EU RISK MANAGEMENT PLAN (RMP)

for

VEYVONDI (vonicog alfa)

RMP Version number: 6.0

Date: 06-March-2025

[redacted]

[redacted]

EU Risk Management Plan for VEYVONDI (vonicog alfa)

Administrative information

RMP version to be assessed as part of this application:

RMP Version number: 6.0

Data lock point (DLP) for this RMP: 31-December-2024

Date of final sign off: 06-March-2025

Rationale for submitting an updated RMP: This Risk Management Plan (RMP) is updated to include the extension of indication for treatment of haemorrhage in children aged less than 18 years, as part of a Type II variation.

Summary of significant changes in this RMP:

RMP Module:	Significant Changes:
Part I product overview	Extension of indication for treatment of haemorrhage in children aged less than 18 years was added.
Part II safety specification	
• **Module SI Epidemiology of the indication(s) and target population(s)**	Updated to align with the indication update and target population.
• **Module SII Non-clinical part of the safety specification**	Not applicable
• **Module SIII Clinical trial exposure**	Updated as per the DLP 31-December-2024
• **Module SIV Populations not studied in clinical trials**	Not applicable
• **Module SV Post-authorisation experience**	Updated as per the DLP 31-December-2024
• **Module SVI Additional EU requirements for the safety specification**	Not applicable
• **Module SVII Identified and potential risks**	Updated as per the DLP 31-December-2024
• **Module SVIII Summary of the safety concerns**	Not applicable
Part III Pharmacovigilance plan	Not applicable
Part IV Plans for post-authorisation efficacy studies	Not applicable
Part V Risk minimisation measures	Not applicable
Part VI Summary of the risk management plan	Not applicable
Part VII Annexes	Annex 8 updated to include the summary of changes.

[redacted]

Other RMP versions under evaluation:

Not applicable

Details of the currently approved RMP:

Version number: 5.0

Approved with procedure: EMEA/H/C/004454/II/0033

Date of approval (opinion date): 11-July-2024

QPPV name: Jean Marie Heim, MD

Please note that signature may also be performed by [redacted] Deputy EU QPPV [redacted] on behalf of the EU QPPV (i.e., 'per procurationem').

QPPV signature: Signatures are available on file.

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List of Abbreviations

Abbreviation	Definition/Description
ADR	Adverse Drug Reaction
AE	Adverse Event
ALT	Alanine aminotransferase
CD4	Clusters of differentiation 4
CAD	Coronary artery disease
CHMP	Committee for Medicinal Products for Human Use
CVAD	Central Venous Access Device
CVD	Cardiovascular Disease
DDAVP	1-deamino-8-D-arginine vasopressin
DLP	Data Lock Point
DVT	Deep Vein Thrombosis
EEA	European Economic Area
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EU	European Union
EUHASS	European Haemophilia Safety Surveillance System
IU	International unit
INR	International Normalized Ratio
Kg	Kilogramme
MAH	Marketing Authorisation Holder
mL	Millilitre
MuIgG	Mouse Immunoglobulin G
NOAEL	No Observed Adverse Effect Level
PASS	Post-authorization Safety Study
PBRER	Periodic Benefit-Risk Evaluation Report
PI	Product Information
PIP	Paediatric Investigation Plan
Pk	Pharmacokinetic
PL	Package Leaflet
PSUR	Periodic Safety Update Report
PT	Preferred Term
QPPV	Qualified Person Responsible for Pharmacovigilance (in the European Union)
rFVIII	recombinant Factor VIII
rVWF	recombinant von Willebrand factor

[redacted]

Abbreviation	Definition/Description
RMP	Risk Management Plan
SAE	Serious Adverse Event
SmPC	Summary of Product Characteristics
ULM	Ultra-large multimers
US	United States
VWD	Von Willebrand Disease
VWF	Von Willebrand factor

[redacted]

PART I: PRODUCT(S) OVERVIEW

Table Part I.1 – Product Overview

Active substance(s) (INN or common name)	Vonicog alfa
Pharmacotherapeutic group(s) (ATC Code)	Antihaemorrhagics, blood coagulation factor, von Willebrand factor (B02BD10)
Marketing authorisation holder (MAH)	Baxalta Innovations GmbH (herein Baxalta) (Baxalta is a subsidiary fully owned by Takeda) Industriestrasse 67, 1221 Vienna Austria
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	VEYVONDI
Marketing authorisation procedure	Centralised
Brief description of the product	<u>Chemical class</u> VEYVONDI, vonicog alfa, is recombinant human von Willebrand factor (rVWF), a large multimeric glycoprotein normally found in plasma. Vonicog alfa belongs to Antihemorrhagics: Blood coagulation factors with ATC code B02BD10.
	<u>Summary of mode of action</u> VEYVONDI behaves in the same way as endogenous von Willebrand factor. VEYVONDI allows for the correction of the haemostatic abnormalities experienced by von Willebrand Disease (VWD) patients by 1) acting as an adhesive molecule, mediating both parts of primary hemostasis, platelet adhesion to damaged vascular sub-endothelial tissues like collagen and platelet aggregation, and 2) functioning as a carrier protein for factor VIII while also protecting it from rapid proteolysis.
	<u>Important information about its composition</u> VEYVONDI is produced and formulated without the addition of any exogenous raw materials of human or animal origin in the cell culture, purification, or formulation of the final container product, therefore, making the risk of transmission of human blood-borne viruses or other adventitious agents a theoretical risk. VEYVONDI contains all sizes of multimers including the ultra-large non-proteolysed multimers that are found in the physiological storage sites, for example the Weibel-Palade bodies. The ultra-large multimers are the most active VWF multimers, which are also observed in the endogenous VWF immediately after secretion from the storage sites. Recombinant VWF has unique functional in vitro properties that are only detectable under flowing blood conditions and is the closest to the endogenous physiological VWF.
Hyperlink to the product	VEYVONDI summary of product characteristics (SmPC)

[redacted]

information (PI)	
Indication(s) in the EEA	Current: Prevention and treatment of haemorrhage or surgical bleeding in adults (age 18 years and older) with von Willebrand disease (VWD), when desmopressin (DDAVP) treatment alone is ineffective or contraindicated. VEYVONDI should not be used in the treatment of haemophilia A.
	Proposed: Prevention and treatment of haemorrhage or surgical bleeding in adults, and treatment of haemorrhage in children aged less than 18 years, with von Willebrand disease (VWD), when desmopressin (DDAVP) treatment alone is ineffective or contraindicated. VEYVONDI should not be used in the treatment of haemophilia A.
Dosage in the EEA	Current: Dosage and frequency of administration must be individualized according to clinical judgement and based on the patient's weight, type and severity of the bleeding episodes/surgical intervention and based on monitoring of appropriate clinical and laboratory measures. Dose based on bodyweight may require adjustment in underweight or overweight patients. Generally, 1 international units (IU)/kg (VWF:RCo/VEYVONDI/ vonicog alfa) raises the plasma VWF:RCo by 0.02 IU/mL (2%). Haemostasis cannot be ensured until factor VIII coagulant activity (FVIII:C) is at least 0.4 IU/mL (≥40 % of normal activity). Depending on the patient's baseline FVIII:C levels, a single infusion of rVWF will, in a majority of patients, lead to an increase above 40% in endogenous FVIII:C activity within 6 hours and will result in sustaining this level up to 72 hours post infusion. The dose and duration of the treatment depend on the clinical status of the patient, the type and severity of the bleeding, and both VWF:RCo and FVIII:C levels. If the patient's baseline plasma FVIII:C level is <40% or is unknown and in all situations where a rapid correction of haemostasis should be achieved, such as treatment of an acute haemorrhage, severe trauma or emergency surgery, it is necessary to administer a recombinant factor VIII product with the first infusion of VEYVONDI, in order to achieve a haemostatic plasma level of FVIII:C. However, if an immediate rise in FVIII:C is not necessary, or if the baseline FVIII:C level is sufficient to ensure haemostasis, the physician may decide to omit the co-administration of rFVIII at the first infusion with VEYVONDI. In case of major bleeding events or major surgeries requiring repeated, frequent infusions, monitoring of FVIII:C levels is recommended, to decide if rFVIII is required for subsequent infusions to avoid excessive rise of FVIII:C. **Treatment of bleeding episodes (on-demand treatment)** The first dose of VEYVONDI should be 40 to 80 IU/kg body weight. Replacement levels of VWF:RCo > 0.6 IU/mL (60%) and FVIII:C > 0.4 IU/mL (40%) should be achieved. VEYVONDI should be administered with recombinant factor VIII if the FVIII:C levels are < 40%, or are unknown, to control

	bleeding. The rFVIII dose should be calculated according to the difference between the patient's baseline plasma FVIII:C level, and the desired peak FVIII:C level to achieve an appropriate plasma FVIII:C level based on the approximate mean recovery of 0.02 (IU/mL)/(IU/kg). The complete dose of VEYVONDI should be administered followed by rFVIII within 10 minutes. A subsequent dose of 40 IU to 60 IU/kg of VEYVONDI should be infused every 8 to 24 hours as per the dosing ranges or as long as clinically appropriate. In major bleeding episodes, maintain trough levels of VWF:RCo greater than 50% for as long as deemed necessary. **Prevention of bleeding/haemorrhage and treatment in case of elective surgery** In patients with inadequate levels of FVIII, a dose of 40-60 IU/kg VEYVONDI should be administered 12-24 hours prior to initiating elective surgery (pre-operative dose), to ensure pre-operative endogenous FVIII levels of at least 0.4 IU/mL for minor and at least 0.8 IU/mL for major surgery. For prevention of excessive bleeding in case of elective surgery, within 3 hours prior to initiation of any surgical procedure, the FVIII:C levels should be assessed. If the FVIII:C levels are at the recommended target level of: • at least 0.4 IU/mL for minor and oral surgery and • at least 0.8 IU/mL for major surgery, a dose of VEYVONDI alone should be administered within 1 hour prior to the procedure. If the FVIII:C levels are not at the recommended target levels, rFVIII should be administered in addition to vonicog alfa to raise VWF:RCo and FVIII:C, within 1 hour prior to the procedure. **Prophylactic treatment** For initiation of long-term prophylaxis against bleeds in patients with VWD, doses of 40 to 60 IU/kg of VEYVONDI administered twice weekly should be considered. Depending on the patient's condition and clinical response, including breakthrough bleeds, higher doses (not exceeding 80 IU/kg) and/or an increased dose frequency (up to three times per week) may be required. **Paediatric population** The safety and efficacy of VEYVONDI in children aged 0 to 18 years have not yet been established. No data are available. For specific recommendations and additional details, please refer SmPC.
	Proposed: Dosage and frequency of administration must be individualized according to clinical judgement and based on the patient's weight, type and severity of the bleeding episodes/surgical intervention and based on monitoring of appropriate clinical and laboratory measures. Dose based on bodyweight may require adjustment in underweight or overweight patients. Generally, 1 IU/kg (VWF:RCo/VEYVONDI/vonicog alfa) raises the plasma VWF:RCo by 0.02 IU/mL (2%). Haemostasis cannot be ensured until factor VIII coagulant activity (FVIII:C) is at least 0.4 IU/mL (≥40 % of normal activity). Depending on the patient's baseline FVIII:C levels, a single infusion of rVWF will, in a majority of patients, lead to an increase above 40% in endogenous FVIII:C activity within 6 hours and will

[redacted]

	result in sustaining this level up to 72 hours post infusion. The dose and duration of the treatment depend on the clinical status of the patient, the type and severity of the bleeding, and both VWF:RCo and FVIII:C levels. If the patient's baseline plasma FVIII:C level is <40% or is unknown and in all situations where a rapid correction of haemostasis should be achieved, such as treatment of an acute haemorrhage, severe trauma or emergency surgery, it is necessary to administer a recombinant factor VIII product with the first infusion of VEYVONDI, in order to achieve a haemostatic plasma level of FVIII:C. However, if an immediate rise in FVIII:C is not necessary, or if the baseline FVIII:C level is sufficient to ensure haemostasis, the physician may decide to omit the co-administration of rFVIII at the first infusion with VEYVONDI. In case of major bleeding events or major surgeries requiring repeated, frequent infusions, monitoring of FVIII:C levels is recommended, to decide if rFVIII is required for subsequent infusions to avoid excessive rise of FVIII:C. **Treatment of bleeding episodes (on-demand treatment) in adults and children** The first dose of VEYVONDI should be 40 to 80 IU/kg body weight. Replacement levels of VWF:RCo > 0.6 IU/mL (60%) and FVIII:C > 0.4 IU/mL (40%) should be achieved. VEYVONDI should be administered with recombinant factor VIII if the FVIII:C levels are < 40%, or are unknown, to control bleeding. The rFVIII dose should be calculated according to the difference between the patient's baseline plasma FVIII:C level, and the desired peak FVIII:C level to achieve an appropriate plasma FVIII:C level based on the approximate mean recovery of 0.02 (IU/mL)/(IU/kg). The complete dose of VEYVONDI should be administered followed by rFVIII within 10 minutes. A subsequent dose of 40 IU to 60 IU/kg of VEYVONDI should be infused every 8 to 24 hours as per the dosing ranges or as long as clinically appropriate. In major bleeding episodes, maintain trough levels of VWF:RCo greater than 50% for as long as deemed necessary. **Prevention of bleeding/haemorrhage and treatment in case of elective surgery in adults** In patients with inadequate levels of FVIII, a dose of 40-60 IU/kg VEYVONDI should be administered 12-24 hours prior to initiating elective surgery (pre-operative dose), to ensure pre-operative endogenous FVIII levels of at least 0.4 IU/mL for minor and at least 0.8 IU/mL for major surgery. For prevention of excessive bleeding in case of elective surgery, within 3 hours prior to initiation of any surgical procedure, the FVIII:C levels should be assessed. If the FVIII:C levels are at the recommended target level of: • at least 0.4 IU/mL for minor and oral surgery and • at least 0.8 IU/mL for major surgery, a dose of VEYVONDI alone should be administered within 1 hour prior to the procedure. If the FVIII:C levels are not at the recommended target levels, rFVIII should be administered in addition to vonicog alfa to raise VWF:RCo and FVIII:C, within 1 hour prior to the procedure.

[redacted]

	Prophylactic treatment in adults For initiation of long-term prophylaxis against bleeds in patients with VWD, doses of 40 to 60 IU/kg of VEYVONDI administered twice weekly should be considered. Depending on the patient's condition and clinical response, including breakthrough bleeds, higher doses (not exceeding 80 IU/kg) and/or an increased dose frequency (up to three times per week) may be required. **Paediatric population** The safety and efficacy of VEYVONDI in children aged less than 18 years have been established for the treatment of haemorrhage. Dosing is based on the same guidelines as for adults. The safety and efficacy for the prevention of haemorrhage and for the perioperative management of surgical bleeding have not yet been established in children aged less than 18 years. For specific recommendations and additional details, please refer SmPC.
Pharmaceutical form(s) and strengths	Current: VEYVONDI 650 IU powder with 5 ml of solvent for solution for injection. VEYVONDI 1,300 IU powder with 10 ml of solvent for solution for injection. VEYVONDI contains approximately 130 IU vonicog alfa per mL after reconstitution.
	Proposed: Not applicable
Is/will the product be subject to additional monitoring in the EU?	No*

*Pursuant to Article 23(3) of Regulation No (EU) 726/2004, VEYVONDI (vonicog alfa) is removed from the additional monitoring list as a new biological following five years of authorisation along with the renewal, which was approved on 23-June-2023.

PART II: SAFETY SPECIFICATION

Part II: MODULE SI - EPIDEMIOLOGY OF THE INDICATION(S) AND TARGET POPULATION(S)

von Willebrand Disease	
Incidence:	Von Willebrand disease (VWD) is an inherited bleeding disorder that is characterised by dysfunction or deficiency of von Willebrand factor (VWF), with an estimated global incidence of 100 per million population[redacted].
Prevalence:	Von Willebrand Disease is one of the most common bleeding disorders, affecting 1% to 2% of the population, with a global prevalence of 13,000 to 16,000 cases per million [redacted]. Most cases are moderate to mild. Clinically severe Type 3 VWD is rare, with a prevalence of 0.1 to 5 cases per million[redacted]. Its prevalence is consistent worldwide based on population screenings [redacted].
Demographics of the target population in the indication:	Patient Demographics: • Predominantly diagnosed in white individuals • Commonly associated with blood group O and family history of VWD or other bleeding disorder[redacted]. Gender and Symptoms: • Affects males and females equally. • Female patients range from 45% to 68% • Symptoms in females become more pronounced during reproductive age, particularly at menarche and childbirth[redacted]. Age at Diagnosis: • Type 1 VWD (mild): Often diagnosed in childhood/adolescence, triggered by significant bleeding events like surgery or menstruation. • Type 2 VWD (moderate): Typically diagnosed in childhood or early adulthood due to more evident bleeding symptoms. • Type 3 VWD (severe): Diagnosed in infancy or early childhood due to severe bleeding issues. Early Diagnosis in Children: • Study of 105 children (<2 years) showed [redacted] o 68% were tested due to family history. o Mean diagnosis age was 7 months. o Type 2 diagnosed earlier than Types 1 or 3 o Family history led to diagnosis ~4 months earlier o 41% of bleeding events occurred before 6 months, and 68% before age 1 year. Blood Type Influence: • Blood type O has 25% lower mean levels of VWF compared to other blood types [redacted].

[redacted]

von Willebrand Disease	
The main existing treatment options:	Treatment Options for Adults and Children: • Desmopressin (DDAVP): Effective for mild to moderate Type 1 VWD. Increases von Willebrand factor release from body's cells. • Replacement therapy: VWF concentrates for severe cases or when desmopressin is ineffective (e.g., plasma derived and for adults, recombinant VWF). • Antifibrinolytic agents: Tranexamic acid or aminocaproic acid to reduce bleeding, especially mucosal (e.g., nosebleeds, dental extractions). • Hormonal therapy: For women and adolescent girls with heavy menstrual bleeding. • Topical agents: Fibrin sealants to control superficial bleeding. • General care: Avoidance of aspirin and NSAIDs which can worsen bleeding.
Natural history of the indicated condition in the population, including mortality and morbidity:	The natural history of VWD varies based on the type and severity of the disorder. Type 1 VWD • Mild and Most Common: Approximately 70-80% of VWD cases. • Symptom Onset: Symptoms may appear in childhood but are often mild, leading to delayed diagnosis. • Symptoms: Easy bruising, frequent nosebleeds, prolonged bleeding from cuts, and heavy menstrual bleeding in girls. • Natural Course: Generally stable, but bleeding risk can vary with physiological changes like puberty, pregnancy, or surgery. Type 2 VWD • Moderate Severity: Covers several subtypes (2A, 2B, 2M, 2N) with different characteristics. • Symptom Onset: Often evident in childhood or early adulthood. • Symptoms: Moderate to severe mucosal bleeding, menorrhagia, bleeding during/after surgery. • Natural Course: Varies by subtype, but generally more severe and unpredictable bleeding episodes than Type 1. Type 3 VWD • Severe and Rare: Around 1-3% of VWD cases. • Symptom Onset: Early childhood, often severe. • Symptoms: Severe mucosal bleeding, spontaneous bleeding into joints and muscles, similar to hemophilia. • Natural Course: Severe, with frequent and potentially life-threatening bleeding episodes without treatment. Morbidity in VWD is mainly due to frequent and prolonged bleeding, leading to anemia, pain, joint damage, and increased surgical/dental bleeding risks. Women may experience menorrhagia and iron deficiency anemia.

[redacted]

von Willebrand Disease	
	As a result of improved treatment and prophylactic care, VWD is not linked to increased mortality, and life expectancy is approaching that of the general population [redacted]. Mortality factors include severe bleeding, particularly in Type 3 VWD, and significant bleeding after trauma or major surgery.
Important co-morbidities:	Von Willebrand Disease (VWD) is associated with several comorbidities due to bleeding tendencies and the body's responses: • Anemia: Chronic blood loss from heavy menstrual bleeding or frequent nosebleeds. • Joint and Muscle Damage: Severe bleeding episodes (especially in Type 3 VWD), causing chronic pain, swelling, and limited mobility. • Bruising and Hematomas: Increased risk of painful bruises and hematomas; easy bruising causing discomfort and emotional distress. • Quality of Life: Frequent bleeding affects daily activities, causing fatigue, stress, and social/psychological issues; disruptive to children's school and activities. • Emotional Impact: Chronic management stress affects the well-being of both adults and children, often causing anxiety and fear of bleeding. • Menorrhagia: Heavy menstrual bleeding in women and adolescent girls, often requiring medical interventions. • Surgical Bleeding: Higher risk of complications during and after surgeries, requiring careful management. • Gastrointestinal Bleeding: A significant concern, especially in Type 3 VWD. People with VWD might have a lower incidence of thrombotic cardiovascular disease due to reduced/dysfunctional VWF, but this varies with individual health and VWD type

[redacted]

Part II: MODULE SII - NON-CLINICAL PART OF THE SAFETY SPECIFICATION

Key safety findings from non-clinical studies and relevance to human usage:

Key Safety Findings	Relevance to human usage
Toxicity: Single dose toxicity Single dose toxicity studies investigating the effect of vonicog alfa administered either alone or with ADVATE were performed in the following animal models: ADAMTS13 knock out mice (study PV1940601), VWd mice (study PV1930601), C57BL/6J mice (study PV1990701), rats (study PV1950601), rabbits (study BAX0009 and PV2140708), and cynomolgus monkeys (study BAX0011 and DI08K001). The No Observed Adverse Effect Level (NOAEL) for vonicog alfa in the C57BL/6J mouse and ADAMTS13 knock out mouse was 250 IU VWF:RCo/kg when administered alone and 250 IU VWF:RCo/kg + 192 IU rFVIII/kg when administered with ADVATE; the NOAEL for vonicog alfa in the von Willebrand deficient (VWd) mouse was 500 IU VWF:RCo/kg + 385 IU rFVIII/kg ADVATE. In rats, no signs of toxicity or thrombogenicity were observed at any of the doses tested; the NOAEL was 1,400 IU VWF:RCo/kg + 1077 IU rFVIII/kg ADVATE, which was the highest dose tested. In rabbits as well as in cynomolgus monkeys the NOAEL was 1200 IU VWF:RCo/kg alone, or 600 IU VWF:RCo/kg + 463 IU rFVIII/kg ADVATE, which were the highest doses tested. Overall, no signs of toxicity were observed in single dose toxicity studies involving rats, rabbits, and cynomolgus monkeys with vonicog alfa (study RD_VB_110702). Signs of microthrombosis were observed in mice, mainly because mouse ADAMTS13 is not capable of sufficiently proteolyse vonicog alfa; and murine ADAMTS13 does not decrease the ultra-large multimers of vonicog alfa. The studies concluded that the observed symptoms of microthrombosis are a species-specific exaggerated pharmacological effect not relevant for human use.	Overall, no signs of toxicity were observed in single dose toxicity studies involving rats, rabbits, and cynomolgus monkeys. The observed symptoms of microthrombosis in mice were considered a species-specific exaggerated pharmacological effect that was not relevant for human use. Assessment of single dose toxicity in animal models supports the conclusion that vonicog alfa is safe for human usage.
Toxicity: Repeat-Dose toxicity Toxicity after repeated administration of vonicog alfa alone or with ADVATE was investigated in rats and in cynomolgus monkeys. In rats, reversible signs of exaggerated pharmacological effects (regenerative anaemia, thrombocytopenia, and treatment-related histopathologic changes in the heart, liver, and spleen) were observed after administration of 1,400 IU VWF:RCo/kg/day + 1,080 IU	Exaggerated pharmacological effects seen in rats were considered a species-specific exaggerated pharmacological effect that was not relevant for human use. The immunogenic response in cynomolgus monkeys was not unexpected after repeated administration of a foreign protein and is not considered relevant for human use. Assessment of repeat-dose toxicity in animal studies supports the conclusion that vonicog

[redacted]

Key Safety Findings	Relevance to human usage
rFVIII/kg/day intravenously once daily for 14 days (study 528575). These findings are interpreted as a species-specific exaggerated pharmacological effect due to the low susceptibility of vonicog alfa to proteolysis by rodent ADAMTS13 (study RD_VB_110702). No toxicologically relevant changes were evident for clinical observations, body weight, feed consumption, ophthalmology, urinalysis, coagulation and serum chemistry parameters, platelet aggregation, and gross pathology. In cynomolgus monkeys, daily intravenous (bolus) administration of vonicog alfa alone at 50 or 100 IU VWF:RCo/kg/day or 100 IU VWF:RCo/kg vonicog alfa with 77 IU/kg rFVIII ADVATE for 14 days did not result in any evidence of adverse effect (study EWA0015). Therefore, 100 IU VWF:RCo/kg/day vonicog alfa with or without 77 IU rFVIII/kg ADVATE was considered the NOAEL in this study. In a 4-week repeat-dose toxicity study in cynomolgus monkeys, administration of vonicog alfa by once daily IV administration was associated with life-threatening anaphylactic and less serious allergic reactions at 800 IU VWF:RCo/kg/day consistent with an immunogenic response which was not unexpected after repeated administration of a foreign protein to cynomolgus monkeys and not considered relevant for human use (study P10632M-SHP677). In terms of potential toxicity, all other changes were well tolerated for 2 weeks at 800 IU VWF:RCo/kg/day and for 4 weeks at up to 300 IU VWF:RCo/kg/day. The test article targeted the clotting pathways and effects consisted primarily of antibody formation and related complement, acute phase protein, haematology and clotting time changes. Based on these results, the NOAEL was 300 IU VWF:RCo/kg/day.	alfa is safe for human usage.
Toxicity: Reproductive/Developmental toxicity No adverse effects on male or female reproductive organs were detected during repeated dose toxicity studies. An ex vivo human placental perfusion study demonstrated that vonicog alfa does not pass the human placenta (Plac-Lab-12-12).	Vonicog alfa is not expected to pass the human placenta.
Toxicity: Genotoxicity Mutagenicity of vonicog alfa was not observed in either the in vitro Salmonella typhimurium Reverse Mutation Assay (Ames Test) conducted with and without metabolic activation (study BAX22), the in vitro chromosomal	Vonicog alfa is a recombinant protein which is not considered to be genotoxic.

[redacted]

Key Safety Findings	Relevance to human usage
aberration test (study BAX0013), or the in vivo micronucleus test (study BAX24).	
Carcinogenicity Vonicog alfa is a recombinant protein which is not considered to be either mutagenic or clastogenic and does not have any carcinogenic potential based on its pharmacological action. Genotoxicity studies confirmed that vonicog alfa is not genotoxic. Due to the lack of concern for the carcinogenic potential of vonicog alfa, no carcinogenicity studies have been conducted or are planned.	Vonicog alfa is a recombinant protein which is not considered to have any carcinogenic potential.
Safety pharmacology: The thrombogenic potential of vonicog alfa and its effects on blood pressure, cardiac and respiratory function and parameters of coagulation activation were investigated in 4 in vivo studies in different animal models. No signs of thrombogenicity could be detected when the thrombogenic potential of vonicog alfa was evaluated in the rabbit stasis model at a dose of 1262 IU VWF:RCo/kg alone or 812.5 IU VWF:RCo/kg + 623.7 IU rFVIII/kg ADVATE (Study PV2010701). Safety pharmacology studies in rats (PV2040705), guinea pigs (study PV1900605) and dogs (study 34572) revealed no increases in anaphylactoid potential of vonicog alfa alone or when administered with ADVATE. • Effects on electro cardiology, blood pressure, and respiration rate were assessed in the 28-day repeat-dose toxicity study in cynomolgus monkeys (study P10632M-SHP677). At 300 IU VWF:RCo/kg, there were no test article-related effects on blood pressure, respiration rate, or ECG.	Assessment of general pharmacology data in animal studies supports the conclusion that vonicog alfa is safe for human usage.
Other toxicity-related information or data: Local tolerance Results from an in vivo, local tolerance study in rabbits after intravenous, intra-arterial or paravenous administration indicated that vonicog alfa administered either alone or with ADVATE is well tolerated (study PV2000701).	Vonicog alfa was well tolerated after intravenous, intra-arterial and paravenous administration in animal studies and should express a similar profile for local tolerance in humans.
Other toxicity-related information or data: Immunogenicity A comparative immunogenicity study of vonicog alfa and highly purified plasma-derived VWF in Balb/c mice was conducted and revealed no gross difference in immunogenicity between the different test items (study FS-IM00907). Neither vonicog alfa nor highly purified pdVWF modulated the immunogenicity of ADVATE in Balb/c mice. A study investigating the influence of administering	Vonicog alfa is not expected to have increased immunogenicity as compared to pdVWF. Vonicog alfa with or without ADVATE is also not expected to negatively modulate the immunogenicity of rFVIII.

[redacted]

Key Safety Findings	Relevance to human usage
vonicog alfa with ADVATE on the immunogenicity of rFVIII in 3 different hemophilic mouse models (E17 hemophilic Balb/c mice, E17 hemophilic C57BL/6J mice and E17 hemophilic human F8 transgenic mice) was performed. The results indicated that vonicog alfa does not negatively impact the immunogenicity of ADVATE in any of the 3 different hemophilic mouse models (study IMM_R&D_017_11).	

[redacted]

Part II: MODULE SIII - CLINICAL TRIAL EXPOSURE

Table SIII.1: Duration of exposure

Cumulative for all indications (person time):		
Duration of exposure	**Patients**	**Person time***
<1 m	101	1.78
1 to <3 m	12	1.72
3 to <6 m	5	1.8
6 to <9 m	6	3.48
9 to <12 m	1	0.99
12 to <15 m	7	8.04
15 to <18 m	1	1.43
Total person time	**19.23**	

Data cutoff date = 31-December-2024
Studies 070701, 071001, 071101, 071301, 071102, and SHP677-304.
*Number of Exposure Days in Observation Period of Safety divided by 365.2425.

Table SIII.2: Age group and gender

Cumulative for all age/gender groups (person time):				
Age group	**Patients**		**Person time***	
	Male	**Female**	**Male**	**Female**
<2 years	1	1	0.08	0.03
2 to 11 years	6	9	0.37	0.3
12 to 17 years	7	6	1.16	0.53
18 to 64 years	48	51	8.21	7.72
65 to 74 years	2	0	0.18	0
75 to 84 years	2	0	0.64	0
Total	**66**	**67**	**10.65**	**8.58**

Data cutoff date = 31-December-2024
Studies 070701, 071001, 071101, 071301, 071102, and SHP677-304.
*Number of Exposure Days in Observation Period of Safety divided by 365.2425.

Table SIII.3: Ethnic origin

Von Willebrand Disease (VWD)		
Ethnic origin	**Patients**	**Person time***
Asian	10	0.11
White	118	17.85
Multiple	1	0.02
Unknown or Not Reported	3	0.82
Other	1	0.42

[redacted]

Von Willebrand Disease (VWD)		
Ethnic origin	**Patients**	**Person time***
Total	**133**	**19.23**

Data cutoff date = 31-December-2024
Studies 070701, 071001, 071101, 071301, 071102, and SHP677-304.
*Number of Exposure Days in Observation Period of Safety divided by 365.2425.

[redacted]

Part II: MODULE SIV - POPULATIONS NOT STUDIED IN CLINICAL TRIALS

SIV.1. EXCLUSION CRITERIA IN PIVOTAL CLINICAL STUDIES WITHIN THE DEVELOPMENT PROGRAMME

Hypersensitivity (including anaphylactic reactions) to the active substance, to any of the excipients (Na_3-citrate x 2 H_2O, Glycine, Trehalose dihydrate, Mannitol, Polysorbate 80 (Tween-80)) or known allergic reaction to mouse or hamster proteins.	
Reason for exclusion:	Including these patients would place them at risk of potentially life-threatening reactions.
Is it considered to be included as missing information?:	No
Rationale:	"Hypersensitivity" is considered an important identified risk.

The subject had a history or presence of VWF inhibitor, or the subject had a history or presence of FVIII inhibitor with a titre ≥0.4 BU (by Nijmegen assay) or ≥0.6 BU (by Bethesda assay).	
Reason for exclusion:	Inhibitors could affect the activity and may cause vonicog alfa to be ineffective.
Is it considered to be included as missing information?:	No
Rationale:	"Inhibitor formation" is considered an important potential risk.

The subject with medical history of a thromboembolic event.	
Reason for exclusion:	There is a risk of occurrence of thrombotic events, particularly in patients with known clinical or laboratory risk factors for thrombosis including low ADAMTS13 levels.
Is it considered to be included as missing information?:	No
Rationale:	"Thromboembolic events" is considered an important identified risk.

Clinically relevant liver disease, as evidenced by, but not limited to, any of the following: serum alanine aminotransferase (ALT) three times the upper limit of normal, hypoalbuminemia, portal vein hypertension (e.g., presence of otherwise unexplained splenomegaly, history of esophageal varices).	
Reason for exclusion:	Altered liver function may contribute to impaired or delayed coagulation.
Is it considered to be included as missing information?:	No
Rationale:	Patients with altered hepatic function may benefit from VEYVONDI to aid in the treatment of bleeding. The benefits and risks of using the product should be carefully weighed against the

[redacted]

Clinically relevant liver disease, as evidenced by, but not limited to, any of the following: serum alanine aminotransferase (ALT) three times the upper limit of normal, hypoalbuminemia, portal vein hypertension (e.g., presence of otherwise unexplained splenomegaly, history of esophageal varices).	
	patient's clinical condition.

Severe renal impairment (serum creatinine > 2.0 mg/dL) at screening.	
Reason for exclusion:	Altered renal function may contribute to impaired coagulation or coagulation complications.
Is it considered to be included as missing information?:	No
Rationale:	Patients with altered renal function may benefit from VEYVONDI to aid in the treatment of bleeding. The benefits and risks of using the product should be carefully weighed against the patient's clinical condition.

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, adverse reactions with a long latency, or those caused by prolonged or cumulative exposure.

SIV.3. LIMITATIONS WITH RESPECT TO POPULATIONS TYPICALLY UNDER-REPRESENTED IN CLINICAL TRIAL DEVELOPMENT PROGRAMMES

Table SIV.2: Exposure of special populations included or not in clinical trial development programmes

Type of special population	Exposure
Children	The safety and efficacy of vonicog alfa are being investigated in paediatric subjects (below 18 years of age) in 3 ongoing studies: two Phase 3 studies (071102 and TAK-577-3001), which are part of the paediatric investigation plan (PIP) approved by EMA Paediatric Committee (initial approval in 2012, last version approved on 18-July-2024 (EMEA-001164-PIP01-11-M08), and a Phase 3b continuation study (SHP-677-304).
Elderly	No studies on efficacy of vonicog alfa have been performed in elderly patients (> 65 years). Surgery study 071101 included 1 elderly person aged 70 years who underwent laparoscopic cholecystectomy with an overall primary hemostatic efficacy rating of "good". Study 071301 included 3 subjects over age 65. A total of four subjects age ≥65 years has been included in the completed and ongoing clinical studies. The number of subjects age ≥65 years was too low to determine whether this age group responds differently than younger subjects.

[redacted]

Type of special population	Exposure
Pregnant women	Not included in the clinical development program.
Breast-feeding women	
Patients with relevant co-morbidities: • Patients with hepatic impairment • Patients with renal impairment	Not included in the clinical development program. Subjects with hepatic impairment (as evidenced by, but not limited to, any of the following: serum ALT three times the upper limit of normal, hypoalbuminemia, portal vein hypertension (e.g., presence of otherwise unexplained splenomegaly, history of esophageal varices)) were not included in the clinical trial program for vonicog alfa. Subjects with renal impairment (serum creatinine level ≥2 mg/dL) were not included in the clinical trial program for vonicog alfa.
Population with relevant different ethnic origin	In the VWD studies, 89% were white (N=116); the remaining 7.7% (n=10) were Asian and for 3%, the ethnic origin was not specified. There were no statistically significant differences in safety or efficacy corresponding to the race of any subject in the clinical trial program for vonicog alfa. It is important to note that as the majority of subjects were white and not all races were represented, it is difficult to make valid inferences regarding safety and efficacy across different racial groups. Please refer to Table SIII.3 for full demographic data for all studies where vonicog alfa was administered.
Subpopulations carrying relevant genetic polymorphisms	Clinical studies for vonicog alfa included subjects with type 1, type 2A, type 2B, type 2N, type 2M, and type 3 (severe VWD). For the pooled studies 070701, 071001 and 071101, the majority of subjects were diagnosed with VWD type 3 (78.8% n=63). The remainder of subjects had VWD type 1 (10.0%; n=8), type 2A (8.8%; n=7), type 2B (1.3%; n=1) or type 2M (1.3%; n=1). In study 071301, 3 subjects (13.0%) had type 1, 1 (4.3%) had type 2A, 1 (4.3%) had type 2B, and 18 (78.3%) had type 3. Detailed VWD gene mutation data are also collected in the clinical trials, but no specific analysis was performed.
Patients with a disease severity different from the inclusion criteria in the clinical trial population	Not included in the clinical development program. A list of medical conditions or diseases with different levels of severity, which have been considered to support exclusion from participation in the clinical studies, is provided below: • The subject had been diagnosed with a hereditary or acquired coagulation disorder other than VWD (including qualitative and quantitative platelet disorders and/or an international normalized ratio [INR]>1.4). • The subject had a medical history of immunological disorders, excluding seasonal allergic rhinitis/conjunctivitis, food allergies, or animal allergies. • The subject was HIV positive with an absolute clusters of differentiation 4 (CD4) count <200/mm^3. • The subject had been diagnosed with CVD, if the subject had been diagnosed with clinically relevant liver disease, as evidenced by, but not limited to, any of the following:

[redacted]

Type of special population	Exposure
	serum ALT three times the upper limit of normal, hypoalbuminemia, portal vein hypertension (e.g., presence of otherwise unexplained splenomegaly, history of esophageal varices). • The subject had been diagnosed with renal disease, with a serum creatinine level ≥2 mg/dL. As per the judgement of the investigator, the subject had another clinically significant concomitant disease (e.g., uncontrolled hypertension, diabetes type II) that may pose additional risks for the subject.

PART II: MODULE SV - POST-AUTHORISATION EXPERIENCE

SV.1. POST-AUTHORISATION EXPOSURE

SV.1.1. Method used to calculate exposure

Patient exposure to vonicog alfa was estimated based on the distribution data available through 31-December-2024. The proportion of patients who use vonicog alfa for treatment likely changes over time. We estimated the annual patient consumption of vonicog alfa data from a prospective, multi-centre phase III study among patients ages 18 to 65 years with severe type 1 and 2A, type 2B, type 2N, or type 3 VWD[redacted] and treated for an average of 1 bleed. Patients enrolled had an average weight of 73 kg. Based on the data from this study, the following for patients on-demand were assumed:

- The median dose of vonicog alfa was 46.5 IU/kg and the median number of infusions per bleed episode was 1.
- The median annual bleed rate in patients treated on-demand was 3.7 bleeds per year.

The average treatment dose (IU) used in the calculation is 46.5 IU/kg (based on data from the study [071001])

Total Units Sold = (O) (Do)

Where:

O = No. of patients-years of vonicog alfa use for treatment of bleeds (i.e., patient-years of exposure to vonicog alfa).

Do = Average annual consumption of vonicog alfa per patient (IUs/patient-year of exposure)

The average annual consumption of vonicog alfa per patient is equivalent to the average consumption of vonicog alfa per patient-year. Calculating Do (vonicog alfa consumption in patients treating individual bleeds on an annual basis).

Where Do = (The average dose per infusion) (no. infusions per episode) (average weight) (median annual bleed rate)

Do = 46.5 IU/kg × 1.0 infusions × 73 kg × 3.7 bleeds

Do = 12,559.65 IU

600,773,687 IUs = (O) (12,559.65 IU)

O (No. patient-years) = 600,773,687 IU/12,559.65 = 47,834 patient-years.

SV.1.2. Exposure

Based on the above methodology, the patient exposure is estimated to be 600,773,687 IUs cumulatively, corresponding to approximately 47,834 patient-years of treatment cumulatively.

There is no generally accepted methodology to model patient exposure in the post-marketing setting and the above-cited method is imprecise. The sales distribution data does not reflect the amount of product that is used for infusion and does not account for product waste, pharmacy inventory.

PART II: MODULE SVI - ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

Potential for misuse for illegal purposes

The potential for misuse of VEYVONDI for illegal purposes is considered unlikely.

PART II: MODULE SVII - IDENTIFIED AND POTENTIAL RISKS

SVII.1. IDENTIFICATION OF SAFETY CONCERNS IN THE INITIAL RMP SUBMISSION

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

None

Reason for not including an identified or potential risk 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

Important Identified Risks	Risk-benefit impact
Hypersensitivity reactions	Hypersensitivity reactions can range from a rash to fatal anaphylactic reactions. Hypersensitivity, allergic reactions, and anaphylaxis may result in a serious medical condition or potentially lead to fatal outcomes. Signs of hypersensitivity reactions may include angioedema, chest tightness, dyspnea, wheezing, urticaria, signs of shock (e.g., hypotension) or pruritus. Cumulatively no serious adverse events (SAEs) were retrieved for this risk term from the clinical studies with vonicog alfa.
Thromboembolic events (particularly in patients with low ADAMTS13 levels as well as other risk factors, and concomitant overuse of FVIII)	Thrombotic events can vary in seriousness and result in a variety of outcomes. Deep vein thrombosis (DVT) may resolve spontaneously with little sequelae while stroke and myocardial infarction may result in significant disability or death. Thromboembolic events (including Pulmonary Embolism, venous thrombosis, arterial thrombosis, and cerebral artery thrombosis) may potentially result in a serious medical condition or fatal outcome. In study 071101, one subject [redacted] underwent a total hip replacement and experienced 2 thrombotic adverse events (AEs) (1 non-serious event of non-occlusive thrombosis at 4 days post-op and 1 serious event of deep vein thrombosis at 8 days post-op) in this confounded surgical case (i.e., total hip replacement surgery and low ADAMTS13 levels). However, the possibility of causal relationship cannot be ruled out based on the nature of the event, the mechanism of action of vonicog alfa, and the close temporal proximity of the event of DVT with the ongoing infusions of vonicog alfa during the post-op period.

Important Potential Risks	Risk-benefit impact
Inhibitor formation	Inhibitor formation may result in a non-serious asymptomatic lack of response to treatment or potentially serious haemorrhage which may be life-threatening depending on the level of inhibitor present. In patients with high levels of inhibitors to VWF or FVIII, VEYVONDI therapy may not be effective, and infusion of this protein may lead to severe adverse reactions, including potentially serious haemorrhage. Cumulatively no confirmed cases for neutralizing antibodies were retrieved for this risk term from the clinical studies with vonicog alfa. Overall, the risk for VWD patients to develop neutralizing or

[redacted]

Important Potential Risks	Risk-benefit impact
	binding antibodies against VEYVONDI or potential impurities present in VEYVONDI can be considered to be low.

Missing Information	Risk-benefit impact
Insufficient clinical data on use in pregnancy and lactation	No pregnant or lactating women were included in the vonicog alfa clinical program to date; therefore, no applicable data are available. Ex vivo, it has been demonstrated that vonicog alfa does not cross the human placenta barrier. It is unknown whether VEYVONDI or its metabolites are excreted in human milk. Use in pregnancy and lactation, if available, will be collected.
Insufficient clinical data on use in geriatric patients	The number of subjects aged 65 and over (n=4) included in clinical trials of rVWF was too low to determine whether they respond differently compared to younger subjects. Use in geriatric patients, if available, will be collected.

SVII.2. NEW SAFETY CONCERNS AND RECLASSIFICATION WITH A SUBMISSION OF AN UPDATED RMP

Not applicable

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

Important Identified Risk: Hypersensitivity reactions	
Potential mechanisms:	Immune mediated response to vonicog alfa or any of the constituents of the product.
Evidence source(s) and strength of evidence:	Clinical trials, potential mechanism of action of risk. Post-marketing and literature.
Characterisation of the risk:	The incidence of anaphylaxis does not appear to vary significantly between countries. Rates globally range from 1-3 cases per 10,000 in the general population [redacted]. However, hypersensitivity drug reactions represent approximately one third of adverse drug reactions (ADR), which can affect 7% of the general population and up to 20% of hospitalized patients[redacted]. In studies, allergic reactions to plasma concentrates of VWF have been reported to occur in ≤6% of patients who may present with symptoms of hives, chest tightness, Rash, pruritus, and swelling[redacted]. Though data are limited, more severe anaphylactoid reactions have rarely been observed, but may be seen following infusion of VWF plasma concentrates in patients with severe type 3 disease[redacted]. However, while responses to plasma concentrates have been reported, the exact incidence and prevalence of hypersensitivity reactions from recombinant VWF treatment remains unknown at this time. Anaphylactic reaction has been reported from post-marketing sources. *Clinical studies* Cumulatively, no SAEs were retrieved for this risk term from the clinical studies with vonicog alfa.

Important Identified Risk: Hypersensitivity reactions	
	Post-marketing experience Cumulatively 42 cases including 60 events (28 serious and 32 non-serious) were reported from post-marketing sources. The reported Preferred terms (PTs) include 12 events of Rash, 9 events of Anaphylactic Reaction, 7 events of Hypersensitivity, 5 events of Drug hypersensitivity, 4 events of Infusion related reaction, 2 events of Anaphylactic shock, 2 events of Swelling face, 2 events of Urticaria, and 1 event of each for Acute kidney injury, Acute respiratory failure, Angioedema, Anuria, Circulatory collapse, Device allergy, Face oedema, Infusion site rash, Mouth swelling, Multiple allergies, Oropharyngeal blistering, Pharyngeal swelling, Rash macular, Rash pruritic, Rhinitis allergic, Shock, and Swollen tongue. The outcome of these ADRs is reported as not recovered/not resolved (n=2),recovered/resolved(n=25),recovering/resolving(n=1) and unknown (n=32). Of the 60 events, Company causality was assessed as related (n=40) and not related (n=20).
Risk factors and risk groups:	Patients with previous history of hypersensitivity to vonicog alfa or any other constituents of the product. VWD patients who have developed antibodies against VWF are at increased risk to develop anaphylactic reactions after re-exposure to VWF [redacted].
Preventability:	Careful intake of patients' medical history for allergic/hypersensitivity reactions. Note history of past hypersensitivity reactions in the patient records. Vonicog alfa is contraindicated in patients with hypersensitivity to the active substance or to any of the excipients or known allergic reaction to mouse of hamster proteins. Patients should be closely monitored and carefully observed for any symptoms throughout the infusion period. Patients and/or their caregivers should be informed of the early signs of hypersensitivity reactions, and they should be advised to discontinue use of the product immediately and contact their physician for support care if such symptoms occur.
Impact on the risk-benefit balance of the product:	Hypersensitivity to the drug or its ingredients is a concern of any medicinal product and may result in a serious medical condition or potentially lead to fatal outcome. Through risk minimisation, the risk of hypersensitivity can be minimised and ensures the potential benefits outweigh the risks.
Public health impact:	Depending on the severity and nature of the hypersensitivity reaction, patients may require medical intervention and hospitalization.

Important Identified Risk: Thromboembolic events (particularly in patients with low ADAMTS13 levels as well as other risk factors and concomitant overuse of FVIII)	
Potential mechanisms:	ADAMTS13 is responsible for proteolytic cleavage of the ultra-large multimers (ULM) of vonicog alfa within minutes of platelet adhesion and aggregation. Thus, the risk for thrombotic events associated with use of vonicog alfa is limited in patients with sufficient levels of ADAMTS13. However, for patients with other concomitant risk factors, such as overuse of FVIII/ADVATE, there still may be a risk for thromboembolic events due to excessive aggregation of platelets at site of endothelial injury, resulting in increased coagulation.

[redacted]

Important Identified Risk: Thromboembolic events (particularly in patients with low ADAMTS13 levels as well as other risk factors and concomitant overuse of FVIII)	
Evidence source(s) and strength of evidence:	Clinical trials, potential mechanism of action of risk. Post-marketing and literature.
Characterisation of the risk:	In patients with VWD, elevated FVIII levels have been reported as an increased risk factor for thrombosis [redacted]. However, this is a rare event in VWD that has been reported only in patients receiving repeated VWF/FVIII concentrate infusions to maintain hemostasis occurring with an incidence of 7 cases per 12,640 treatments annually [redacted]. Additionally, ADAMTS13 deficiency may lead to platelet aggregation which promotes the formation of thrombi and ultimately vascular occlusion [redacted]. Therefore, VWD patients with ADAMTS13 deficiency who receive excessive FVIII replacement may have an increased risk of myocardial infarction and other arterial occlusions [redacted]. Even so, the exact incidence of thromboembolic events in patients with VWD and low levels of ADAMTS13 is currently unknown. *Clinical studies* Cumulatively, 2 SAEs were retrieved for this risk term from the clinical studies with vonicog alfa. The reported PTs included Deep vein thrombosis and Haemorrhoids thrombosed. Causality was assessed as possible for 1 SAE and not related for another SAE. The outcome of both events was reported as recovered. *Post-marketing experience* Cumulatively, 27 cases including 33 events (32 serious and 1 non-serious) were reported from post-marketing sources. The 32 serious events included 5 events of Deep vein thrombosis, 5 events of Thrombosis, 5 events of Pulmonary embolism, 3 events of Myocardial infarction, 2 events of Cerebrovascular accident, 2 events of Pelvic venous thrombosis and 1 event each of Blindness transient, Cerebral thrombosis, Cerebral venous thrombosis, Embolism venous, Infusion site thrombosis, Post procedural pulmonary embolism, Stress cardiomyopathy, Superficial vein thrombosis, Thrombotic microangiopathy, and Vascular stent thrombosis. The outcome of these ADRs is reported as fatal (n=1), not recovered/not resolved (n=5), recovering/resolving (n=3), recovered/resolved (n=5), and unknown (n=18). Out of 32 serious events, Company causality was assessed as related (n=14) and not related (n=18) and 1 non-serious event was assessed as not related.
Risk factors and risk groups:	Thromboembolic events can occur, particularly in patients with known clinical or laboratory risk factors including low ADAMTS13 levels. Administration of vonicog alfa with a FVIII product containing VWF would pose an additional risk of thrombotic events. Patients with sustained excessive FVIII:C plasma levels may be at increased risk of thrombotic events.
Preventability:	Patients with known clinical or laboratory risk factors for thrombosis have to be monitored for early signs of thrombosis, and prophylaxis measures against venous thromboembolism should be instituted according to current recommendations and standard of care. Monitor plasma levels for FVIII:C activity to decide if rFVIII is required for subsequent infusions in patients requiring frequent doses of vonicog alfa in combination with recombinant factor VIII to avoid sustained

[redacted]

Important Identified Risk: Thromboembolic events (particularly in patients with low ADAMTS13 levels as well as other risk factors and concomitant overuse of FVIII)	
	excessive FVIII:C plasma levels.
Impact on the risk-benefit balance of the product:	Thromboembolic events may result in a serious medical condition with persistent injury or fatal outcome. Through risk minimisation, the risk of thromboembolic events can be minimised and ensures the potential benefits outweigh the risks.
Public health impact:	Thromboembolic events may result in hospitalization or life-threatening injury. Injury may require lifelong costly therapy. Injury may also result in loss of days of school and/or work, persistent disability, and impact upon caregivers.

Important Potential Risk: Inhibitor formation	
Potential mechanisms:	Upon administration of vonicog alfa, the body may perceive vonicog alfa as a foreign antigen, thus triggering an immune response leading to the development of neutralizing antibodies aiming to counteract the hemostatic efficacy of the drug. High titre non-neutralizing antibodies against vonicog alfa can be associated with decreased vWF:Ag post infusion and consequently decreased vonicog alfa associated biological activities.
Evidence source(s) and strength of evidence:	Potential mechanism of risk.
Characterisation of the risk:	None of the subjects treated in studies 070701, 071001, 071101 or 071301 developed neutralizing antibodies against vonicog alfa or FVIII. Furthermore, an analysis of a second pharmacokinetic (PK) infusion repeated 6 months after the initial PK at 80 IU/kg VWF:RCo in the phase 3 study 071001 demonstrated no difference between PK infusions for all vonicog alfa PK parameters, confirming the absence of subclinical inhibitors after repeated doses of vonicog alfa. The development of inhibitor antibodies against VWF represents a rare but serious complication of treatment in patients administered plasma concentrates, occurring in 5% to 10% of VWD patients, primarily with type 3 disease [redacted]. Patients who develop inhibitors may present with loss of response to VWF concentrate, sometimes with an associated Anaphylactic Reaction[redacted]. However, while responses to plasma concentrates have been reported, the exact incidence and prevalence of inhibitor formation from recombinant VWF treatment remains unknown at this time. *Clinical studies* Cumulatively, no SAEs were retrieved for this risk term from the clinical studies with vonicog alfa. *Post-marketing experience* Cumulatively, 3 serious events with PT Von Willebrand's factor antibody positive (n=2) and PT Von Willebrand's factor inhibition (n=1) were retrieved for this risk from post-marketing sources. Company causality of the 3 events was assessed as related to VWF. The events outcome was recovering/resolving (n=1) and unknown (n=2).
Risk factors and risk groups:	VWD patients who have developed antibodies against VWF are at risk to develop anaphylactic reactions after re-exposure to VWF. Inhibitor development in patients with VWD is a rare complication of treatment and mainly occurs in patients with severe inherited type 3

[redacted]

Important Potential Risk: Inhibitor formation	
	VWD [redacted]. The risk for VWD patients to develop antibodies in response to exogenously administered VWF is highly variable in individual patients and can only partially be explained by genetic factors. Mutations in the VWF gene which have been reported to be associated with VWD are very heterogeneous [redacted]. The development of neutralizing antibodies against VWF is frequently reported in patients with partial or complete VWF gene deletions but also in patients carrying nonsense or frameshift mutations [redacted]. Since not all cases of type 3 VWD caused by large gene deletions are associated with the development of anti-VWF antibodies, it is highly probable that additional genetic or environmental factors contribute to the risk of developing antibodies against VWF. A positive family history of anti-VWF antibodies is considered as a major risk factor [redacted]. Patients previously treated with pdVWF concentrates may be at risk to express binding antibodies against VWF prior to first exposure to vonicog alfa.
Preventability:	Patients using vonicog alfa should be regularly evaluated for the development of inhibitors by appropriate clinical observations (e.g., bleeding that is not controlled with an expected dose) and laboratory tests. If bleeding cannot be controlled, an assay that measures inhibitor concentration should be performed. Inhibitor testing should also be performed if the patient experiences hypersensitivity or anaphylactic reactions when exposed to vonicog alfa.
Impact on the risk-benefit balance of the product:	In patients with high levels of anti-VWF antibodies, von Willebrand factor therapy may not be effective and other therapeutic options should be considered. Inhibitors may result in reduced or lack of response to treatment and subsequent acute bleeding episodes potentially affecting joints, muscles, mucosa, body cavities, and the central nervous system, which may require additional therapies (e.g., central venous access device (CVAD) placement). Left untreated, the patient could experience fatal uncontrolled bleeding. Through risk minimisation, the risk of inhibitor formation can be minimised and ensures the potential benefits outweigh the risks.
Public health impact:	Uncontrolled bleeding episodes may result in hospitalization or life-threatening injury. Once an inhibitor exists, there may be lifelong costly therapy, e.g., with bypassing agents. Injury may also result in loss of days of school and/or work, persistent disability, and impact upon caregivers.

SVII.3.2. Presentation of the missing information

Missing information: Insufficient clinical data on use in pregnancy and lactation	
Evidence source:	No pregnant or lactating women were included in the vonicog alfa clinical program to date; therefore, no applicable data are available.

Missing information: Insufficient clinical data on use in geriatric patients	
Evidence source:	The number of subjects aged 65 and over included in clinical trials of rVWF was too low to determine whether they respond differently compared to younger subjects.

[redacted]

PART II: MODULE SVIII - SUMMARY OF THE SAFETY CONCERNS

Table SVIII.1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	• Hypersensitivity reactions • Thromboembolic events (particularly in patients with low ADAMTS13 levels as well as other risk factors, and concomitant overuse of FVIII)
Important potential risks	• Inhibitor formation
Missing information	• Insufficient clinical data on use in pregnancy and lactation • Insufficient clinical data on use in geriatric patients

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

III.1. ROUTINE PHARMACOVIGILANCE ACTIVITIES

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

There are no routine pharmacovigilance activities beyond adverse reactions reporting and signal detection.

Specific adverse reaction follow-up questionnaires:

None

Other forms of routine pharmacovigilance activities:

None

III.2. ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

European Haemophilia Safety Surveillance System (EUHASS) registry summary
Study short name and title: Participation in EUHASS registry and review of the data provided by the registry to further characterise the safety concerns for long-term safety follow-up.
Rationale and study objectives: • To monitor the safety of treatments for people with inherited bleeding disorders in Europe. • To inform clinicians, regulators and other interested parties of the treatment patterns and AEs reported for these patients in Europe. • To set up a publicly available database of all the Haemophilia centres in Europe with details of how they can be accessed by patients, and information on relevant patient, doctor, nurse and physiotherapist organisations in each country. • To set up a publicly available directory containing information and publications lists for all the clotting factor products used in Europe to treat inherited bleeding disorders.
Study design: The MAH aims to collaborate with established European Haemophilia Registries (i.e. EUHASS) to collect prospective AEs.
Study population: Patients with VWD.
Milestones: Regular updates Data will be reviewed on an ongoing basis as part of signal detection and reported within periodic safety update report (PSUR)/ periodic benefit-risk evaluation report (PBRERs) when available.

III.3. SUMMARY TABLE OF ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

Table Part III.1: Ongoing and planned additional pharmacovigilance activities

Study Status	**Summary of objectives**	**Safety concerns addressed**	**Milestones**	**Due dates**
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
None				

[redacted]

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
None				
Category 3 - Required additional pharmacovigilance activities				
Participation in registries (e.g., EUHASS registry) and review of the data provided by the registries to further characterise the safety concerns for long-term safety follow-up. Ongoing	The EUHASS registry serve to collect further safety information in patients with VWD.	• Hypersensitivity reactions • Thromboembolic events (particularly in patients with low ADAMTS13 levels as well as other risk factors, and concomitant overuse of FVIII). • Inhibitor formation. • Insufficient clinical data on use in pregnancy and lactation. • Insufficient clinical data on use in geriatric patients.	Regular updates	Data are reviewed on an ongoing basis as part of signal detection and reported within PSUR/ PBRERs when available.

[redacted]

PART IV: PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

Not applicable

[redacted]

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

Risk Minimisation Plan

V.1. ROUTINE RISK MINIMISATION MEASURES

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

Safety concern	Routine risk minimisation activities
Hypersensitivity reactions	**Routine risk communication:** SmPC sections 4.3, 4.4 and 4.8 Package leaflet (PL) section 2 and 4 **Routine risk minimisation activities recommending specific clinical measures to address the risk:** SmPC section 4.4 mentions • Patients and/or caregivers should be informed of the early signs of hypersensitivity reactions. Patients should be closely monitored and carefully observed for any symptoms throughout the infusion period. If signs and symptoms of severe allergic reactions occur, immediately discontinue administration of VEYVONDI and provide appropriate supportive care. • Adequate medical treatment and provisions should be available for immediate use for a potential anaphylactic reaction, especially for patients with a history of allergic reactions. • Patients treated with VEYVONDI may develop hypersensitivity reactions to non-human mammalian proteins (mouse immunoglobulin G (MuIgG) and Hamster proteins) due to their presence in VEYVONDI. Symptoms of severe allergic reactions and if present, patients should stop infusion immediately and contact doctor is mentioned in PL section 2 and 4. **Other routine risk minimisation measures beyond the Product Information:** None
Thromboembolic events (particularly in patients with low ADAMTS13 levels as well as other risk factors, and concomitant overuse of FVIII)	**Routine risk communication:** SmPC sections 4.4, 4.8 and 4.9 PL section 2 and 3 **Routine risk minimisation activities recommending specific clinical measures to address the risk:** SmPC section 4.4 mentions: • Patients at risk for thrombotic events have to be monitored for early signs and prophylaxis measures should be instituted. • Any FVIII that would be administered along with VEYVONDI should be a pure FVIII product. SmPC section 4.8 mentions Patients at risk for thrombotic events have to be monitored for early signs and prophylaxis measures should be instituted. PL section 2 mentions patients who have previously had thromboembolic complications should inform their doctor immediately.

Safety concern	Routine risk minimisation activities
	Other routine risk minimisation measures beyond the Product Information: None
Inhibitor formation	**Routine risk communication:** SmPC sections 4.4 and 4.8 PL sections 2 and 4 **Routine risk minimisation activities recommending specific clinical measures to address the risk:** SmPC section 4.4 mentions: • If the expected plasma levels of VWF:RCo are not attained, or if bleeding is not controlled with an appropriate dose, an appropriate assay should be performed to determine if a von Willebrand factor inhibitor. • In patients with high levels of anti-VWF antibodies, von Willebrand factor therapy may not be effective and other therapeutic options should be considered. • VWD patients who have high titre binding antibodies may require a higher VEYVONDI dose to overcome the binding antibody effect and such patients could be managed clinically by administration of higher doses of vonicog alfa based on the PK data for each individual patient. SmPC section 4.8 mentions patients experiencing hypersensitivity or anaphylactic reactions should be tested and evaluated for the presence of an inhibitor. PL section 2 mentions that if bleeding is not controlled with VEYVONDI, patients should inform their doctor immediately. **Other routine risk minimisation measures beyond the Product Information:** None.
Insufficient clinical data on use in pregnancy and lactation	**Routine risk communication:** SmPC section 4.6 PL section 2 **Routine risk minimisation activities recommending specific clinical measures to address the risk:** SmPC section 4.6 mentions VEYVONDI should be administered to pregnant or lactating VWF deficient women only if clearly indicated. PL section 2 mentions patients who are pregnant or breast-feeding, think they may be pregnant or are planning to have a baby, should ask their doctor for advice before taking VEYVONDI. **Other routine risk minimisation measures beyond the Product Information:** None
Insufficient clinical data on use in geriatric patients	**Routine risk communication:** None **Routine risk minimisation activities recommending specific clinical measures to address the risk:** None

[redacted]

Safety concern	Routine risk minimisation activities
	Other routine risk minimisation measures beyond the Product Information: None

V.2. ADDITIONAL RISK MINIMISATION MEASURES

Routine risk minimisation activities as described in Part V.1 are sufficient to manage the safety concerns of the medicinal product.

V.3. SUMMARY OF RISK MINIMISATION MEASURES

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

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Hypersensitivity reactions	**Routine risk minimisation measures:** SmPC sections 4.3, 4.4 and 4.8. PL section 2 and 4 **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** EUHASS registry
Thromboembolic events (particularly in patients with low ADAMTS13 levels as well as other risk factors, and concomitant overuse of FVIII)	**Routine risk minimisation measures:** SmPC sections 4.4, 4.8 and 4.9. PL section 2 and 3 **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** EUHASS registry
Inhibitor formation	**Routine risk minimisation measures:** SmPC sections 4.4 and 4.8. PL section 2 and 4 **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** EUHASS registry
Insufficient clinical data on use in pregnancy and lactation	**Routine risk minimisation measures:** SmPC section 4.6 PL section 2 **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:**

Safety concern	Risk minimisation measures	Pharmacovigilance activities
		EUHASS registry
Insufficient clinical data on use in geriatric patients	**Routine risk minimisation measures:** None **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** EUHASS registry

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of risk management plan for VEYVONDI® (Vonicog alfa)

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

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

This summary of the RMP for VEYVONDI 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 VEYVONDI's RMP.

I. THE MEDICINE AND WHAT IT IS USED FOR

VEYVONDI is authorised for von Willebrand disease (VWD) (see SmPC for the full indication). It contains vonicog alfa as the active substance and it is given by intravenous infusion.

Further information about the evaluation of VEYVONDI's benefits can be found in VEYVONDI's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage: https://www.ema.europa.eu/en/medicines/human/EPAR/veyvondi.

II. RISKS ASSOCIATED WITH THE MEDICINE AND ACTIVITIES TO MINIMISE OR FURTHER CHARACTERISE THE RISKS

Important risks of VEYVONDI, together with measures to minimise such risks and the proposed studies for learning more about VEYVONDI'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 periodic safety update report (PSUR) assessment so that immediate action can be taken, as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of VEYVONDI is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of VEYVONDI 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 VEYVONDI. 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);

List of important risks and missing information	
Important identified risks	• Hypersensitivity reactions • Thromboembolic events (particularly in patients with low ADAMTS13 levels as well as other risk factors, and concomitant overuse of FVIII)
Important potential risks	• Inhibitor formation
Missing information	• Insufficient clinical data on use in pregnancy and lactation • Insufficient clinical data on use in geriatric patients

II.B Summary of important risks

Important Identified Risk: Hypersensitivity reactions	
Evidence for linking the risk to the medicine	Clinical trials, potential mechanism of action of risk.
Risk factors and risk groups	Patients with previous history of hypersensitivity to vonicog alfa or any other constituents of the product. VWD patients who have developed antibodies against VWF are at increased risk to develop anaphylactic reactions after re-exposure to VWF.
Risk minimisation measures	Routine risk minimisation measures: SmPC sections 4.3, 4.4 and 4.8. PL section 2 and 4. Additional risk minimisation measures: No additional risk minimisation measures
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • European Haemophilia Safety Surveillance System (EUHASS registry) See Section II.C of this summary for an overview of the post-authorisation development plan.

Important Identified Risk: Thromboembolic events (particularly in patients with low ADAMTS13 levels as well as other risk factors, and concomitant overuse of FVIII)	
Evidence for linking the risk to the medicine	Clinical trials, potential mechanism of action of risk.
Risk factors and risk groups	Thromboembolic events can occur, particularly in patients with known clinical or laboratory risk factors including low ADAMTS13 levels. Administration of vonicog alfa with a FVIII product containing VWF would pose an additional risk of thrombotic events. Patients with sustained excessive FVIII:C plasma levels may be at increased risk of thrombotic events.
Risk minimisation measures	Routine risk minimisation measures: SmPC sections 4.4, 4.8 and 4.9. PL section 2 and 3. Additional risk minimisation measures: No additional risk minimisation measures

[redacted]

Important Identified Risk: Thromboembolic events (particularly in patients with low ADAMTS13 levels as well as other risk factors, and concomitant overuse of FVIII)	
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • EUHASS registry See Section II.C of this summary for an overview of the post-authorisation development plan.

Important Potential Risk: Inhibitor formation	
Evidence for linking the risk to the medicine	Potential mechanism of action of risk.
Risk factors and risk groups	VWD patients who have developed antibodies against VWF are at risk to develop anaphylactic reactions after re-exposure to VWF. Inhibitor development in patients with VWD is a rare complication of treatment and mainly occurs in patients with severe inherited type 3 VWD. The risk for VWD patients to develop antibodies in response to exogenously administered VWF is highly variable in individual patients and can only partially be explained by genetic factors. Mutations in the VWF gene which have been reported to be associated with VWD are very heterogeneous. The development of neutralizing antibodies against VWF is frequently reported in patients with partial or complete VWF gene deletions but also in patients carrying nonsense or frameshift mutations. Since not all cases of type 3 VWD caused by large gene deletions are associated with the development of anti- VWF antibodies, it is highly probable that additional genetic or environmental factors contribute to the risk of developing antibodies against VWF. A positive family history of anti-VWF antibodies is considered as a major risk factor. Patients previously treated with pdVWF concentrates may be at risk to express binding antibodies against VWF prior to first exposure to vonicog alfa.
Risk minimisation measures	Routine risk minimisation measures: SmPC sections 4.4 and 4.8. PL section 2 and 4. Additional risk minimisation measures: No additional risk minimisation measures
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • EUHASS registry See Section II.C of this summary for an overview of the post-authorisation development plan.

Missing Information: Insufficient clinical data on use in pregnancy and lactation	
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.6. PL section 2. Additional risk minimisation measures: No additional risk minimisation measures
Additional	Additional pharmacovigilance activities:

[redacted]

Missing Information: Insufficient clinical data on use in pregnancy and lactation	
pharmacovigilance activities	EUHASS registry See Section II.C of this summary for an overview of the post-authorisation development plan.

Missing Information: Insufficient clinical data on use in geriatric patients	
Risk minimisation measures	Routine risk minimisation measures: None. Additional risk minimisation measures: See Section II.C of this summary for an overview of the post-authorisation development plan.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: EUHASS registry See Section II.C of this summary for an overview of the post-authorisation development plan.

II.C. Post-authorisation development plan

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

There are no studies which are conditions of the marketing authorisation or specific obligation of VEYVONDI.

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

Study name: EUHASS registry.

Purpose of the study: The EUHASS registry serve to collect further safety information in patients with VWD.

[redacted]

PART VII: ANNEXES

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[redacted]

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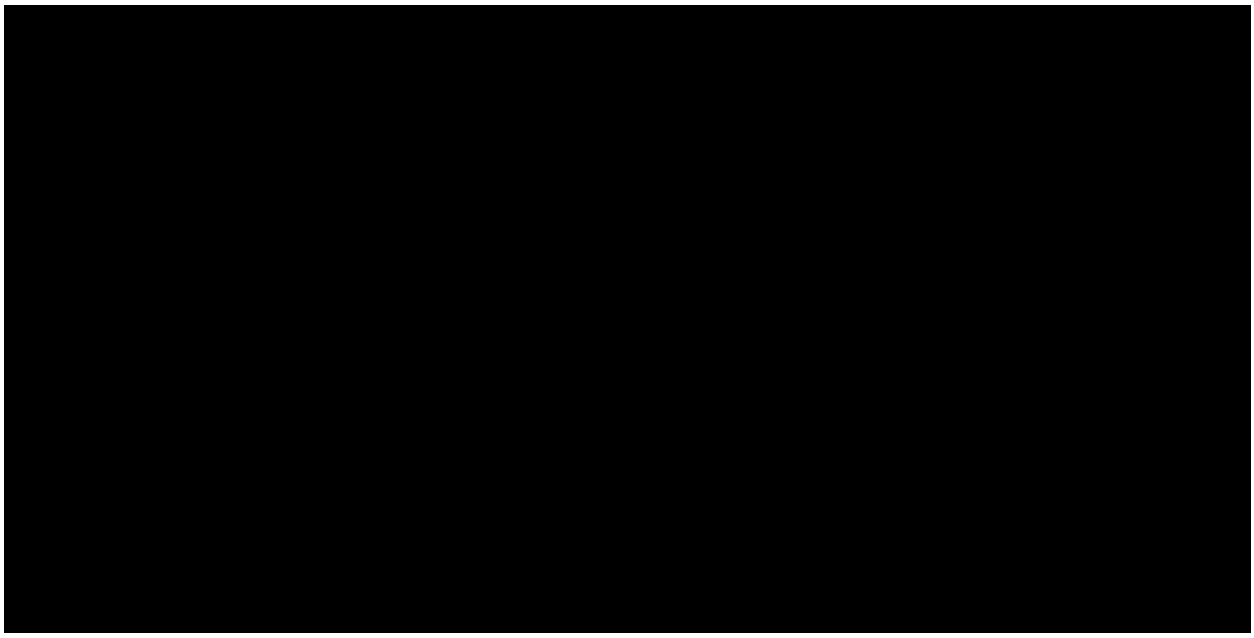

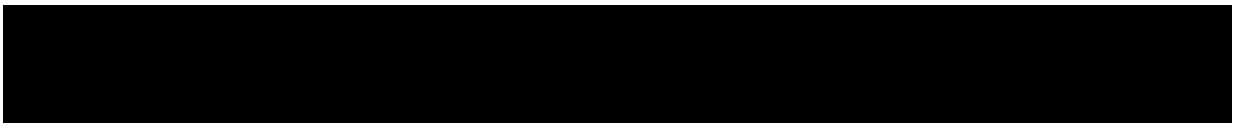

Annex 4: Specific adverse drug reaction follow-up forms

Not applicable

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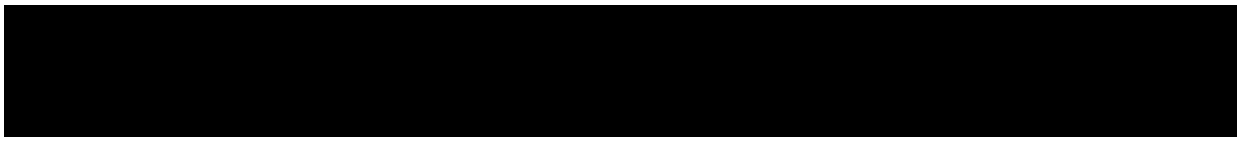

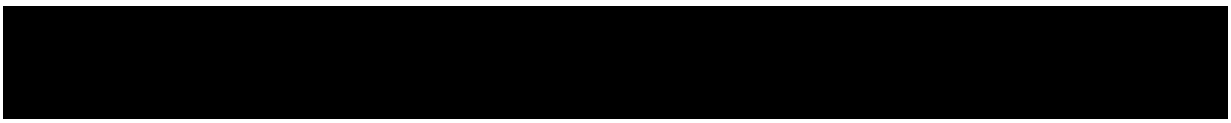

Annex 6: Details of proposed additional risk minimisation activities

Not applicable

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