Diphtheria toxoid (reduced dose), acellular Pertussis Vaccine
$TdaP_{gen}$	Td vaccine combined to Pertagen®, aP_{gen} vaccine components
$Tdap_{chem}$	Td vaccine combined to acellular Pertussis vaccine containing chemically detoxified Pertussis Toxin
Thai FDA	Food and Drug Administration, Thailand
TT	Tetanus Toxoid
UK	United Kingdom
US	United States of America
VAERS	Vaccine Adverse Event Reporting System
WHO	World Health Organization
wP	Whole-cell Pertussis

Part I: Product overview

Table I-1 Product overview

<table>
<tr><td>Active substance
(INN or common name)</td><td>Purified acellular pertussis antigens
[recombinant Pertussis Toxin (PT_{gen}) and Filamentous Haemagglutinin (FHA)]</td></tr>
<tr><td>Pharmaco-therapeutic group (ATC Code)</td><td>Bacterial vaccines
(J07AJ02; Pertussis vaccine, purified antigen)</td></tr>
<tr><td>Marketing Authorisation Holder / Applicant</td><td>BIONET EUROPE SAS
41 Quai Fulchiron, 69005 LYON,
France</td></tr>
<tr><td>Number of medicinal products to which this RMP refers</td><td>1</td></tr>
<tr><td>Product concerned (brand name)</td><td>Recombinant acellular pertussis (aP_{gen}) vaccine adsorbed</td></tr>
<tr><td>Marketing authorisation procedure</td><td>Centralised</td></tr>
<tr><td>Brief description of the product</td><td>Summary of mode of action:
VacPertagen (aP_{gen}) vaccine can induce immunity against pertussis disease in recipients following immunisation.

<u>Important information about its composition:</u>
Each single human dose (0.5 mL presented in pre-filled syringe) contains:
<table>
<tr><th>Name of ingredients</th><th>Quantity</th></tr>
<tr><td colspan="2">Active substance</td></tr>
<tr><td>Recombinant Pertussis Toxin (PT_{gen}))</td><td>5 µg</td></tr>
<tr><td>Filamentous Haemagglutinin (FHA)</td><td>5 µg</td></tr>
<tr><td colspan="2">Excipients</td></tr>
<tr><td>Aluminum Hydroxide</td><td>0.3 mg (as Al3+)</td></tr>
<tr><td>Sodium Chloride</td><td>4.38 mg</td></tr>
<tr><td>Water for Injection</td><td>q.s. to 0.5 mL</td></tr>
</table></td></tr>
<tr><td>Hyperlink to the product information</td><td>Module 1, section 1.3 - Product Information</td></tr>
</table>

Indications in the EEA	Proposed: VacPertagen is indicated for • booster immunisation against pertussis of individuals 12 years of age and older • passive protection against pertussis in early infancy following maternal immunisation during pregnancy. The use of this vaccine should be in accordance with official recommendations.
Dosage in the EEA	Proposed: <u>*Individuals 12 years of age and older*</u> A single dose of 0.5 mL dose should be administered. *Pregnant women* A single dose of 0.5 mL should be administered during the second or third trimester of pregnancy. <u>*Paediatric population*</u> The safety and immunogenicity of VacPertagen in children less than 12 years of age has not yet been established. No data are available. Limited data in pregnant adolescents (12-17 years) are available.
Pharmaceutical form(s) and strengths	Proposed: Suspension for injection 0.5 mL single dose pre-filled syringe containing 5 µg PT_{gen}[1,2] and 5 µg FHA[1] [1] adsorbed on aluminum hydroxide [2] produced in *Bordetella pertussis* as a genetically detoxified PT
Is the product subject to additional monitoring in the EU?	Yes

Part II: Module SI Epidemiology of the indication and target population

SI.1 The disease

Pertussis is a highly infectious respiratory disease caused by a bacterium, *Bordetella pertussis*. It is spread from one person to another by coughing and sneezing. The incubation period of pertussis is commonly from 7-10 days (range of 5-21 days) (1). The classical clinical manifestations of pertussis can be divided into catarrhal, paroxysmal and convalescent stages (2).

Catarrhal stage: This stage lasts for about 1-2 weeks. It begins with mild upper respiratory tract symptoms similar to the common cold, such as coryza, sneezing, cough and low-grade or no fever.

Paroxysmal stage: This stage lasts 4-6 weeks, with outside limits of 1-10 weeks. The cough comes in paroxysmal explosive bursts. During the first 1-2 weeks of this stage, the attacks increase in severity and frequency and then remain at about the same level for a variable period, usually 1-3 weeks and then gradually decline. A series of 5-10 or more severe, rapid cough are given on one expiration and are followed by a sudden inspiration associated with a characteristic high-pitched crowing sound or whoop. The number of paroxysmal attacks varies from 4-5 daily in mild cases to as many as 40 in more severe forms.

Convalescent stage: This stage is marked by cessation of whooping and vomiting, little by little the number and severity of paroxysm decrease. The cough fades away in about 2-3 weeks. With subsequent respiratory infection, some patients will develop recurrent paroxysmal coughing attacks, complete with whoop and vomiting. This episode may occur repeatedly for months or even for 1-2 years.

The clinical presentation of pertussis in older adolescents and adults was demonstrated in a large Canadian study (3). Senzilet and colleagues (2001) found adults have higher incidence of complications than adolescents, including pneumonia (3). Complications in adolescents and adults include syncope, sleep disturbance, incontinence, rib fracture and pneumonia. In a prospective study conducted by Suntarattiwong and colleagues (2019) in Thai children aged between 0 and 18 years, majority had paroxysmal cough and post-tussive vomiting (96.4% and 92.9% respectively) while whoop was not common (17.9%). In addition, cyanosis was observed in half of the children with pertussis (4). According to US CDC, about half of infants with pertussis are hospitalized, with complications that include apnea (61%), pneumonia (23%), seizures (1.1%), encephalopathy (0.3%) with 1% fatality (5). Furthermore, these complications are associated with increased risk of death in infants in their first few months of life (6). In pregnant women, changes in their immune response during gestation may interfere with specific immune response to pathogens which makes them (and the foetus) susceptible to certain infectious diseases (7) including pertussis.

SI.2 Incidence

Pertussis is endemic worldwide and epidemic cycles would occur every 2-5 years despite effective vaccination programs and high childhood vaccination coverage estimated at 86% in 2014 (8). According to WHO in 2013, around 63,000 pertussis-related deaths have occurred in children <5 years of age. Furthermore in 2018, there were 151,074 cases of pertussis globally based on WHO data.

The annual incidence of pertussis increased to 1.2 cases per 100,000 population in the United States (US) from 1980 to 1989 followed by several epidemic of pertussis in the 1990s and 2000s (2, 10). A resurgence of pertussis has therefore emerged, with substantial evidence of rapidly waning protection following the switch from whole-cell pertussis (wP) to acellular pertussis (aP) vaccine in 1997 in the US (2). The burden of disease shifted to young infants, adolescents and adults (2). An increase in cases mostly in infants <6 months and adolescents were noted in 2004, 2005, and 2012, but in 2011-2012, a rise in pertussis cases included all age groups (11). Furthermore, a number of studies have documented pertussis in 13-32% of adolescents and adults with cough lasting more than 7 days (2).

A resurgence of pertussis has also occurred in other countries including the UK, Australia, Brazil, Chile and Portugal (11). The incidence of laboratory-confirmed pertussis in the UK increased predominantly in children 10-14 years and infants <1 year of age since 2011 (11). It was hypothesized that the increase in pertussis cases was at least in part due to an aP-induced waning of immunity and reduced acquisition of natural immunity, particularly in adolescents aged 10-14 years (11). Similarly, in Australia, discontinuation of the 18-month booster dose appears to have contributed to resurgence in pertussis among 2- to 4-year-olds, with early waning immunity following the last acellular vaccine dose at 6 months (11).

SI.3 Prevalence

Among countries in the Asia-Pacific, the age cohort with the highest pertussis burden are the following: infants (Philippines), <1 year old (Indonesia, South Korea, Taiwan), <4 year old (China, Thailand), <5 year old (Pakistan, Singapore, Vietnam), <5 year old but beginning to be recognized in older children and adults (India), 0-14 year old (Australia) and school-aged children (New Zealand) and in Japan, previously infants but incidence is increasing in older cohorts (16). Furthermore, in Australia, there were 91,780 notifications of pertussis between 2013 and 2018. The average annual all-age national notification rate was 63.6 per 100,000 population, a 40% reduction compared to the previous 6 years (2006–2012) which was 103.1 per 100,000 population (17). In Europe, notification rates estimated by the European Centre for Disease Prevention and Control (ECDC) were 9.4 in 2017, and 7.9 in 2018 (51). According to ECDC, more than 25 000 cases of pertussis were reported in 2023, and more than 32 000 between January and March 2024. These numbers observed were similar to 2016 with 41 026 cases and 2019 with 34 468 cases, indicating a larger epidemics every three to five years, event with high vaccination coverage. (52). In France, a total of 132 confirmed pertussis cases (including 109 laboratory- and 23 epidemiologically-confirmed) were reported between 2017 and 2020 (53). The incidence rates per 100,000 inhabitants were estimated at 17 cases (95% CI: 12-22) in 2017, 10 cases (95% CI: 6-14) in 2018, 15 cases (95% CI: 10-20) in 2019 and 3

cases (95% CI: 1-5) in 2020. In the UK, cases of pertussis are increasing with 716 notifications in 2023 compared to just 217 cases in 2022, 213 in 2021 and only 72 in 2020 (54). For Belgium the Risk Assessment Group reported an increase in Belgian cases of pertussis in 2023 until August with 1 258 cases, with the highest incidences noted in the age groups 5-9 years and 10-14 years old patients (55).

SI.4 Demographics of the target population – age, sex, race/ethnic origin

The target population includes male and female children, adolescents and adults (including the elderly and pregnant women).

Risk factors for the disease

Waning of vaccine-derived protection and reduced boosting of immunity by circulating *B. pertussis* are likely to increase the susceptibility of children, adolescents and adults (8). Adolescents and adults are primary sources of pertussis infection in infants particularly those who are too young to be vaccinated or complete the primary vaccine series (18, 19). Infants less than 3 months of age are at high risk of hospitalization and death from pertussis (20). Moreover, premature infants are at high risk for severe, potentially fatal disease (2).

SI.5 Main existing treatment options

The standard of care includes giving macrolide antibiotics, such as erythromycin. They may prevent or lessen the severity of clinical pertussis when given early either during incubation period or catarrhal stage (8). However, when these antibiotics are given during the paroxysmal phase of the disease, they may only eliminate the bacterium from the nasopharynx resulting to reduced disease transmission (8).

SI.6 Prevention of pertussis

Experts have encouraged immunisation with aP vaccines for adolescents and adults (18). Similarly, immunisation of pregnant women can protect them directly against vaccine-preventable infections including pertussis, and in so doing potentially protect the foetus. It can also directly protect the foetus and infant via specific antibodies transferred from the mother during the pregnancy (7). In Thailand, a study by Suntarattiwong and colleagues (2019) had shown that pertussis in Thai children is not infrequent with most cases occurring in young infants who have not completed the primary series of pertussis vaccine at six months of age (4). This further highlights the importance of maternal pertussis immunisation as maternally-acquired antibodies are critical in protecting infants during the first months of their lives (4). In Australia, pertussis is the second most frequently reported vaccine preventable disease with unimmunized infants who are too young to be fully immunized having the highest risk of hospitalizations and deaths (17). Vaccinating pregnant women has been reported to reduce pertussis disease in infants by 80-91% (21, 22).

SI.7 Important co-morbidities

No significant co-morbidities have been identified in the target populations.

Part II: Module SII Non-clinical part of safety specification

Table II-1 Summary of non-clinical toxicity studies, activities to prevent and control toxicity and relevance to human usage

Non-clinical toxicity study	Evidence of toxicity	Activities to be done to prevent toxicity	Activities to be done to decrease or control toxicity	Relevance to human usage
1. Single-dose toxicity of aP_{gen} vaccines [comparability study of VacPertagen, 2-component aP (PT_{gen} and FHA), versus 3-component aP_{gen} vaccine and of Td-VacPertagen ($TdaP_{gen}$ vaccine containing 2-component aP_{gen}) versus $TdaP_{gen}$ vaccine containing 3-component aP_{gen}] [redacted]Study No. 15018	No evidence of local and systemic adverse reactions in rats.	No activity is required since no evidence of toxicity has been identified.	No activity is required since no evidence of toxicity has been identified.	The dose of vaccine (0.5 mL) used in single-dose toxicity study was the same as that for single human dose.
2. Reproductive and developmental toxicity of Td-VacPertagen [$TdaP_{gen}$ vaccine containing 2-component aP_{gen} (PT_{gen} and FHA) and VacPertagen [2-component aP_{gen} (PT_{gen} and FHA) vaccine]. [redacted]Study No. 15661	No adverse effects on pregnancy, parturition, lactation, embryo-foetal, pre-natal or post-natal development in rats.	No activity is required since no evidence of toxicity has been identified.	No activity is required since no evidence of toxicity has been identified.	The dose of vaccine (0.25 mL) used in the reproductive and developmental toxicity study was half of the single human dose.
3. Pre- and postnatal development study of pertussis vaccine (containing per 0.5-mL dose 5 µg of PT_{gen}, 5 µg of FHA, 7.5 Lf of TT and 2.5 Lf of DT), in rats, including maternal function, Study No. [redacted]348502	No adverse effects on pregnancy, parturition, lactation, embryo-foetal, pre-natal or post-natal development in rats.	No activity is required since no evidence of toxicity has been identified.	No activity is required since no evidence of toxicity has been identified.	The dose of vaccine dosage level of 5 µg (2.5 µg/injection). administered on 4 treatment days as 2 intramuscular (bolus) injections, at 2 separate injection sites.

Note: Although the study was not performed with VacPertagen (aP_{gen} vaccine), this is considered as a supportive study since Td-VacPertagen ($TdaP_{gen}$ vaccine) contains aP_{gen} antigens (PT_{gen} and FHA) of VacPertagen in addition to Diphtheria and Tetanus Toxoids.

No general safety pharmacology studies, or studies on drug or vaccine interactions (including studies on co-administration with other vaccines) have been conducted.

Conclusions on non-clinical data

Single-dose and repeat-dose toxicity studies adequately evaluated the 2-component (PT_{gen} and FHA) vaccine. The aP_{gen} vaccine was well tolerated in all the toxicity studies that were carried out. Results from single-dose toxicity study showed that the 2-component aP_{gen} did not cause death nor induce any local and systemic adverse reactions. In the repeat-dose toxicity study, it has shown similar toxicity profile to a licensed TdaP vaccine [redacted] widely used in Canada, USA and several other countries.

No RMP safety concerns have been identified from available non-clinical data.

Part II: Module SIII Clinical trial exposure

SIII.1 Brief overview of development

The first aP vaccine was developed in Japan in 1981, after which aP vaccines have gradually become the predominant type used in industrialized countries (8). These vaccines contain one or more of the following purified antigens: Pertussis toxin (PT), Filamentous Haemagglutinin (FHA), Pertactin (PRN), and Fimbriae (FIM) types 2 and 3, and differ not only in the number of antigens (1 [PT only], 2 [PT and FHA], 3 [PT, FHA, and PRN] or 5 [PT, FHA, PRN, and FIM types 2 and 3] components) and concentration of the antigen components, but also with methods of purification and detoxification (i.e. glutaraldehyde, formaldehyde, H_2O_2 or genetic method) (8).

Acellular pertussis vaccines have been successfully introduced in many national immunisation programs. However, resurgence of pertussis has been reported in recent years, especially in countries using aP vaccines (11). Potential factors for resurgence of pertussis include age-related waning of immunity in older children and adults (23, 24). The aP vaccines containing chemically detoxified Pertussis Toxin (cPT)-induced insufficient T-cell type 1 (Th1) immunity (25, 26) and wanes within 2-4 years (27). The insufficient immune response is explained by the fact that chemical inactivation of cPT dramatically changes the protein structure resulting in a great reduction (80%) of T-cell binding epitope compared to native PT (28, 29).

A call for new pertussis vaccine containing genetically detoxified Pertussis Toxin and more booster immunisations have been proposed (30, 31). Genetically-inactivated PT mutants were developed simultaneously in Italy and US at the National Institute of Allergy and Infectious Diseases (NIAID). The rPT contains two mutations of R9K and E129G in the S1 peptide (32)

resulting in a loss of toxicity of PT. Inactivation of PT by chemical treatment is therefore unnecessary. The physicochemical and antigenic property of rPT was similar to those of native PT (33). Studies of aP vaccine containing 5 µg rPT, 2.5 µg FHA and 2.5 µg PRN in combination with diphtheria and tetanus conducted in infants and adolescents showed similar safety profile and efficacy (84%, 95% CI: 76-90%) with more Th1 immune response compared to aP containing cPT at 5-times higher PT content (25,34,35). The protective efficacy was sustained for 6 years after primary immunisation (36). These aP vaccines containing rPT were launched in several countries (including Italy, Korea and Thailand) but was withdrawn in the year 2000s due to patent issues. However, the patent expired a few years ago.

BioNet has developed a new recombinant *B. pertussis* strain expressing a genetically detoxified PT (PT_{gen}) for recombinant aP vaccine production which has been filed for patent application in many countries (37). Two mutations of the S1 subunit (R9K and E129G) were introduced into *B. pertussis* strain by site specific integration to obtain a recombinant *B. pertussis* strain [redacted] expressing a non-toxic PT antigen (38). The molecular characterization and genetic stability of this recombinant [redacted] strain have been confirmed.

The evaluation of the clinical efficacy of VacPertagen vaccine was based on its ability to elicit antibodies against PT_{gen} and FHA antigens. In the 90s, the clinical efficacy of aP vaccines in preventing pertussis has been shown in several efficacy trials (5) for aP vaccines with 1 component (PT), 2 components (PT and FHA), 3 components (PT, FHA and PRN), or 5 components (PT, FHA, PRN and Fimbriae 2/3). All aP vaccines were licensed based on the results of these efficacy studies. Effectiveness of aP vaccines was shown to be similar for aP vaccines with any antigenic formulation (i.e., from 1 component to 5 components). A 3-component aP vaccine containing rPT was shown to be highly efficacious six years after vaccination in infancy (36). A study by Knuf et al (2008) assessed whether early neonatal immunisation with acellular pertussis would be of particular benefit (39). They found that early neonatal immunisation with aP vaccine was safe, well tolerated, and resulted in earlier antibody responses, seen after the first dose of a Diphtheria toxoid, Tetanus toxoid, acellular pertussis (DTaP) vaccine (39). Another study by Wood et al (2010) found that 2 doses of monovalent acellular pertussis vaccine given before 2 months of age was well tolerated (40). Additionally, by 2 months of age, 22 of 25 (88%) of 2 dose recipients had detectable IgG antibody to PT (IgG PT) compared with 9 of 21 (43%) who received a birth dose only and 3 of 20 (15%) in the control group (40). Data suggest that stand-alone aP at birth and 1 month induces significantly higher IgG antibody against pertussis antigens by 2 months of age without reducing subsequent pertussis antibody responses (40).

Recombinant aP_{gen} vaccines adsorbed onto aluminum hydroxide as a monovalent vaccine and in combination with tetanus and diphtheria toxoids for booster use was developed in accordance with international standards including World Health Organization (WHO) guidelines, European Pharmacopoeia (Ph. Eur.) and local Thai regulations.

A 2-component aP_{gen} (PT_{gen} and FHA) vaccine has been developed as a monovalent vaccine (VacPertagen, aP_{gen} vaccine containing 5 µg PT_{gen} and 5 µg FHA per dose) and in combination with tetanus and diphtheria toxoids (Td-VacPertagen, $TdaP_{gen}$ vaccine containing 5 µg PT_{gen}

and 5 µg FHA, 7.5 Lf TT and 2 Lf DT). VacPertagen and Td-VacPertagen were evaluated in a non-inferiority phase II/III trial in healthy Thai adolescents aged 12-17 years old (TDA202). Findings from this study led to licensure of recombinant acellular pertussis vaccines in Thailand for the booster immunisation in adults and children aged 11 years and onwards. In addition, a phase III randomised controlled study in healthy adults and elderly between 18-75 years (TDA206) was conducted to compare the safety and immunogenicity of VacPertagen and Td-VacPertagen to another licensed Tdap vaccine.

As part of the clinical development plan for VacPertagen, additional studies are being performed in other countries. In Australia, a phase II/III randomised, observer-blind, controlled trial in healthy young adults aged 18-30 years is ongoing to assess the immune response and safety of VacPertagen compared to Boostrix® (Pertaprime-01). In Switzerland, a phase II/III randomised, double-blind controlled study in adults aged 18-30 years previously primed and boosted with acellular pertussis vaccines is in progress to assess safety and determine whether giving two doses of VacPertagen at 6 months interval induces stronger immune responses than a single dose (Pertagen 2x). Another study in Switzerland has been completed whereby VacPertagen was evaluated in an investigator-driven proof-of-concept phase II randomised controlled trial (Pertagen in Adolescents (PertADO) Geneva trial) among healthy adolescents aged 11-15 years old. Lastly, in Uganda (Africa), a phase II randomised, observer-blind, controlled study involving HIV-infected pregnant women (intervention group) and HIV-uninfected pregnant women (as comparator) aged 18 years or older to determine the safety and immunogenicity of BioNet TdaP (Td-VacPertagen) given during pregnancy (WoMANPOWER study) has been completed and published (50).

Td-VacPertagen was also evaluated for safety and immunogenicity in healthy women of childbearing age (TDA203) and in healthy pregnant women (TDA204) enrolled in phase II randomised, observer-blind, active-controlled trials in Thailand. Td-VacPertagen has a similar formulation to VacPertagen and hence the data generated with Td-VacPertagen was added as a supportive data in this risk management plan.

Two more studies in healthy Thai pregnant women were conducted on VacPertagen and Td-VacPertagen, of which one, an observational study (PerMIT) has been completed and published (59) and the other, a randomised clinical trial (TDA207) was completed and has shown good safety profile with no major issues until delivery.

A summary of completed and ongoing BioNet clinical studies is shown in Table III.2-1.

SIII.2 Clinical trial exposure

Table III.2-1 Summary of clinical studies of VacPertagen and vaccines containing VacPertagen components

No.	Title of Study / Study Protocol Number or Name / Registry Number / Publication	Phase / Country	Age (Years)	Number of Subjects who Received VacPertagen (aP_{gen}) or Vaccines Containing VacPertagen Components[1] / Status
1	A phase II/III randomised, observer-blind, controlled study to demonstrate non-inferior immunogenicity of a combined Tetanus-diphtheria-acellular Pertussis vaccine as compared to Adacel® vaccine in healthy subjects aged 12-17 years Study protocol number: TDA202 Thai Clinical Trials Registry number: TCTR20150703002 Published: 1. Sricharoenchai et al., Lancet Infect Dis. 2018 (41) (Data up to 28 days post vaccination) 2. Pitisuttithum et al., Lancet Infect Dis. 2018 (42) (Data up to 1 year post-vaccination)	II/III Thailand	12-17	1. VacPertagen 150 subjects 2. Td-VacPertagen 150 subjects
2	Antibody persistence at 2 years after a single dose vaccination of acellular pertussis vaccines among Thai adolescents Study protocol number: TDA202 2-year follow-up ClinicalTrials.gov Identifier: NCT04113655 Published: Pitisuttithum et al., EClinicalMedicine. 2021 (56)	Follow-up post TDA202 vaccination cohort after 2 years	13-19	NA[2]
3	Antibody persistence at 3 years after a single dose vaccination of acellular pertussis vaccines containing genetically-detoxified pertussis toxin Study protocol number: TDA202 3-year follow-up ClinicalTrials.gov Identifier: NCT04102137 Published: Pitisuttithum et al., EClinicalMedicine. 2021 (56)	Follow-up post TDA202 vaccination cohort after 3 years	15-21	NA[2]
4	Antibody persistence at 5 years after a single dose vaccination of acellular pertussis vaccines containing genetically-detoxified pertussis toxin Study protocol number: TDA202 5-year follow-up ClinicalTrials.gov Identifier: NCT04529720	Follow-up post TDA202 vaccination cohort after 5 years	17-21	NA[2]
5	A phase II randomised, observer-blind, active-controlled study to evaluate the immunogenicity and safety of a	II Thailand	18-40	Td-VacPertagen 50 subjects

No.	Title of Study / Study Protocol Number or Name / Registry Number / Publication	Phase / Country	Age (Years)	Number of Subjects who Received VacPertagen (aP_{gen}) or Vaccines Containing VacPertagen Components[1] / Status
	single dose of BioNet- Asia's acellular pertussis-only vaccine and its combined tetanus- diphtheria-acellular pertussis vaccine at multiple dose levels or Boostagen® in comparison to Boostrix™, when administered to women of childbearing age Study protocol number: TDA203 Thai Clinical Trials Registry number: TCTR20180321004 Published: Chokephaibulkit et al., Vaccine 2022 (43)			
6	A phase II randomised, observer-blind, active-controlled study to evaluate the immunogenicity and safety of a single dose of BioNet-Asia's acellular pertussis-only vaccine and its combined tetanus-diphtheria-acellular pertussis vaccine at multiple dose levels Study protocol number: TDA204 Thai Clinical Trials Registry number: TCTR20180725004 Published: 1. Puthanakit et al., Vaccine 2023 (44) (This paper includes safety data of healthy pregnant women 28 days post-vaccination) 2. Chokephaibulkit et al., Vaccine 2024 (57) (This paper includes data at delivery and at 2 months after delivery) 3. Puthanakit et al., Pediatr Infect Dis J. 2025 (This paper includes data in infants until 13 months of age (58)	II Thailand	18-40	Td-VacPertagen 80 subjects
7	A phase III randomised, observer-blind, active-controlled study to compare the safety and immunogenicity of an investigational combined Tetanus-diphtheria-recombinant acellular pertussis vaccine (BioNet Tdap) and licensed recombinant TdaP vaccine (Boostagen®), investigational recombinant monovalent acellular pertussis vaccine (BioNet ap) and licensed recombinant aP vaccine (Pertagen®) and another licensed Tdap vaccine, when administered to healthy adults aged of 18-75 years old Study protocol number: TDA206 (PreBoost Adult) Thai Clinical Trials Registry number: TCTR20190927006	III Thailand	18-75	VacPertagen 150 subjects Td-VacPertagen 150 subjects

No.	Title of Study / Study Protocol Number or Name / Registry Number / Publication	Phase / Country	Age (Years)	Number of Subjects who Received VacPertagen (aP_{gen}) or Vaccines Containing VacPertagen Components[1] / Status
8	A phase II randomised, observer-blind, active-controlled study to evaluate the immunogenicity and the safety of BioNet recombinant pertussis vaccines with different doses of genetically detoxified pertussis toxin (PT_{gen}) when administered to healthy pregnant women Study protocol number: TDA207 (PreBoost Pregnant women) Thai Clinical Trials Registry number: TCTR20210128004	II Thailand	18-40	VacPertagen 40 subjects Td-VacPertagen 40 subjects
9	A Phase II randomised, observer-blind controlled pilot study to compare the safety and immunogenicity of acellular pertussis vaccines including chemically or genetically-detoxified pertussis toxin in adolescents aged 11-15 years previously immunized with acellular pertussis vaccines Study protocol name: The PertADO Geneva trial ClinicalTrials.gov Identifier: NCT02946190 Published: Rohner et al., Clin Infect Dis. 2019 (45)	II Switzerland	11-15	VacPertagen with Td 31 subjects
10	An investigator-driven phase II/III randomised, observer-blind, controlled trial to demonstrate non-inferior immunogenicity of Pertagen® in comparison to Boostrix® in healthy young Australian adults aged 18-30 years Study protocol name: Pertaprime-01 Australian New Zealand Clinical Trials Registry number: ACTRN12619000944134	II/III Australia	18-30	Results on safety and immunogenicity 28 days and 1 year post vaccination were obtained. VacPertagen 68 subjects
11	A Phase II/III randomised, double-blind controlled study to compare the safety and immunogenicity of 1 or 2 doses of acellular pertussis vaccines containing genetically-detoxified pertussis toxin in young adults previously primed with acellular pertussis vaccines Study protocol name: Pertagen 2x ClinicalTrials.gov Identifier: NCT05193734	II/III Switzerland	18-30	VacPertagen 101 subjects

No.	Title of Study / Study Protocol Number or Name / Registry Number / Publication	Phase / Country	Age (Years)	Number of Subjects who Received VacPertagen (aP_{gen}) or Vaccines Containing VacPertagen Components[1] / Status
12	The safety and immunogenicity of combined Pertussis-containing vaccine (Tdap) for HIV-infected pregnant Women and their newborns - A randomised clinical trial Study protocol name: WOMANPOWER – Uganda ClinicalTrials.gov Identifier: NCT04589312 Published: Nakabembe E, et al. Lancet Glob Health. 2025 (60)	II Uganda	18-44	Td-VacPertagen 90 subjects
13	A randomised, observer-blind, active-controlled study to describe the safety of recombinant acellular pertussis (aP) vaccine when administered to healthy adults aged of 18-75 years old Study protocol name: APV301 (PertaSafe) Clinicaltrials.gov registration number: NCT06798831	III Thailand	18-75	VacPertagen 2100 subjects

[1] Td containing VacPertagen vaccine (aP_{gen}) components

[2] Not applicable as this is a serological follow-up study. A cohort of participants who were vaccinated with a single dose of one of the three study vaccines and had completed the TDA202 study in 2016 (one-year follow-up visit) at study site no.2: VTC, Faculty of Tropical Medicine, Mahidol University were recruited for the 2 and 3-year visits. Serum samples were collected and immunogenicity testing was performed.

Table III.2-2 Individuals exposed to VacPertagen (aP_{gen})

a. Age group (by indication in adolescents and pregnant women) and gender

Age group	Male	Female
Adolescents (11 to 17 years)	77[a]	104[a]
Adults (18 to 64 years)	839[b]	1326[b]
Elderly people (65-75 years)	41[c]	112[c]
Pregnant women	0	40
Total	957	1582

[a] This number includes subjects from TDA202 and PertADO Geneva trial

[b] This number includes subjects from APV301, TDA206, Pertaprime-01 and TDA207 studies

[c] This number includes subjects from APV301 and TDA206 studies.

b. Ethnicity

Ethnicity	Individuals
Aboriginal and/or Torres Strait Islander	2
Black or African	1

Asian	2443
Asian/Caucasian	2
Anglo/Indian/Burmese	3
Caucasian	82
Indian-subcontinent	4
Latino (South American)	1
Other	1
Total	2539

Table III.2-3 Individuals exposed to Td-VacPertagen ($TdaP_{gen}$)

a. Age group and gender

Age group	Male	Female
Adolescents (11 to 17 years)	66	84
Adults (18 to 64 years)	39	590
Elderly people (65-75 years)	10	20
Total	115	694

b. Ethnicity

Ethnicity	Individuals
African	90
Asian	572

Part II: Module SIV Populations not studied in clinical trials

SIV.1 Exclusion criteria in pivotal clinical studies within the development programme

- Hypersensitivity to any component of the vaccine
  Reason for exclusion: Patient risk
  Is it considered to be included as missing information: No
  Rationale: Hypersensitivity to the ingredient is a contraindication as per proposed SmPC.

- Cardiovascular, renal, or hepatic disease in acute or active phase
  Reason for exclusion: Symptoms of disease may cause study bias
  Is it considered to be included as missing information: No
  Rationale: No change in safety profile expected in this population

- Any chronic or active neurologic disorder (incl. seizures, uncontrolled epilepsy)

Reason for exclusion: Symptoms of disease may cause study bias; vaccination may lead to symptom aggravation
Is it considered to be included as missing information: No
Rationale: No change in safety profile expected in this population

- Breastfeeding women with HIV
  Reason for exclusion: Infection may cause study bias, particularly in immunocompromised women
  Is it considered to be included as missing information: No
  Rationale: No change in safety profile expected in this population - of note, a randomised controlled study in pregnant women with HIV has been completed in Uganda, Africa (WOMANPOWER – Uganda; ClinicalTrials.gov Identifier: NCT04589312).

SIV.2 Limitations to detect adverse reactions in clinical trial development programmes

The clinical development programme is unlikely to detect certain types of adverse reactions, such as rare adverse reactions and adverse reactions with a long latency.

As VacPertagen is indicated for single use, prolonged or cumulative exposure is not foreseen to lead to safety concerns.

During clinical trials, all ADRs were monitored appropriately.

SIV.3 Limitations in respect to populations typically under-represented in clinical trial development programmes

- Elderly (persons aged 65 years and older)

  A phase III randomised, observer-blind, active-controlled study to evaluate safety and immunogenicity of VacPertagen (aP_{gen}) or Td-VacPertagen compared to another licensed non-recombinant Tdap vaccine (TDA206; Thai Clinical Trials Registry number: TCTR20190927006) was performed in this group with 30 participants enrolled aged between 65 to 75 years.

  In order to extend the safety database of VacPertagen in this age group, a phase III randomised, observer-blind, active-controlled study was conducted in Thailand (APV301; Clinicaltrials.gov registration number: NCT06798831). This study recruited 2400 (2100 received VacPertagen and 300 received Boostrix) healthy adults aged 18 to 75 years old. In this study, there are 123 participants enrolled aged between 65 to 75 years.

- Pregnant women

  A study on Td-VacPertagen ($TdaP_{gen}$) was performed in this group (TDA204; Thai Clinical Trials Registry number: TCTR20180725004). In addition, studies on VacPertagen (aP_{gen})

and/or Td-VacPertagen are completed (TDA207; Thai Clinical Trials Registry number: TCTR20210128004 and WOMANPOWER-Uganda study; ClinicalTrials.gov Identifier: NCT04589312). An observational study in healthy pregnant women previously vaccinated with either VacPertagen or Td-VacPertagen as part of antenatal care was also conducted (PerMIT; Thai Clinical Trials Registry number: TCTR20200528006). A total of 2385 pregnant women were exposed to VacPertagen and 459 pregnant women were exposed to Td-VacPertagen from TDA204, TDA207, WOMANPOWER-Uganda and PerMIT studies.

Women of childbearing age were included in TDA202 study (since the study population was 12 to 17 years of age). No case of pregnancy was reported during the first 28 days of the clinical trial. During Day 29 – Day 336±28 of the clinical trial, a total of 5 pregnancy cases were reported by the study investigators, of which two were reported in the VacPertagen group.

- Patients with relevant co-morbidities such as clinically significant renal, hepatic, or cardiac impairment

  No studies on VacPertagen were performed in this group

- Populations of different racial and/or ethnic origin

  VacPertagen has been studied in populations of diverse racial and ethnic backgrounds. The PertADO Geneva trial (ClinicalTrials.gov Identifier: NCT02946190) (45) was conducted in Switzerland among adolescents of various ethnicities. Two additional studies in young adults have been completed: one in Switzerland among individuals previously primed with acellular pertussis vaccines (Pertagen 2x; NCT05193734), and another in Australia (Pertaprime-01; ACTRN12619000944134).

  - Immunocompromised patients

  A phase II randomised, observer-blind, controlled clinical trial (WOMANPOWER-Uganda study; ClinicalTrials.gov Identifier: NCT04589312) in HIV-infected pregnant women assessed the safety and immunogenicity of VacPertagen containing vaccine (Td-VacPertagen) compared to HIV-uninfected pregnant women. A total of 40 HIV-infected pregnant women were exposed to Td-VacPertagen.

- Subpopulations carrying relevant genetic polymorphisms

  No studies on VacPertagen were performed in this group.

Part II: Module SV Post-authorisation experience

SV.1 Post-authorisation exposure

No post-authorisation data are available for the EEA for VacPertagen, or for Td-VacPertagen, $TdaP_{gen}$ or $DTaP_{gen.}$

There is extensive non-EEA exposure for VacPertagen.

In addition to randomised controlled trials, several observational studies have been conducted outside Europe to assess the real-world safety and use of VacPertagen in pregnant women. These include the PerMIT study (Thailand) (59), which evaluated antibody transfer in 497 women immunised with VacPertagen or Td-VacPertagen; the PerMIS-01 study (Thailand), a large safety surveillance in approximately 1980 pregnant women, and the Pertagen-MOMS study (Thailand), assessing obstetric and neonatal outcomes in 585 women aged 15-44 years.

In non-EU countries, VacPertagen is also authorised for booster immunisation against pertussis in individuals from 3 years of age onwards. VacPertagen has received marketing authorisation in Thailand (since 30 September 2016) and Singapore (since 23 July 2021).

SV.1.1 Method used to calculate exposure

Exposure was calculated as one single 0.5 mL dose corresponding to one vaccinee. Please note that this may include persons <12 years of age, depending on local approved posology.

SV.1.2 Exposure

Year	Period	Dose (mL)	Unit Pack Size	No. of Units Sold
2018 - 2025	2018 - 31 August 2025	0.5 mL	1	700481
TOTAL				700481

The patient exposure is estimated based on the sold units of VacPertagen. Based on this assumption, between 2018 and 31 August 2025 about 700481 vaccinees have been vaccinated with VacPertagen.

Part II: Module SVI Additional EU requirements for the safety specification

Potential for misuse for illegal purposes

There is no potential for misuse for illegal purposes foreseeable for this product, which will be administered by healthcare professionals just once.

Part II: Module SVII Identified and Potential Risks

SVII.1 Identification of safety concerns in the initial RMP submission

Table SVII.1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	None
Missing information	Limited information on use in pregnant women in the European population.

SVII.1.1. Risks not considered important for inclusion in the list of safety concerns in the RMP

Reason for not including an identified or potential risk in the list of safety concerns in the RMP:

Risks with minimal clinical impact on patients (in relation to the severity of the indication treated):

- Local vaccination site reactions, e.g., bruising, induration, pain, pruritus, redness, swelling
- Systemic vaccination reactions, e.g., arthralgia, chills, dizziness, fatigue, fever, headache, malaise, myalgia, pain in extremity (often summarized as influenza-like illness), diarrhoea, nausea, vomiting (gastro-intestinal symptoms)

Known risks that require no further characterisation and are followed up via routine PV (namely through signal detection and adverse reaction reporting), and for which the risk minimisation messages in the PI are adhered by prescribers (e.g., actions being part of standard clinical practice):

- Anaphylaxis, hypersensitivity reactions

Class effects for vaccines:

- As with any vaccines, a protective immune response may not be elicited in all vaccinees.
- Limited data indicate that maternal antibodies interfere with induction of PT-specific immune response to primary immunisation with DTwP/DTaP in infants born to women vaccinated with VacPertagen during pregnancy.

SVII.1.2. Risks considered important for inclusion in the list of safety concerns in the RMP

Risks identified have been assessed as having no negative impact on the risk-benefit balance or a negative public health impact for the medicinal product; none of these is considered to warrant further evaluation as part of the PV plan or risk minimisation activities. Hence, no RMP important risks are proposed.

SVII.2 New safety concerns and reclassification with a submission of an updated RMP

Not applicable, as this is the first submitted RMP.

SVII.3 Details of important identified risks, important potential risks, and missing information

SVII.3.1. Presentation of important identified risks and important potential risks

Not applicable, as no important identified risks or important potential risks have been identified.

SVII.3.2. Missing information

Limited information on use in pregnant women in the European population.

Evidence source: Though limited data are available for this patient group, the importance of maternal and neonate safety indicates the need of further evaluation.

Population in need of further characterisation: Pregnant women and neonates in the EU.

Part II: Module SVIII Summary of safety concerns

Table SVIII.1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	None
Missing information	Limited information on use in pregnant women in the European population

Part III: Pharmacovigilance Plan (including post-authorisation safety studies)

III.1 Routine pharmacovigilance activities

Routine PV activities for BioNet comply with GVP and fulfil the legal requirements per Directive 2001/83/EC and Regulation (EC) No. 726/2004. Routine PV includes management of Individual Case Safety Reports (ICSRs), including submission to regulators, PSURs, monitoring of safety profiles, and safety signal detection and evaluation (incl. updates of the SmPC / PIL as needed). For details, please refer to the PV System Master File and respective SOPs.

III.2 Additional pharmacovigilance activities

The MAH will conduct a post-authorisation safety study (PASS) in the EU to collect structured safety data from pregnant women vaccinated with VacPertagen, including information on pregnancy outcomes and infant health status.

III.2.1 PASS summary

Study short name and title:

Post-Authorisation Safety Study (PASS) to Assess Pregnancy Outcomes Following Administration of VacPertagen in Pregnant Women in the EU.

Rationale and study objective:

Studies have shown that Tdap vaccines are safe and well-tolerated in pregnant women. Common side effects include mild pain or redness at the injection site, fatigue, and mild fever, all of which are similar to the reactions seen in non-pregnant individuals. Serious side effects are rare. Importantly, there is no evidence to suggest that the vaccine poses a risk to pregnancy, foetal development, or long-term infant health.

VacPertagen clinical safety data are limited. A PASS as an additional pharmacovigilance activity is proposed in the VacPertagen Risk Management Plan to further confirm the safety of VacPertagen on exposure in the second and third trimesters of pregnancy. This PASS will systematically collect safety data on pregnancy exposures and evaluate the risk of key obstetric and neonatal outcomes.

Given the need for data applicable to the EU population, the study will be conducted in Europe where VacPertagen is recommended for maternal immunisation. Site selection will ensure demographic, clinical practice, and healthcare system comparability with the broader EU population.

A feasibility assessment to confirm availability, accessibility, and suitability of data sources for implementation of the PASS in the EU will be conducted.

The primary objective of this study is to evaluate the safety of VacPertagen when given according to national recommendations during pregnancy, particularly in relation to maternal and neonatal health outcomes. The study will monitor adverse events (AEs) in both the pregnant population and their infants following vaccination.

As a secondary objective, the effectiveness of maternal vaccination with VacPertagen in reducing the risk of pertussis in infants born to vaccinated mothers will be estimated by comparing pertussis incidence in infants whose mothers received VacPertagen during pregnancy with infants of unvaccinated mothers, where appropriate data are available.

Study design:

This observational national-based cohort study (> 10 000 births/year) is non-interventional PASS conducted to evaluate safety in pregnant women and their infants (pregnancy and neonatal outcomes) following vaccination with VacPertagen during pregnancy. A prospective pregnancy exposure registry will enroll pregnant women who receive VacPertagen during pregnancy. Supplementary analysis using existing health data sources may be incorporated to enhance sample size and outcome ascertainment if feasible. The study is observational and non-interventional, following routine clinical practice.

Study population:

Inclusion: Pregnant women receiving VacPertagen in accordance with official recommendations and routine clinical practice (i.e., usually during the second or the third trimester of pregnancy).

Comparator group: Where data allow, a cohort of pregnant women not vaccinated during the same pregnancy period may be used for contextual comparison.

Infant follow-up: Neonates will be followed up for early-life outcomes (e.g., congenital anomalies, neonatal complications, hospitalisations).

Effectiveness analyses will be performed using observational data sources capable of linking maternal vaccination status to infant health outcomes. Comparative analytical approaches (e.g., cohort or case-control methods) may be applied to estimate the relative reduction in pertussis risk among infants of vaccinated mothers.

Milestones:

Feasibility assessment: within 4-6 months following the EC decision (if granted)

PASS protocol submission: within 6 months from the EC decision

Registry initiation and site activation: within the 6 months following the implementation of the official recommendation of VacPertagen in pregnant women

Enrollment period: 24-36 months or until sufficient events accrued

Final report to PRAC: Within 12 months of data lock

III.3 Summary Table of additional Pharmacovigilance activities

Table Part III.1: On-going and planned additional pharmacovigilance activities

Category 3 - Required additional pharmacovigilance activities				
Study / Status	**Summary of objectives**	**Safety concerns addressed**	**Milestones**	**Due dates**
Planned	• Evaluation of the safety of VacPertagen in the second and third trimesters of pregnancy in relation to maternal and neonatal health outcomes.	Limited information on use in pregnant women in the European population	Feasibility assessment	Within four to six months of EC decision
			Protocol submission	Within six months of EC decision (end of procedure)
			Registration in EU PAS	Within two weeks after protocol approval
			Start of data collection	Within nine months of study approval

	• Estimation of the effectiveness of maternal vaccination with VacPertagen in reducing the risk of pertussis in infants born to vaccinated mothers by comparing pertussis incidence in infants whose mothers received VacPertagen during pregnancy with infants of unvaccinated mothers, where appropriate data are available.		End of data collection	After completion of follow up period for last patient in
			Final study report completion and submission	Within 12 months of data lock.

Part IV: Plans for post-authorisation efficacy studies

None proposed.

Part V: Risk Minimisation Measures (incl. evaluation of the effectiveness of risk minimisation activities)

V.1 Routine risk minimisation measures

Routine risk minimisation measures include the SmPC and the PIL sections on risks, the pack size (1 pre-filled syringe per box), and the legal status (prescription only).

These are considered adequate to manage the safety profile of VacPertagen; no safety concerns have been identified requiring other routine risk minimisation measures.

Table Part V.1: Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation measures (SmPC/PL references)	Legal status and pack size
Missing information: Limited information on use in pregnant women in the European population	SmPC: section 4.1 (passive protection following maternal immunisation), section 4.2 (dose in pregnancy), section 4.4 (maternal antibody interference and limitations of effectiveness), section 4.6 (pregnancy and lactation), section 4.8 (safety profile including pregnant women) PL: section 1 (use during pregnancy to protect the infant), section 2 (advice for pregnant women), section 4 (possible side effects) Routine measures: use according to official recommendations.	Legal status: Prescription only Pack size: 1 pre-filled syringe (0.5 mL) per box (SmPC section 6.5).

V.2 Additional risk minimisation measures

Not applicable, as no additional risk minimisation measures are proposed.

V.3 Summary of risk minimisation measures

Table Part V.3: Summary table of PV activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Missing information: Limited information on use in pregnant women in the European population	Routine risk minimisation measures: SmPC: section 4.1 (passive protection following maternal immunisation), section 4.2 (dose in pregnancy), section 4.4 (maternal antibody interference and limitations of effectiveness), section 4.6 (pregnancy and lactation), section 4.8 (safety profile including pregnant women)	Routine pharmacovigilance activities as per current regulatory guidance Additional pharmacovigilance activities: PASS in the EU to collect structured safety data from pregnant women vaccinated with VacPertagen, including information on pregnancy outcomes and infant health status

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	PL: section 1 (use during pregnancy to protect the infant), section 2 (advice for pregnant women), section 4 (possible side effects) Additional risk minimisation measures: No additional risk minimisation measures	

Part VI: Summary of the risk management plan

Summary of risk management plan for VacPertagen (recombinant acellular pertussis vaccine)

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

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

This summary of the RMP for VacPertagen should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all 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 VacPertagen's RMP.

I. The medicine and what it is used for

VacPertagen is authorised for

• booster immunisation against pertussis of individuals 12 years of age and older,

• passive protection against pertussis in early infancy following maternal immunisation during pregnancy.

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

It contains recombinant acellular pertussis vaccine as the active substance and it is given by intramuscular injection.

Further information about the evaluation of VacPertagen's benefits can be found in VacPertagen's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage:

II. Risks associated with the medicine and activities to minimise or further characterise the risks

II.A List of important risks and missing information

Important identified risks	None
Important potential risks	None
Missing information	Limited information on use in pregnant women in the European population

Important risks of VacPertagen, together with measures to minimise such risks and the proposed studies for learning more about VacPertagen'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 patients 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 patient (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 reactions is collected continuously and regularly analysed, including assessment of periodic safety update reports, so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

Important risks of VacPertagen 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 VacPertagen. 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).

II.B Summary of important risks

No important risks have been identified for VacPertagen. See table below for information on missing information.

Missing information	
Evidence	Though limited data are available for this patient group, the importance of maternal and neonate safety indicates the need of further evaluation.
Risk factors and risk groups	Pregnant women and neonates in the EU

Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.1 (passive protection following maternal immunisation), section 4.2 (dose in pregnancy), section 4.4 (maternal antibody interference and limitations of effectiveness), section 4.6 (pregnancy and lactation), section 4.8 (safety profile including pregnant women); PL section 1 (use during pregnancy to protect the infant), section 2 (advice for pregnant women), section 4 (possible side effects) Additional risk minimisation measures: No additional risk minimisation measures
Additional pharmacovigilance activities	Additional pharmacovigilance activities: PASS in the EU to collect structured safety data from pregnant women vaccinated with VacPertagen, including information on pregnancy outcomes and infant health status

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no safety studies imposed as condition of the marketing authorisation (category 1), or as a specific obligation in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances (category 2).

II.C.2 Other studies in post-authorisation development plan

The MAH will conduct a post-authorisation safety study (PASS) in the EU to collect structured safety data from pregnant women vaccinated with VacPertagen, including information on pregnancy outcomes and infant health status (category 3).

Study short name:

Post-Authorisation Safety Study (PASS) to Assess Pregnancy Outcomes Following Administration of VacPertagen in Pregnant Women in the EU.

Purpose of the study:

Studies have shown that Tdap vaccines are safe and well-tolerated in pregnant women. Common side effects include mild pain or redness at the injection site, fatigue, and mild fever, all of which are similar to the reactions seen in non-pregnant individuals. Serious side effects are rare. Importantly, there is no evidence to suggest that the vaccine poses a risk to pregnancy, foetal development, or long-term infant health.

VacPertagen clinical safety data are limited. A PASS as an additional pharmacovigilance activity is proposed in the VacPertagen Risk Management Plan to further confirm the safety of VacPertagen on exposure in the second and third trimesters of pregnancy. This PASS will systematically collect safety data on pregnancy exposures and evaluate the risk of key obstetric and neonatal outcomes.

Given the need for data applicable to the EU population, the study will be conducted in Europe where VacPertagen is recommended for maternal immunisation. Site selection will ensure demographic, clinical practice, and healthcare system comparability with the broader EU population.

A feasibility assessment to confirm availability, accessibility, and suitability of data sources for implementation of the PASS in the EU will be conducted.

The primary objective of this study is to evaluate the safety of VacPertagen when given according to national recommendations during pregnancy, particularly in relation to maternal and neonatal health outcomes. The study will monitor adverse events (AEs) in both the pregnant population and their infants following vaccination.

As a secondary objective, the effectiveness of maternal vaccination with VacPertagen in reducing the risk of pertussis in infants born to vaccinated mothers will be estimated by comparing pertussis incidence in infants whose mothers received VacPertagen during pregnancy with infants of unvaccinated mothers, where appropriate data are available.

Part VII: Annexes

Part VII ANNEX 4: Specific adverse drug reaction follow-up forms

Not applicable.

Part VII ANNEX 6: Details of proposed additional risk minimisation measures

Not applicable.

Part VII ANNEX 7: Other supporting data (incl. referenced material)

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