13 November 2025
EMADOC-1700519818-2738998
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Veyvondi

International non-proprietary name: Vonicog alfa

Procedure No. EMA/VR/0000264863

Note

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

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
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List of abbreviations

Abbreviation	Definition
ABR	Annualized bleeding rate
ADA	Anti-drug antibody
ADR	Adverse drug reaction
AE	Adverse event
AESI	Adverse event of special interest
$AUC_{0\text{-}96h}$	AUC from time 0 to 96 hours
BE	Bleeding event
CHO	Chinese hamster ovary
CI	Confidence interval
CL	Clearance
C_{max}	Maximum plasma concentration
DCO	Data cut-off
DDAVP	Desmopressin
DVT	Deep vein thrombosis
EEA	European economic area
EMA	European medicines agency
EOI	Extension of indication
EOS	End of study
ER	Exposure-response
EU	European union
FAS	Full analysis set
FVIII	Factor VIII
FVIII:C	Factor VIII clotting activity
GCP	Good clinical practice
GI	Gastrointestinal
HTCs	Haemophilia treatment centres
IgG	Immunoglobulin G
IR	Incremental recovery
IRR	Infusion-related reactions
IU	International unit
IV	Intravenous
kDa	KiloDalton
kg	Kilogram
MAH	Marketing authorisation holder
MRT	Mean residence time
OD	On-demand
PD	Pharmacodynamic(s)
PDCO	Paediatric committee
PIP	Paediatric investigation plan
PK	Pharmacokinetic(s)
PKPDAS	Pharmacokinetic and pharmacodynamic analysis set
PPAS	Per-protocol analysis
rVWF	Recombinant von Willebrand factor
SAE	Serious adverse event
SD	Standard deviation
SmPC	Summary of product characteristics
$T_{1/2}$	Half life
TEAEs	Treatment-emergent adverse event
T_{max}	Minimum time to reach the maximum concentration
Vss	Volume of distribution at steady state
VWD	Von Willebrand disease
VWF	Von Willebrand factor
VWF: RCo	Von Willebrand factor ristocetin cofactor
VWF:Ag	Von Willebrand factor antigen
VWF:CB	Von Willebrand factor collagen binding

Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, BAXALTA INNOVATIONS GmbH submitted to the European Medicines Agency on 07 April 2025 an application for a variation.

The following changes were proposed:

Variation(s) requested		**Type**
C.I.6.a	C.I.6.a Addition of a new therapeutic indication or modification of an approved one	Variation type II

Extension of indication to include treatment of haemorrhage in children aged less than 18 years for VEYVONDI, based on results from studies 071102 and SHP677-304. Study 071102 is a phase 3, prospective, multicenter, uncontrolled, open-label clinical study to determine the efficacy, safety, and tolerability of the recombinant von Willebrand factor (rVWF) with or without ADVATE (octocog alfa) in the treatment and control of bleeding episodes, the efficacy and safety of rVWF in elective and emergency surgeries, and the pharmacokinetics (PK) of rVWF in children diagnosed with severe von Willebrand disease (VWD); study SHP677-304 is a phase 3B, prospective, open-label, uncontrolled, multicenter study on long term safety and efficacy of vonicog alfa in pediatric and adult subjects with severe VWD. As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated accordingly. Version 6.0 of the RMP has also been submitted. In addition, the Marketing authorisation holder (MAH) took the opportunity to bring the PI in line with the latest QRD template version 10.4, to update the PI in accordance with the latest EMA excipients guideline, and to implement editorial changes to the PI.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0236/2024 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0236/2024 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

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

Scientific advice/ Protocol assistance

Scientific Advice / Protocol Assistance was received for the development of the proposed product in 2009 (EMEA/H/SA/1378/1/2009/III), 2011 (EMEA/H/SA/1378/2/2011/PA/III), 2012 (EMEA/H/SA/1378/3/2012/PA/II), 2013 (EMEA/H/SA/1378/1/FU/1/2013/PA/I), 2014 (EMEA/H/SA/1378/2/FU/1/2014/PA/II) and 2018 (EMEA/H/SA/1378/4/2018/II).

From the above procedures, only the last one (EMEA/H/SA/1378/4/2018/II) is pertinent to the main studies discussed in the current extension of indication. In that procedure, the applicant put forward clinical questions regarding the study SHP677-304 and in particular its design and key elements (including population and size, dosing regimen, efficacy and safety endpoints) towards supporting an indication in children of all age groups that would include prevention and treatment of haemorrhage or surgical bleeding when desmopressin alone is ineffective or not indicated; the possibility of extrapolating clinical data for prevention of haemorrhages in children was also discussed in that context.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Jan Mueller-Berghaus Co-Rapporteur: Daniela Philadelphy

Timetable	Actual dates
Submission date	7 April 2025
Start of procedure:	26 April 2025
CHMP Rapporteur's preliminary assessment report circulated on:	23 June 2025
PRAC Rapporteur's preliminary assessment report circulated on:	27 June 2025
Joint Rapporteur's updated assessment report circulated on:	17 July 2025
Request for supplementary information and extension of timetable adopted by the CHMP on:	24 July 2025
MAH's responses submitted to the CHMP on:	11 September 2025
CHMP Rapporteur's preliminary assessment report on the MAH's responses circulated on:	10 October 2025
Joint Rapporteur's updated assessment report on the MAH's responses circulated on:	24 October 2025
PRAC RMP advice and assessment overview adopted by PRAC	30 October 2025
CHMP Rapporteur's updated assessment report circulated on:	6 November 2025
CHMP opinion:	13 November 2025

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

The purpose of this application is to seek approval for the use of vonicog alfa (Veyvondi) to treat haemorrhage in children aged less than 18 years with von Willebrand disease (VWD).

Disease or condition

Von Willebrand disease (VWD) is a hereditary bleeding disorder caused by a loss or defective function of von Willebrand factor (VWF). VWF is a large multimeric glycoprotein, ranging in molecular weight from 500 to >20,000 kDa, normally found in plasma, alpha-granules of platelets and storage granules of endothelial cells, known as the Weibel-Palade bodies. VWF plays a key role in primary haemostasis, facilitating platelet adhesion to the sub-endothelium at sites of vascular injury, one of the key functions in primary haemostasis, thereby initiating clot formation. Additionally, VWF acts as a carrier molecule for Factor VIII (FVIII), an essential cofactor of secondary haemostasis that leads to fibrin clot formation.

VWD is a heterogeneous disease and classified into three different types. Type 1 VWD (accounting for 70 to 80% of cases), is characterized by a mild or moderate quantitative deficiency of VWF, whereas type 2 summarizes different forms of qualitative defects known to affect function rather than the plasma levels of VWF antigen. Type 3 VWD is rare (<5% of cases, approx. 1 in 1 million people) and represents the most severe form caused by an almost complete loss of circulating von Willebrand factor.

Claimed therapeutic indication

With this application, the MAH applied for an extension of the therapeutic indication for vonicog alfa to expand the use of Veyvondi to treat haemorrhage in children aged less than 18 years.

The initially proposed therapeutic indication is as follows (proposed new text in bold, removed text as strikethrough):

*"Prevention and treatment of haemorrhage or surgical bleeding in adults**, and treatment of haemorrhage in children*** *~~(~~age**d less than*** *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."

The agreed indication is highlighted below in bold:

*"Prevention and treatment of haemorrhage or surgical bleeding in adults (age**d** 18 years and older) with von Willebrand disease (VWD), when desmopressin (DDAVP) treatment alone is ineffective or contraindicated.*

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."

Epidemiology

VWD represents the most common inherited human bleeding disorder with a prevalence of 0.6-1.3%. The results from population-based prevalence and the mutational landscape of VWD using large-scale genetic databases indicate a considerably higher than expected prevalence of putative disease alleles and variants associated with VWD, suggesting that a large number of patients with VWD are undiagnosed. Paediatric patients (aged <18 years) are less frequently diagnosed and tend to be less symptomatic; this trend is even more pronounced in younger patients (aged ≤10 years). Data collected from 54 haemophilia treatment centres (HTCs) in Italy found that paediatric patients (aged <18 years) accounted for 10.6% of all VWD patients (Giampaolo et al. 2017). In a study of

16 HTCs enrolled in the Italian VWD registry, 5.9% patients with VWD were <10 years of age. In a single HTC in the US, 6.0% patients with VWD were <5 years of age.

Clinical presentation

Clinical presentation of VWD shows strong variations among patients and critically depends on the amount and functionality of residual VWF, as well as the patient's age and sex. The main burden of the disease results from bleeding symptoms which are primarily caused by defective platelet adhesion and aggregation in mucosa-associated bleedings like for instance epistaxis or menorrhagia. In general, bleeding symptoms are more severe in type 2 and type 3 than in type 1 VWD. Disease subtypes with markedly reduced FVIII levels (type 2N and type 3 VWD) are further complicated by ''haemophilia-type'' joint and deep subcutaneous tissue bleeds, eventually leading to long-term damages and disabilities. The majority of patients (60-80%) experience excessive bleeding after surgery or dental extractions. A well-known, serious, and possibly life-threatening complication affecting patients with severe disease phenotypes is gastrointestinal bleeding resulting from angiodysplasia.

Management

Treatment of VWD largely depends on the type and severity of the disease. The basic principle of treatment is to support haemostasis which can be achieved by chemical agents like tranexamic acid or aminocaproic acid or by an iatrogenic correction of the reduced plasma VWF activity. An increase of plasma VWF levels can be achieved by desmopressin (DDAVP) which promotes its release from endogenous stores. When DDAVP treatment alone is ineffective or contra-indicated, endogenous VWF can be replaced by infusion of VWF containing medicinal products. Currently available concentrates are plasma-derived and contain different amounts and ratios of VWF and FVIII. Besides the problem of varying composition and overall plasma donor availability, drawbacks of plasma-derived VWF/FVIII products are given by an at least theoretical risk of pathogen transmission as well as the presence of extraneous plasma proteins which may trigger allergic responses. A serious although rare complication of VWF replacement therapy is the development of anti-drug antibodies (ADAs) which have been shown to develop in 5-10% of type 3 VWD patients and might result in treatment failure or trigger anaphylaxis with subsequent exposures.

The mainstay of treatment is on-demand (OD) to control spontaneous or traumatic bleeding or to prevent excessive bleeding during surgical procedures. However, a subset of patients with severe VWD (i.e. suffering from frequent and severe bleeding events [BEs]) may also benefit from long-term prophylactic treatment.

Currently, several plasma-derived VWF/FVIII products are available for the treatment of haemorrhage in children in the EU.

2.1.2. About the product

Vonicog alfa (also known as BAX111, SHP677, TAK-577, and rVWF) is a purified recombinant VWF in the drug class of blood coagulation factors, and the Anatomical Therapeutic Chemical System classification code is B02BD10.

In patients with VWD, vonicog alfa acts (1) to promote haemostasis by mediating platelet adhesion to damaged vascular subendothelial matrix (for example, collagen) and platelet aggregation, and (2) as a carrier protein for FVIII, protecting it from rapid proteolysis. The adhesive activity of VWF depends on the size of its multimers, with larger multimers being the most effective in supporting

interactions with collagen and platelet receptors. The binding capacity and affinity of vonicog alfa to FVIII in plasma is comparable to that of endogenous VWF, allowing for vonicog alfa to reduce FVIII clearance.

Vonicog alfa is the first and the only rVWF authorized for marketing in the United States, Canada, China, Japan (under the trade name VONVENDI), the European Economic Area (EEA), the United Kingdom, Switzerland, and Australia (under the trade name VEYVONDI).

Currently, Veyvondi is approved in the EEA for the 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.

2.1.3. The development programme/compliance with CHMP guidance/scientific advice

The Paediatric Study 071102 is part of an agreed PIP. On 08 September 2023, the PDCO accepted the proposed change in the number of subjects for Cohort 3 (<6 years) in the OD arm of Study 071102, reducing it from 8 to 5 subjects (EMEA-001164-PIP01-11-M07). On 31 May 2024, the PDCO accepted the inclusion of the OD arm of Study 071102 as an additional PIP measure (Study 5) to aid the compliance check procedure (EMEA-001164-PIP01-11-M08). On 13 December 2024, PDCO confirmed that the PIP study 5 (OD arm of Study 071102) is compliant with the latest PIP as set out in the EMA's Decision (P/0236/2024) of 18 July 2024.

2.1.4. General comments on compliance with GCP

The clinical trials providing data to support the requested variation (i.e. Studies 071102 and SHP677-304) were conducted in accordance with Good Clinical Practice.

2.2. Non-clinical aspects

No new clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.2.1. Ecotoxicity/environmental risk assessment

Veyvondi contains a naturally occurring protein as the active pharmaceutical ingredient, which due to its nature is unlikely to result in a significant risk to the environment. Therefore, Veyvondi is not expected to pose a risk to the environment and the absence of ERA studies is considered justified.

2.2.2. Conclusion on the non-clinical aspects

No new non-clinical data was submitted with this application, which is considered acceptable by CHMP.

Vonicog alfa is not expected to pose a risk to the environment.

2.3. Clinical aspects

2.3.1. Introduction

The requested extension of indication to include on-demand treatment of haemorrhage in children (i.e. patients <18 years of age) with VWD is supported by results from the phase 3 paediatric Study 071102 and an interim analysis of its phase 3b continuation study SHP677-304. These studies also enrolled subjects to determine the efficacy and safety of vonicog alfa in elective and emergency surgeries. However, paediatric subjects in surgery arms or adult subjects are outside the scope of this procedure and were not further considered in this report. Section 4.2 of the summary of product characteristics (SmPC) states that the safety and efficacy of VEYVONDI for prophylactic treatment or the prevention or treatment of surgical bleeding have not yet been established in children.

GCP

The clinical trials were performed in accordance with GCP as claimed by the MAH.

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

- Tabular overview of clinical studies

Study Number/ Study Status	Description	Main Criteria for Inclusion	Dose Range and Frequency	Sample Size Planned Actual
071102/ Ongoing	Vonicog alfa in paediatric subjects A Phase 3, prospective, multicenter, uncontrolled, open-label clinical study to determine the efficacy, safety, and tolerability of rVWF with or without ADVATE in the treatment and control of BEs, the efficacy and safety of rVWF in elective and emergency surgeries, and the PK of rVWF in children diagnosed with severe VWD.	0 to <18 years with severe VWD (VWF: RCo <20 IU/dL). Type 1, type 2A, type 2B, type 2N, type 2M, or type 3 VWD.	PK assessments: 50 ± 5 IU/kg VWF:RCo (single-dose infusion) OD treatment of nonsurgical bleeding: 40 to a maximum of 80 IU/kg VWF: RCo, with or without 30 to 45 IU/kg ADVATE. Subsequent doses every 8 to 24 hours with or without ADVATE as long as deemed necessary by the investigator. Surgical procedures: dose tailored to raise the VWF:RCo concentration to 100% of normal for major surgeries and to 50% to 60% of normal for minor and oral surgeries; dose and frequency of administration of VWF:RCo dependent on the type of surgery, PK results (when available), and VWF and FVIII levels. ADVATE, at a dose of 30 to 45 IU/kg, may be infused in subjects whose FVIII plasma levels are (or are highly likely to be) less than 40 to 50 IU/dL for minor/oral	Planned: OD arm: 24 subjects evaluable for treatment and control of nonsurgical bleeding, with 8 subjects in each of the 3 age cohorts (<6, 6 to <12, and 12 to <18). At least 10 subjects undergoing 12 procedures. Actual (Enrolment by interim analysis as of DCO date [01 December 2023]): OD arm: 25 subjects (SAF) (closed) Age (years) group <6 n=5 ≥6 to <12 n=11 ≥12 to <18 n=9 Type 1 n=5 Type 2A n=6 Type 2B n=3 Type 3 n=11 Surgery arms n=2 (elective surgery n=1, emergency surgery n=1) (1 subject enrolled in both OD and emergency

Study Number/ Study Status	Description	Main Criteria for Inclusion	Dose Range and Frequency	Sample Size Planned Actual
			surgery or 80 to 100 IU/dL for major surgery.	surgery arm)
SHP677-304/ Ongoing as of DCO date for the interim analysis	Phase 3b Continuation Study: A Phase 3b, prospective, open-label, uncontrolled, multicenter study on long-term safety and efficacy of rVWF in paediatric and adult subjects with severe VWD.	Paediatric and adult subjects with severe VWD (VWF: RCo <20 IU/dL). Type 1, type 2A, type 2B, type 2M, or type 3 VWD. Prophylactic treatment arm cohorts: 1. Adult subjects transitioning from the phase 3 prophylaxis parent study (Study 071301) who remained on the same prophylactic dose as in Study 071301. 2. Adult subjects transitioning from Study 071301 with no clinically significant bleeding episode for the past 6 months who started this phase 3b continuation study at a lower dose/frequency compared to the dose received in Study 071301. 3. Paediatric and adolescent subjects aged 12 to <18 years transitioning from the phase 3 paediatric study (Study 071102) who switched from receiving OD treatment to receiving once-weekly or twice-weekly prophylaxis. 4. Newly enrolled adult and paediatric and adolescent (aged 12 to <18 years) subjects switched from OD treatment with VWF products and started once-weekly prophylaxis with vonicog alfa in this phase 3b continuation study. OD treatment arm cohorts: 5. Paediatric subjects of all ages from Study 071102 who continued with receiving OD treatment. 6. Adult subjects from Study 071301 who switched back from prophylactic treatment to OD treatment.	PK assessments (cohort 4 only): 50 (±5) IU/kg VWF: RCo Prophylaxis: dose depending on previous treatment (prophylaxis or OD) and BEs in the past 6 months. Treatment of BEs: individualized based on weight, VWD type and severity of BEs, and monitoring of appropriate clinical and laboratory measures; with or without ADVATE. Perioperative bleeding: dose tailored to raise the VWF:RCo concentration to 100% of normal for major surgeries and to 50% to 60% of normal for minor and oral surgeries; dose and frequency individualized based on type of surgery, PK results, and VWF and FVIII levels.	Planned: Up to 71 adult and paediatric subjects with severe VWD in 6 cohorts including rollover subjects transitioning from previous studies or newly enrolled subjects. Actual number of subjects included in the submission (Enrolment by interim analysis as of DCO date [26 January 2024]): **Paediatric OD cohort (Cohort 5)** 19 subjects rolled over from 071102 (n=16 OD treated) Age (years) for n=16 OD treated <6 n=3 ≥6 to <12 n=5 ≥12 to <18 n=8 Type 1 n=4 Type 2A n=1 Type 2B n=3 Type 3 n=8 Paediatric surgery sample: n=4 (2 subjects in OD cohort, 2 subjects in prophylaxis cohorts)

Study Number/ Study Status	Description	Main Criteria for Inclusion	Dose Range and Frequency	Sample Size Planned Actual

Note: All arms/cohorts are described in this table. Paediatric subjects in surgery arms or adult subjects are outside the scope of the requested extension of indication.

2.3.2. Pharmacokinetics and Pharmacodynamics

Pharmacokinetics (PK) and pharmacodynamics (PD) data provided to support the requested extension of indication (EOI) were obtained in Study 071102. PK and PD assessments in Study SHP677-304 were limited to prophylaxis arms.

Study 071102

For a detailed description of study 071102, reference is made to section 2.4.1.

The PK/PD properties following intravenous (IV) infusions of vonicog alfa (50 ± 5 IU/kg rVWF:RCo after a 168-hour washout period) were investigated in paediatric subjects with VWD across 3 age groups (<6 years, ≥6 to <12 years, and ≥12 to <18 years).

To minimize the burden of frequent blood sampling on paediatric subjects, sparse PK/PD samples were collected up to 96 hours post PK infusions at the baseline visit, according to 3 sample collection sequences, with 4 samples planned per subject. To ensure that the 3 different sequences over the 96-hour time period were equally distributed among subjects, subjects in the 3 age cohorts were randomized separately into 1 of the 3 different post-infusion blood drawing sequences (Sequence 1: 60 ± 5 min, 24 ± 2 hours, and 72 ± 2 hours; Sequence 2: 15 ± 2 min, 12 ± 2 hours, and 48 ± 2 hours; Sequence 3: 6 ± 2 hours, 30 ± 2 hours, and 96 ± 2 hours). If a subject experienced a BE during the PK assessment, the BE was treated, and the PK assessment was repeated fully after a washout of at least 168 hours to replace the previously interrupted/failed PK assessment.

PK properties of vonicog alfa were determined for VWF:RCo, VWF:Ag, VWF:CB and PD was evaluated by means of FVIII:C activity. Point estimates for $AUC_{0\text{-}96h}$, C_{max}, and T_{max} for VWF:RCo, VWF:Ag, VWF:CB, and FVIII activity, with and without pre-infusion correction were derived using a noncompartmental estimation approach for sparse sampling designs.

Due to sparse sampling, the PK/PD of vonicog alfa (including the PK parameters C_{max}, T_{max}, $AUC_{0\text{-}96h}$, $AUC_{0\text{-}\infty}$, MRT, CL, IR, $T_{1/2}$, and V_{ss}) were further analysed using a population PK modelling approach (see section 2.3.3).

The Pharmacokinetic and Pharmacodynamic Analysis Set (PKPDAS) consisted of all enrolled subjects who completed the required washout, received the PK infusion, were not actively bleeding at the time of the PK infusion, had no bleeding episode during the PK/PD assessment, and had at least 1 quantifiable post-dose PK or PD measurement.

Results:

Study 071102 included a total of 22 paediatric subjects (5 subjects aged <6 years [n= 2 with type 3 VWD], 10 subjects aged ≥6 to <12 years [n= 4 with type 3 VWD] and 7 subjects aged ≥12 years [n= 3 with type 3 VWD]) for sparse sampling collection.

Median levels of VWF:RCo and FVIII:C after infusion of 50 IU/kg of VEYONDI are shown in Figures 1 and 2. Median values of VWF:RCo appear to be the highest at 15 minutes post-infusion, decrease steadily through 12 hours, and gradually through the last assessment at 96 hours. Median levels of

FVIII:C show a trend of increase through the 30-hour assessment then a decrease through the 96-hour assessment. The peak levels for FVIII:C occur at a later time, which is expected based on the disposition and PK/PD relationship of vonicog alfa.

Figure 1. Observed VWF:RCo activity (IU/dL) over time

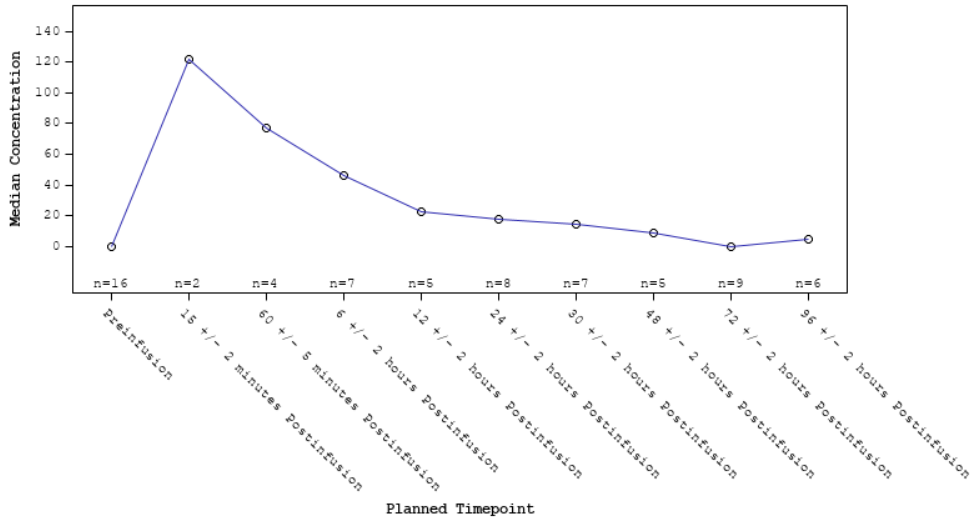
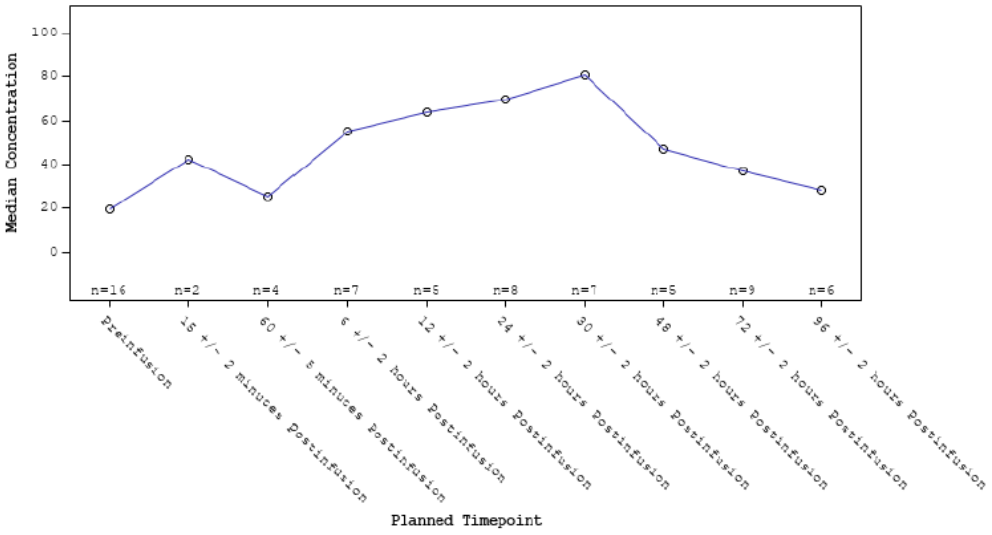


Figure 2. Observed FVIII activity (IU/dL) over time



The PK/PD exposure parameters for VWF:RCo and FVIII:C by age cohort with and without individual baseline correction are summarized in Table 1.

Table 1. PK/PD parameters, by age cohort

Source	Parameter (Unit)	≥12 to <18 Years (N = 7)	≥6 to <12 Years (N = 10)	<6 years (N = 5)	Total [a] (N = 22)
VWF:RCo					
Without baseline correction	$AUC_{0\text{-}96h}$ (h*IU/dL)	920.2875	2028.7375	2064.3	1707.6625
	C_{max} (IU/dL)	78.5	106.6	60.5	75.4
	T_{max} (h)	1	0.25	1	1
With baseline correction	$AUC_{0\text{-}96h}$ (h*IU/dL)	904.8375	1210.9625	857.1375	951.9625
	C_{max} (IU/dL)	78.5	106.6	60.5	62.3
	T_{max} (h)	1	0.25	1	1

FVIII:C					
Without baseline correction	$AUC_{0\text{-}96h}$ (h*IU/dL)	4712.0625	6255.25	3539.625	4809.75
	C_{max} (IU/dL)	91.5	94.5	99	81
	T_{max} (h)	30	30	0.25	30
With baseline correction	$AUC_{0\text{-}96h}$ (h*IU/dL)	3418.75	3425.5	1766.25	3216
	C_{max} (IU/dL)	86.5	75	87	66
	T_{max} (h)	30	12	0.25	30

2.3.3. PK/PD modelling

To support the use of vonicog alfa for OD treatment of BEs in paediatric subjects and to support the recommended dosing, existing population PK and PK/PD models (previously used to support prophylactic treatment in adults) were updated by including the newly collected data from paediatric subjects.

In the population PK model, the PK properties of VWF were described for VWF:RCo. In addition, the PK/PD relationship was assessed by linking VWF:RCo activity to FVIII:C activity.

Population PK

A total of 134 unique subjects who participated in vonicog alfa phase 1 and phase 3 studies (070701, 071001, 071101, 071102, 071301, and SHP677-304) had at least 1 measurable value of VWF:RCo collected post dose and were included in the population PK analysis. The population included a total of 66 (49.3%) male and 68 (50.7%) female subjects, a total of 106 (79.1%) adult subjects (aged ≥18 years) and 28 (20.9%) paediatric subjects (aged <18 years). The population included a total of 17 (12.7%) subjects with VWD type 1, 22 (16.4%) subjects with VWD type 2, and 95 (70.9%) subjects with VWD type 3. A total of 94 (70.1%) subjects received vonicog alfa, 32 (23.9%) subjects received vonicog alfa/ADVATE, and 8 (6.0%) subjects received dVWF:pdFVIII.

Key findings relevant to the requested EOI were summarised as follows:

- In line with previous PK findings, covariate analyses of clearance (CL) of VWF:RCo was dependent on body weight and age, and the Vc was dependent on body weight.
    - The exponent for the effect of body weight on CL was 0.647 [that is, $(WT/70)^{0.647}$], suggesting a lower CL of VWF:RCo in paediatric subjects with lower body weight; the exponent for the effect of age on CL was -0.212 [that is, $(Age/35)^{-0.212}$], suggesting a faster CL of VWF:RCo in paediatric patients.
- VWD type (1-2 versus 3), race, sex, BEs, and co-administration with rFVIII did not affect the CL and Vc of VWF:RCo. CL and Vc were dose-independent for a dose range of 2.0 to 80 IU/kg.

PK properties in the paediatric population

The population PK model was used to simulate the PK parameters for the paediatric subjects who received a single dose of 50±5 IU/kg vonicog alfa in Study 071102. Simulated PK and exposure parameters are summarized by age group in Table 2.

Table 2. Summary of PK and exposure parameters in paediatric subjects (Study 071102, 50±5 IU/kg single dose)

PK Parameters	<6 years (N=5)	6 to <12 years (N=10)	12 to <18 years (N=9)	<18 years (N=24)
$t_{1/2}$ (h)				
Mean (95%CI)	12.4 (9.91; 15.0)	14.5 (13.6; 15.4)	15.1 (14.2; 16.1)	14.3 (13.5; 15.1)
SD	2.90	1.47	1.50	2.03
CL ([dL/kg]/h)				
Mean (95% CI)	0.0825 (0.0470; 0.118)	0.0514 (0.0414; 0.0613)	0.0432 (0.383; 0.0482)	0.0548 (0.0447; 0.0649)
SD	0.0406	0.0160	0.00753	0.0251
IR based on C_{max} ([IU/dL]/[IU/kg])				
Mean (95% CI)	1.25 (0.917; 1.58)	1.54 (1.30; 1.77)	1.58 (1.43; 1.72)	1.49 (1.36; 1.63)
SD	0.378	0.378	0.225	0.339
$AUC_{0-\infty}$ (IU*h/dL)				
Mean (95% CI)	1260 (690; 1840)	1630 (1080; 2170)	1600 (1140; 2060)	1540 (1240; 1840)
SD	654	882	704	757
$AUC_{0-\infty}$/Dose ([IU*h/dL]/[IU/kg])				
Mean (95% CI)	25.6 (14.4; 36.9)	32.5 (21.3; 43.7)	32.6 (23.2; 41.9)	31.1 (25.0; 37.2)
SD	12.8	18.1	14.3	15.3

PK model-based exposure (as evaluated by AUC and C_{max} of VWF:RCo) in adults and paediatrics across age groups receiving the same vonicog alfa dose 50 IU/kg is shown in Table 3.

Table 3. Descriptive statistics of exposure parameters of VWF:RCo – adult versus paediatrics

Age Group	Statistic	Baseline VWF:RCo (IU/dL)	Single Dose 50 IU/kg Vonicog Alfa		
			AUC_{0-72} (IU*h/dL)	C_{max} (IU/dL)	C_{last} (IU/dL)
Adult (≥18 years)	N	62	62	62	62
	Mean (CV%)	2.66 (186.0)	1695 (34.6)	92.3 (25.9)	6.73 (82.7)
	SD	4.94	587	23.9	5.57
	Geometric Mean (CV%)	0.976 (187.0)	1595 (37.0)	89.2 (27.4)	5.01 (94.0)
	Median	0.5	1692	89.5	5.45
	Range	0.500-26.3	593-3443	35.2-154	0.800-27.6
Pediatric Sub-Group 12 to <18 years	N	12	12	12	12
	Mean (CV%)	4.29 (111.0)	1385 (33.4)	81.3 (16.6)	5.98 (84.4)
	SD	4.76	462	13.5	5.05
	Geometric Mean (CV%)	2.07 (230.0)	1322 (32.0)	80.4 (15.4)	4.19 (113.0)
	Median	2.95	1296	77.9	4.95
	Range	0.500-12.7	869-2281	64.9-115	1.20-15.2
Pediatric Sub-Group 6 to <12 years	N	11	11	11	11
	Mean (CV%)	5.63 (112.0)	1445 (43.7)	82.3 (25.3)	7.26 (92.0)
	SD	6.29	631	20.8	6.69
	Geometric Mean (CV%)	2.35 (314.0)	1323 (47.0)	79.9 (25.9)	4.59 (145.0)
	Median	3.8	1329	80.7	5.1
	Range	0.500-17.7	674-2742	53.4-124	1.10-20.2
Pediatric Sub-Group <6 years	N	5	5	5	5
	Mean (CV%)	8.29 (93.2)	1302 (39.1)	70.7 (25.8)	9.14 (81.1)
	SD	7.73	509	18.3	7.41
	Geometric Mean (CV%)	3.53 (496.0)	1234 (36.7)	68.8 (26.3)	6.13 (154.0)
	Median	9.17	1056	63.9	9.3
	Range	0.500-17.7	872-2134	50.6-90.3	1.80-18.8

Population PK/PD

A PK/PD model was developed where the FVIII PD response was described using an indirect response model in which the degradation of FVIII (K_{out}) was inhibited by the PK model-predicted activity of VWF:RCo in a concentration-dependent manner.

A total of 89 subjects with at least 1 measurable value of FVIII:C post vonicog alfa dose were included in the population PK/PD analysis (Studies 071001, 071101, 071102, and 071301/SHP677-304). Of the 89 subjects included in the PK/PD analysis, 12 (13.5%) presented with VWD type 1, 18 (20.2%) presented with VWD type 2, and 59 (66.3%) presented with VWD type 3. The analysis included 61 (68.5%) adult patients and 28 (31.5%) paediatric patients.

Key findings relevant to the requested EOI were summarised as follows:

- Similar to PK, age was identified as an important covariate describing variability in the K_{out} of FVIII:C. The exponent for the effect of age on K_{out} was -0.476 [that is, $(Age/35)^{-0.476}$], suggesting a faster K_{out} of FVIII:C in paediatric patients.
- The PK/PD relationship in patients with type 1/type 2 VWD was less steep, with a Hill effect of 1 (that is, 2.16 × 0.468). The less steep PK/PD relationship in patients with type 1/type 2 VWD is likely due to the higher measurable endogenous levels of VWF:RCo prior to administration of vonicog alfa.

PK/PD model-based evaluations of exposure to FVIII (as determined by AUC and C_{max} for FVIII:C) provided the following results:

- AUC: the median (min, max) values of AUC_{0-72} were 4830 (2189, 8265), 4484 (2636, 7443), 4497 (2101, 9169), and 3060 (1924, 4770) IU×h/dL for adult subjects (aged ≥18 years), paediatric subjects (aged 12 to<18 years), paediatric subjects (aged 6 to <12 years) and paediatric subjects (aged <6 years), respectively.
- C_{max}: the median (min, max) values of C_{max} were 83.3 (43.8, 167), 84.4 (58.7, 151), 97.6 (47.9, 137), and 62.3 (57.7, 86.6) IU/dL, respectively.

2.3.4. Discussion on clinical pharmacology

To support the requested indication for on-demand treatment of BE in children, the MAH performed non-compartmental analysis (NCA) to evaluate PK/PD properties of vonicog alfa based on samples from 22 children in Study 071102. These included 5 children aged <6 years (n=2 with type 3 VWD), 10 children aged ≥6 to <12 years (n= 4 with type 3 VWD) and 7 children aged ≥12 years (n= 3 with type 3 VWD). In Study SHP677-304, PK/PD assessments were limited to prophylaxis arms.

The PK/PD properties of vonicog alfa were evaluated after a 168-hour washout period, following IV infusions of 50 ± 5 IU/kg rVWF:RCo and using a sparse sample collection approach (with only 3 post-infusion blood draws per subject up to 96 hours post PK infusions) to minimize the blood drawn for children. Three different blood drawing sequences for PK assessment were defined in the protocol (sequence 1: blood draw at 60 ± 5 minutes, 24 ± 2 hours, 72 ± 2 hours; sequence 2: blood draw at 15 ± 2 minutes, 12 ± 2 hours, 48 ± 2 hours; sequence 3: blood draw at 6 ± 2 hours, 30 ± 2 hours, 96 ± 2 hours). The three individual sequences included participants from all three paediatric age subgroups.

While this sparse sampling approach is not optimal from a scientific point of view, it is acceptable to reduce the burden in children. Nevertheless, for interpretation of the data, it should be

considered that the PK/PD profiles are based on combinations of individual patients who contributed to the samples collected at specified time points.

Point estimates for $AUC_{0\text{-}96h}$, C_{max}, and T_{max} for VWF:RCo, VWF:Ag, VWF:CB and FVIII:C activity, with and without pre-infusion correction, were derived using a noncompartmental estimation approach for sparse sampling designs.

In addition, to the NCA, population PK and PK/PD modelling analyses were performed using data from 134 unique adult and paediatric subjects who participated in 6 vonicog alfa clinical studies. Previously existing models were updated by including additional data collected in Study 071102 and from paediatric and newly enrolled prophylaxis subjects in Study SHP677-304.

As required by the EMA clinical guideline for plasma-derived VWF products (CPMP/BPWG/220/02), Study 071102 included an investigation of VWF multimer distribution, including a comparison with data obtained in former studies of vonicog alfa in adults (studies 071001 and 070701), which did not reveal any significant age-related differences. The omission of a repeated PK assessment in the setting of OD treatment is considered acceptable.

A comparison of observed PK/PD data between the different paediatric age groups indicate largely comparable C_{max} values but a trend towards lower $AUC_{0\text{-}96}$ values for VWF:RCo and FVIII:C (despite baseline correction) in children <6 years of age. However, interpretation of the observed PK/PD data is strongly hampered by the small numbers of samples per time point and sparse sampling resulting in a contribution of several patients to individual PK/PD profiles. The sample sizes at the different time points (e.g., n=2 at 15 minutes after infusion and n=4 at 60 minutes after infusion) are very low and having more blood draws at the 15-minute time-point would have been helpful to get more confidence in the peak concentrations. However, it is acknowledged that taking two samples within a short time (at baseline and 15 minutes thereafter) would be particularly burdensome, especially in younger children.

Besides the sparse sampling with combined PK/PD profiles and low sample sizes per time point, inherently different baseline levels of VWF:RCo, VWF:Ag, VWF:CB and FVIII:C, depending on the type of VWD, should also be considered for interpretation.

PK model-based covariate analysis of CL of VWF:RCo suggest faster CL in paediatric patients with an exponent of the effect of age of -0.212 [that is, (Age/35)-0.212]. Accordingly, the PK model e.g., suggests that for children aged <6 years, CL of VWF:RCo increases by 45% relative to a typical 35-year-old adult.

Consistent with this, model-based simulations of PK parameters for the PKPDAS of Study 071102 indicate an inverse relationship between age and clearance and half-life. In addition, PK/PD model-based simulations of exposures ($AUC_{0\text{-}72}$ and C_{max} for VWF:RCo and FVIII:C) following an administration of 50 IU/kg of vonicog alfa indicate age-dependent decreases with median (min, max) values of C_{max} of 63.9 (50.6, 90.3) IU/dL for VWF:RCo and 62.3 (57.7, 86.6) IU/dL for FVIII:C in children <6 years of age.

Accordingly, the estimated median C_{max} of VWF:RCo falls only slightly above the recommended target threshold of 60 IU/dl to achieve haemostasis, as specified in section 4.2 of the Core SmPC for human plasma-derived VWF (CPMP/BPWG/278/02). In contrast, the predicted median (min, max) C_{max} of FVIII:C falls well above the recommended target threshold of 40 IU/dl. However, as these predictions are based on source data from patients suffering from different types of VWD (with known substantial differences in baseline FVIII:C levels) and treatment with either vonicog alfa alone or in combination with ADVATE, particularly the predicted FVIII:C levels remain difficult to interpret.

A higher clearance in younger age groups, is consistent with alternative coagulation factor products. While this could question the appropriateness of the proposed dosing (i.e. same dosing as in adults), it also needs to be considered that dosing is mainly based on clinical response. This is clearly explained in section 4.2 of the SmPC stating that "dosing should be adjusted to the clinical condition of the patient, as well as their VWF:RCo and FVIII:C plasma levels".

2.3.5. Conclusions on clinical pharmacology

Results of the submitted PK/PD data in study 071102 together with the supportive evidence from population PK/PD modelling support the proposed posology for on-demand treatment of BE in children with VWD.

2.4. Clinical efficacy

The clinical efficacy data that support the requested EOI include data from paediatric subjects who received OD treatment in Study 071102 (N=18) and its continuation study SHP677-304 (N=16). In addition, for subjects who completed Study 071102 and entered Study SHP677-304, the MAH performed an integrated analysis of efficacy data from the day of the first dose of vonicog alfa in Study 071102 through the data cut-off (DCO) for each study (01 December 2023 for Study 071102 and 26 January 2024 for Study SHP677-304).

2.4.1. Main studies

Study 071102

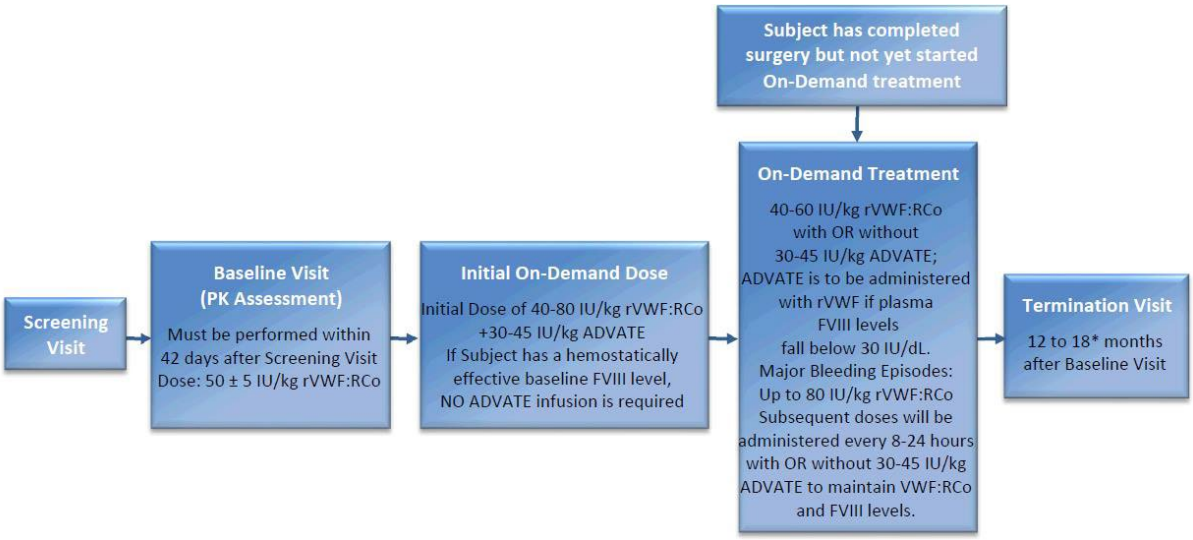
A Phase 3, prospective, multicenter, uncontrolled, open-label clinical study to determine the efficacy, safety, and tolerability of rVWF with or without ADVATE in the treatment and control of bleeding episodes, the efficacy and safety of rVWF in elective and emergency surgeries, and the pharmacokinetics (PK) of rVWF in children diagnosed with severe von Willebrand disease.

Methods

Study 071102 is an ongoing phase 3, open-label, uncontrolled, multicenter study designed to evaluate the efficacy, safety, and tolerability of vonicog alfa with or without ADVATE in the treatment and control of nonsurgical BEs and bleeding associated with elective and emergency surgeries, as well as the PK of vonicog alfa in paediatric subjects with severe VWD.

The study consisted of 3 treatment arms: OD, elective surgery, and emergency surgery. Subjects in the OD treatment arm received vonicog alfa treatment for nonsurgical BEs over a 12-month period (up to 18 months for some subjects who rolled over into the continuation study [SHP677-304]). Vonicog alfa was evaluated for haemostatic efficacy and safety for OD treatment of BEs and perioperative management of bleeding. An interim analysis was planned when either the OD treatment arm or the surgery arms were completed, whichever occurred first. The OD treatment arm of this study has been completed and an interim analysis for OD and surgery was prepared with a DCO date of 01 December 2023. Enrolment in the surgery arms was continuing as of the DCO date. Details on the study design for the OD treatment arm are provided in Figure 3.

Figure 3. Design of Study 071102: OD treatment arm



The study has been conducted in 45 sites in the US (15 sites), France (8 sites), Italy (4 sites), Germany, Russia, and Turkey (3 sites each), Austria and Spain (2 sites each), Belgium, Czech Republic, Netherlands, Ukraine, and the UK (1 site each).

Study participants

Subjects who met all the following criteria were eligible for this study:

1. Diagnosis of severe VWD (defined as VWF: ristocetin cofactor [VWF:RCo] <20%):
    a. Type 1 (VWF:RCo <20 IU/dL); or
    b. Type 2A (VWF:RCo <20 IU/dL), type 2B (as diagnosed by genotype), type 2N (FVIII: coagulation activity [C] <10% and historically documented genetics), type 2M; or
    c. Type 3 (VWF: antigen [VWF:Ag] ≤3 IU/dL)
2. Age 0 to <18 years at the time of screening.
3. The subject had provided assent (if appropriate) and legally authorized representative(s) had provided informed consent.
4. If female of childbearing potential, subject presented with a negative serum pregnancy test.
5. If applicable, the subject agreed to employ adequate birth control measures for the duration of the study. Refer to Appendix 16.1.1 Protocol Amendment 9 dated 20 December 2021, Section 20.5 for a list of adequate contraceptive methods for female subjects of childbearing potential and for male subjects.
6. The subject and/or legal representative were willing and able to comply with the requirements of the protocol, which was also confirmed based on a pre-screening evaluation held between the investigator and the sponsor, to ensure no eminent risk was present that could challenge the subject's compliance with the study requirements.

Additional inclusion criteria for both previously treated subjects, as well as for subjects undergoing surgery, were as follows:

1. Unable to tolerate or were inadequately responsive to DDAVP.
2. The subject had a minimum of 1 documented bleed requiring VWF coagulation factor replacement therapy (i.e. treatment with a VWF product) during the previous 12 months prior to enrolment, and overall, 3 or more exposure days historically to VWF replacement therapy.

Additional inclusion criterion for previously untreated subjects were as follows:

1. The subject had not received prior VWF coagulation factor replacement therapy.

Subjects who met any of the following criteria were not eligible for this study:

1. Diagnosis of pseudo-VWD or another hereditary or acquired coagulation disorder (e.g., qualitative and quantitative platelet disorders or elevated prothrombin time/international normalized ratio [INR] >1.4).
2. History or presence of a VWF inhibitor at screening.
3. History or presence of a FVIII inhibitor with a titer ≥0.4 Bethesda units (BU) (by Nijmegen assay) or ≥0.6 BU (by Bethesda assay).
4. Documented history of a VWF:RCo half-life (T½) <6 hours.
5. Known hypersensitivity to any of the components of the study drug, such as mouse or hamster proteins.
6. Medical history of immunological disorders, excluding seasonal allergic rhinitis/conjunctivitis/asthma, food allergies, or animal allergies.
7. Medical history of a thromboembolic event.
8. Human immunodeficiency virus (HIV) positive, with an absolute CD4 count <200/mm3.
9. In the judgment of the investigator, the subject had another clinically significant concomitant disease (e.g., uncontrolled hypertension, cancer) that may pose additional risk for the subject.
10. Diagnosis of significant liver disease, as evidenced by, but not limited to, any of the following: serum alanine aminotransferase (ALT) of 5 times the upper limit of normal, hypoalbuminemia, portal vein hypertension (e.g., presence of otherwise unexplained splenomegaly, history of oesophageal varices), or liver cirrhosis classified as Child B or C.
11. Diagnosis of renal disease, with a serum creatinine level ≥2.5 mg/dL.
12. Immunomodulatory drug treatment other than anti-retroviral chemotherapy (e.g., α-interferon, or corticosteroid agents) at a dose equivalent to hydrocortisone >10 mg/day (excluding topical treatment [e.g., ointments, nasal sprays]), within 30 days prior to signing the informed consent (or assent, if appropriate).
13. If female, the subject was pregnant or lactating at the time informed consent (or assent, if appropriate) was obtained.
14. The subject had participated in another clinical study involving a study drug, other than vonicog alfa with or without ADVATE, or an investigational device within 30 days prior to enrolment, or was scheduled to participate in another clinical study involving a study drug other than vonicog alfa or investigational device during the course of this study.
15. Subject's legal representative was a family member or employee of the investigator.

Treatments

For the OD treatment of BEs, an initial dose of 40 to 60 IU/kg vonicog alfa was infused, along with 30 to 45 IU/kg ADVATE unless the subject had a haemostatically effective baseline FVIII level. In case of major BEs, a dose of vonicog alfa up to 80 IU/kg could be used. Subsequent doses were administered every 8 to 24 hours, with or without additional ADVATE, in order to maintain VWF:RCo and FVIII levels for as long as deemed necessary by the investigator.

Objectives

The overall objectives of Study 071102 were as follows:

Primary Objective: To evaluate the haemostatic efficacy and safety of vonicog alfa, with or without ADVATE, in the treatment and control of nonsurgical bleeding events in paediatric subjects (<18 years of age) diagnosed with severe, hereditary von Willebrand Disease (VWD).

Secondary Objectives:

- An overall assessment of haemostatic efficacy after the last perioperative vonicog alfa infusion in paediatric subjects undergoing elective or emergency surgery.
- To assess the overall adverse event (AE) profile of vonicog alfa by frequency, severity, and seriousness. A focused review of thrombotic events and severe hypersensitivity events was also performed.
- To assess the pharmacokinetics (PK) of vonicog alfa

Outcomes/endpoints

The primary and secondary endpoints relating to efficacy of OD treatment in paediatric subjects were as follows:

Primary Endpoint:

- Haemostatic efficacy, defined as the number of paediatric subjects with treatment success for vonicog alfa-treated nonsurgical BEs (using a 4-point scale).

Treatment success was defined as a mean efficacy rating score of <2.5 for a subject's treated BEs. If a subject experienced only 1 treated BE, the rating score for the single bleed was used to determine treatment success. The individual haemostatic efficacy rating for each bleed was assigned scores as outlined in Table 4, before the mean score was determined.

Table 4. Efficacy rating scale

Rating	Efficacy Rating Criterion	
	Minor and Moderate Bleeding Events	Major Bleeding Events
Excellent (=1)	Actual number of infusions ≤ estimated number of infusions required to treat that BE. No additional VWF containing coagulation factor containing product required.	Actual number of infusions ≤ estimated number of infusions required to treat that BE. No additional VWF containing coagulation factor containing product required.
Good (=2)	1 to 2 infusions greater than estimated required to control that BE. No additional VWF containing coagulation factor containing product required.	<1.5 × infusions greater than estimated required to control that BE. No additional VWF containing coagulation factor containing product required [a]
Moderate (=3)	3 or more infusions greater than estimated required to control that BE. No additional VWF containing coagulation factor containing product required.	≥1.5 × infusions greater than estimated required to control that BE. No additional VWF containing coagulation factor containing product required.
None (=4)	Severe uncontrolled bleeding or intensity of bleeding not changed. Additional VWF containing coagulation factor containing product required.	Severe uncontrolled bleeding or intensity of bleeding not changed. Additional VWF containing coagulation factor containing product required.

[a] Example: If estimated number of infusions was 1, then 2 actual infusions sufficient to stop the bleeding were considered "Good". If estimated number of infusions was 2, then 3 actual infusions were considered "Good". If estimated number of infusions was 2, then 1 actual infusion was considered "Excellent".

Secondary Endpoints:

- Number of treated nonsurgical BEs with an efficacy rating of "excellent" or "good".
- Number of infusions, vonicog alfa units, and ADVATE units (if needed), per BE.

Sample size

The sample size of at least 24 paediatric subjects with severe VWD disease was planned based on the Guideline on the Clinical Investigation of Human Plasma Derived VWF Products (CPMP/BPWG/220/02). The sample size calculation was not based on a power calculation for a significance test.

Randomisation

Not applicable as this is a single arm study.

Blinding (masking)

Not applicable as this is an open label study.

Statistical methods

Analysis sets for efficacy were the following:

- The FAS consisted of all subjects who signed an informed consent form (or provided assent, if appropriate), were enrolled and met all inclusion and none of the exclusion criteria, had received any amount of study drug, and provided at least 1 haemostatic assessment within 24 hours of a study drug infusion with or without ADVATE. The FAS was used for primary and secondary efficacy endpoints.

- The per-protocol analysis (PPAS) consisted of subjects in the FAS who met all study entry criteria and who had no major protocol violations that might affect haemostatic efficacy assessment. The analysis of primary efficacy endpoints was repeated using the PPAS.

The analysis for the primary outcome measure did not include inferential testing of statistical hypotheses.

Tests of statistical hypotheses and CIs, when used, were nominal and unadjusted for multiplicity.

Results

Participant flow

Subject disposition is presented in Table 5. Overall, 26 subjects received at least 1 dose of vonicog alfa and were included in the SAF (safety analysis set). This included 25 subjects in the OD treatment arm, 1 subject in the elective surgery arm, and 1 subject in the emergency surgery arm (1 subject was enrolled in both the OD treatment arm and the emergency surgery arm). Of the 25 subjects in the OD treatment arm, 7 (28.0%) received at least 1 dose of ADVATE, and 24 (96.0%) completed the study after a treatment period of approximately 12 to 17 months. One subject discontinued from the study due to physician decision (to start prophylaxis), 319 days after the baseline PK dose of vonicog alfa (the last dose was received on Day 313).

The efficacy analysis (FAS) for OD treatment included 18 of the 25 subjects; 7 subjects from the OD treatment arm were excluded from the FAS because these subjects did not have any BE that required treatment with the study drug (these 7 subjects received vonicog alfa only for PK assessment at baseline).

Table 5. Subject disposition in Study 071102

	OD (N=28) n (%)
Not treated	3
SAF [a]	25 (100)
FAS [b]	18 (72.0)
PPAS [c]	17 (68.0)
PK and PD analysis set [d]	21 (84.0)
Subjects who received at least one dose of vonicog alfa	25 (100)
Subjects who received at least one dose of ADVATE	7 (28.0)
Completed study	24 (96.0)
Still on study	0
Discontinued	1 (4.0)
Reason for discontinuation from study [e]	
Physician decision	1 (100)

[a] All subjects in the ENR who received any infusion or part of an infusion of study drug (vonicog alfa) with or without ADVATE as recorded on the baseline PK infusion eCRF panel or in the study drug administration diary.

[b] All subjects in the ENR who were enrolled and met all inclusion and none of the exclusion criteria, had received any amount of study drug and provided at least 1 hemostatic assessment within 24 hours of a study drug infusion with or without ADVATE.

[c] All subjects in the FAS who had no major protocol violations that might impact efficacy evaluation.

[d] All subjects in the ENR that completed the required washout, received a PK infusion, were not actively bleeding at the time of the PK infusion, have no BE during the PK assessment and have at least 1 quantifiable postdose measurement.

[e] Percentages were based on the number of subjects who discontinued from study.

Recruitment

Between 06 November 2017 (date first subject signed informed consent form) and 01 December 2023 (DCO of the presented analysis), a total of 41 subjects were screened, of whom 12 subjects were screen failures and 3 subjects were not treated (discontinued before receiving vonicog alfa for PK assessment or for a BE).

Conduct of the study

The initial version of the protocol dated 10 June 2016 was amended 9 times, including 3 global amendments, as summarized in section 9.8.1 of the CSR.

Overall, of the 41 subjects who signed informed consent, 18 (43.9%) subjects reported major protocol deviations and 30 (73.2%) subjects reported minor protocol deviations. Major protocol deviations are summarized in Table 6. One subject was excluded from the PPAS due to major deviations of lack of source documentation and high volume of missing efficacy data that could have impacted the efficacy analysis.

Table 6. Summary of major protocol deviations

Classification Category	Total (N = 41) n (%)
Major protocol deviations	18 (43.9)
Efficacy criteria	2 (4.9)
Study drug administration	9 (22.0)
Study drug conditions	2 (4.9)
Laboratory assessment	1 (2.4)
Other	4 (9.8)
Protocol schedule	13 (31.7)
Study procedures	4 (9.8)
Subject study drug compliance	1 (2.4)
Visit schedule	2 (4.9)

Baseline data

The mean (SD) age for subjects included in the FAS of OD treatment arm was 10.4 (5.00) years (range: 1-17 years).

- Six (33.3%) subjects were aged ≥12 to <18 years; the mean (SD) age was 16.0 (1.55) years (range: 13-17 years).
- Nine (50.0%) subjects were aged ≥6 to <12 years; the mean (SD) age was 9.1 (2.15) years (range: 6-11 years).
- Three (16.7%) subjects were aged <6 years; the mean (SD) age was 3.0 (2.00) years (range: 1-5 years).

Of the 18 subjects included in this treatment arm, 2 (11.1%) subjects had type 1 VWD, 3 (16.7%) subjects had type 2A VWD, 2 (11.1%) subjects had type 2B VWD, and 11 (61.1%) subjects had type 3 VWD.

Numbers analysed

A total of 104 nonsurgical BEs were treated with the study drug in the 18 subjects of the OD treatment arm. These BEs were characterized as follows:

- Cause: spontaneous (33 BEs) in 13 subjects, traumatic (52 BEs) in 15 subjects, menstrual bleeding (11 BEs) in 2 subjects, and unknown cause (8 BEs) in 5 subjects.
- Severity: mild (48 BEs) in 13 subjects, moderate (31 BEs) in 13 subjects, severe (2 BEs) in 2 subjects, and unknown severity (23 BEs) in 3 subjects.

- Location: mucosal nose (25 BEs) in 7 subjects, joint (17 BEs) in 6 subjects, mucosal gum (11 BEs) in 5 subjects, muscle (7 BEs) in 4 subjects, skin (4 BEs) in 3 subjects, soft tissue (3 BEs) in 3 subjects, mucosal mouth (3 BEs) in 2 subjects, unknown (1 BE) in 1 subject, and multiple/other (33 BEs) in 13 subjects.

Outcomes and estimation

Haemostatic efficacy of OD treatment

Table 7 presents the overall treatment success for treated nonsurgical BEs in the OD treatment arm FAS. All 18 (100.0%) subjects achieved treatment success with a mean (SD) efficacy rating score of 1.01 (0.039) and a 95% CI of 81.5% to 100.0%. The mean (SD) number of treated BEs per subject was 5.8 (4.98). Of 104 treated nonsurgical BEs, 98 episodes had a known haemostatic efficacy rating, and all had an 'excellent' (97 BEs) or 'good' (1 BE) treatment outcome with a 95% CI of 96.3% to 100.0%.

Subgroup analysis by each age group (<6 years, ≥6 to <12 years, and ≥12 to <18 years) showed consistent efficacy results. All subjects achieved treatment success irrespective of age group; VWD type; and cause, severity, and location of BEs (summarized in Table 8).

Table 7. Overall treatment success for treated nonsurgical BEs (Study 071102)

Parameter Response or Statistic	Total (N=18)
Number of treated nonsurgical BEs	104
Hemostatic efficacy ratings by episode, m (%)	
1: Excellent	97 (99.0)
2: Good	1 (1.0)
3: Moderate	0
4: None	0
Not reported	6
Number of episodes per subject	
n	18
Mean (SD)	5.8 (4.98)
Median	4.0
Q1, Q3	3.0, 7.0
Min, max	1, 22
Mean efficacy rating per subject	
n	18
Mean (SD)	1.01 (0.039)
Median	1.00
Q1, Q3	1.00, 1.00
Min, max	1.0, 1.2
Number of subjects with treatment success [a]	
n (%)	18 (100)
95% CI	(81.5, 100.0)

Source: 071102 iCSR, Table 11.e.

"n" represents the number of subjects with available data, and "m" the number of BEs.

Percentages were based on BEs with known hemostatic efficacy ratings.

[a] Treatment success was defined as a mean efficacy rating score of <2.5 for a subject's study drug-treated BEs. CIs for the percentage of subjects with treatment success were 2-sided exact 95% CI, calculated using the Clopper-Pearson method.

Table 8. Haemostatic efficacy by age group, VWD type and severity of BE (Study 071102)

	N	Number of Treated Nonsurgical BEs with Efficacy Rating	Efficacy Rating n (%)
Overall	18	98	Excellent: 97 (99.0); Good: 1 (1.0)
By age group			
≥12-<18 years	6	52	Excellent: 52 (100)
≥6-<12 years	9	36	Excellent: 35 (97.2); Good: 1 (2.8)
<6 years	3	10	Excellent: 10 (100)
By VWD type			
Type 1	2	12	Excellent: 12 (100)
Type 2A	3	32	Excellent: 32 (100)
Type 2B	2	5	Excellent: 5 (100)
Type 3	11	49	Excellent: 48 (98.0); Good: 1 (2.0)
By Severity			
Minor	13	48	Excellent: 48 (100)
Moderate	13	30	Excellent: 29 (96.7); Good: 1 (3.3)
Major/severe	2	2	Excellent: 2 (100)
Unknown	3	18	Excellent: 18 (100)

Endpoints related to vonicog alfa infusions and weight-based consumption

Overall drug consumption in the OD treatment arm is summarised in Table 9. Regardless of the subjects' age group or VWD type, the majority of the nonsurgical BEs (80 of 104 [81.6%]) were treated with 1 infusion of vonicog alfa.

Twelve (12.2%) BEs were treated with 2 infusions, 4 (4.1%) BEs required 3 infusions, and 2 (2.0%) BEs required >5 infusions of vonicog alfa. The mean (SD) total dose of vonicog alfa per bleed was 64.40 (48.349) IU/kg and the average dose per infusion per bleed was 48.36 (8.079) IU/kg. These values were similar in all age groups and VWD types.

ADVATE was administered for 28 BEs in 7 subjects; all required 1 ADVATE infusion. The mean (SD) total dose of ADVATE per bleed was 30.75 (8.576) IU/kg.

The mean average and total doses of vonicog alfa and ADVATE by BE severity are summarised in Table 10. The majority of BEs of mild/moderate or unknown severity were treated with 1 infusion of vonicog alfa; the 2 severe BEs were treated with 1 or 3 infusions of vonicog alfa. The 2 BEs that required >5 infusions of vonicog alfa were both moderate of severity. ADVATE was administered for 15 mild, 12 moderate, and 1 unknown severity BEs.

Table 9. Consumption data (Study 071102)

Parameter Response or Statistic	Overall	Age Cohort		
		≥12 to <18 years	≥6 to <12 years	<6 years
Number of subjects with BE	18	6	9	3
Number of treated nonsurgical BEs	104	57	37	10
Number of actual vonicog alfa infusions per bleed, n (%) [a]				
1	80 (81.6)	44 (84.6)	28 (77.8)	8 (80.0)
2	12 (12.2)	7 (13.5)	5 (13.9)	0
3	4 (4.1)	1 (1.9)	3 (8.3)	0
>5	2 (2.0)	0	0	2 (20.0)
Missing	6	5	1	0
Number of actual ADVATE infusions per bleed, n (%) [a]				
1	28 (100)	15 (100)	9 (100)	4 (100)
Total dose per bleed for vonicog alfa (IU/kg)				
n	98	52	36	10
Mean (SD)	64.40 (48.349)	56.78 (22.629)	62.61 (32.195)	110.51 (124.704)
Median	51.03	49.76	51.94	53.01
Min, max	17.6, 365.9	17.6, 145.5	18.3, 169.8	41.2, 365.9
Missing	6	5	1	0
Average dose per infusion per bleed for vonicog alfa (IU/kg)				
n	98	52	36	10
Mean (SD)	48.36 (8.079)	48.35 (7.545)	48.06 (9.014)	49.43 (7.954)
Median	48.51	48.51	51.27	49.69
Min, max	17.6, 63.0	17.6, 59.7	18.3, 63.0	40.7, 62.4
Missing	6	5	1	0
Total dose per bleed for ADVATE (IU/kg)				
n	28	15	9	4
Mean (SD)	30.75 (8.576)	32.17 (8.804)	27.48 (9.687)	32.79 (1.508)
Median	32.94	35.41	26.11	32.94
Min, max	9.1, 45.0	18.0, 42.7	9.1, 45.0	30.8, 34.5
Average dose per infusion per bleed for ADVATE (IU/kg)	Same as the total dose			

Table 10. Consumption data by bleeding severity (Study 071102)

Parameter Response or Statistic	Severity			
	Mild	Moderate	Severe	Unknown
Number of subjects with BE	13	13	2	3
Number of treated nonsurgical BE	48	31	2	23
Number of actual vonicog alfa infusions per bleed, n (%) [a]				
1	37 (84.1)	23 (76.7)	1 (50.0)	19 (86.4)
2	6 (13.6)	4 (13.3)	0	2 (9.1)
3	1 (2.3)	1 (3.3)	1 (50.0)	1 (4.5)
>5	0	2 (6.7)	0	0
Missing	4	1	0	1
Number of actual ADVATE infusions per bleed, n (%) [a]				
1	15 (100)	12 (100)	0	1 (100)
Total dose per bleed for vonicog alfa (IU/kg)				
n	44	30	2	22
Mean (SD)	55.07 (24.772)	79.38 (75.448)	108.42 (86.797)	58.63 (24.473)
Median	50.64	53.01	108.42	48.51
Min, max	17.6, 156.7	42.7, 365.9	47.0, 169.8	46.9, 145.5
Missing	4	1	0	1
Average dose per infusion per bleed for vonicog alfa (IU/kg)				
n	44	30	2	22
Mean (SD)	46.43 (10.377)	49.96 (6.229)	51.82 (6.755)	49.71 (3.276)
Median	47.13	51.25	51.82	48.51
Min, max	17.6, 59.7	37.9, 62.4	47.0, 56.6	46.9, 63.0
Missing	4	1	0	1
Total dose per bleed for ADVATE (IU/kg)				
n	15	12	0	1
Mean (SD)	27.60 (9.383)	34.23 (6.240)	- (-)	36.32 (-)
Median	26.11	34.63	-	36.32
Min, max	9.1, 42.7	18.0, 45.0	-, -	36.3, 36.3
Average dose per infusion per bleed for ADVATE (IU/kg)	Same as the total dose			

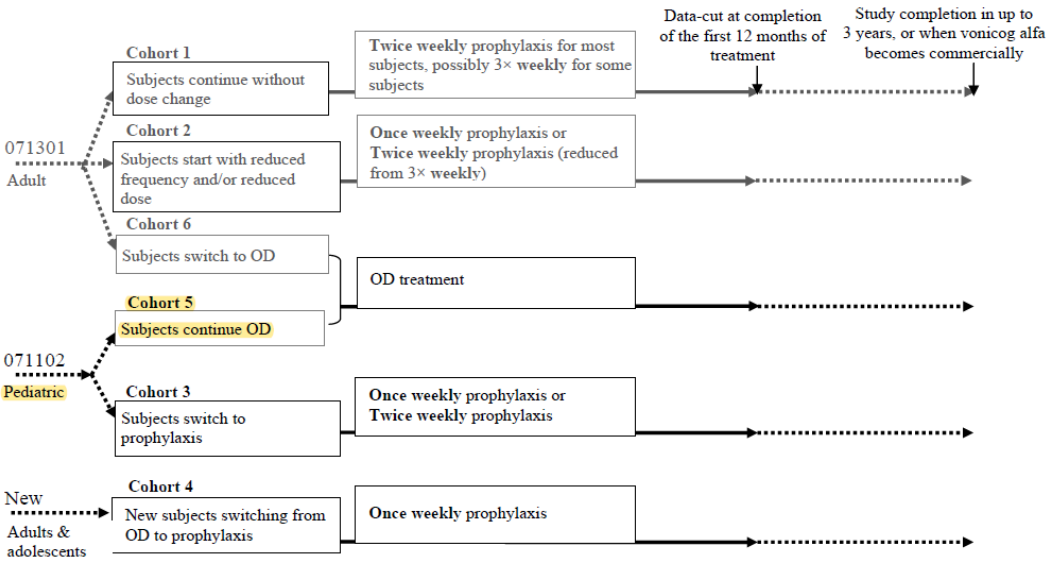
Study SHP677-304

A Phase 3b, prospective, open-label, uncontrolled, multicenter study on long-term safety and efficacy of rVWF in paediatric and adult subjects with severe von Willebrand disease (VWD).

Methods

Study SHP677-304 is a phase 3b, prospective, open-label, uncontrolled, non-randomized, multicentre study evaluating long-term safety and efficacy of vonicog alfa for prophylaxis and OD treatment of BEs in paediatric and adult subjects with severe VWD. The prophylactic and OD treatment cohorts of this study are illustrated in Figure 4. To support the current variation request, the MAH submitted an interim analysis of data obtained in Cohort 5 of this study which includes paediatric subjects transitioning from Study 071102 who continued receiving OD treatment in this continuation study (DCO date of 26 January 2024).

Figure 4. Overall design of Study SHP677-304



The minimum observation time was 12 months. After this initial 12-month period, subjects could continue to be enrolled in the study until vonicog alfa was commercially available in their respective countries, or until subjects had been treated in the study for a maximum of 3 years, whichever occurred first.

Study participants

See Study 071102.

Treatments

See Study 071102.

Outcomes/endpoints

The primary endpoint of Study SHP677-304 (spontaneous annualized bleeding rate(ABR) during prophylactic treatment) relates to the efficacy of prophylaxis and was therefore not included in the submitted interim analysis supporting OD treatment in paediatric subjects. The secondary endpoints relating to efficacy of paediatric OD treatment are as follows:

- Overall haemostatic efficacy rating at the resolution of bleed with respect to the treatment of BEs for the initial 12 months on-study treatment.
- Number of infusions of vonicog alfa and ADVATE utilized to treat BEs while enrolled in the study.
- Weight-adjusted consumption of vonicog alfa and ADVATE per BE while enrolled in the study.

Sample size

Sample size was not based on a power calculation for a significance test. No formal statistical tests were planned in the study. The number of subjects was driven by practical considerations and EMA

Guideline on Clinical Investigation of Human Plasma Derived von Willebrand Factor Products (CPMP/BPWG/220/02).

Randomisation

Not applicable as this is a single arm study.

Blinding (masking)

Not applicable as this is an open label study.

Statistical methods

No statistical hypothesis testing was done in this study. The analysis set for efficacy was the FAS, which consisted of all subjects who satisfied all entry criteria and received any amount of vonicog alfa for the treatment of nonsurgical bleeding episodes (i.e. subjects comprising Cohort 5).

Results

Participant flow

A total of 19 subjects transitioned from Study 071102 into the OD treatment cohort (Cohort 5). Three subjects were not dosed and were not included in the FAS of the presented interim analysis. Sixteen subjects from Cohort 5 received OD treatment and were included in the FAS. As of the cut-off date of 26 January 2024, 14 (87.5%) of the 16 OD Cohort 5 subjects have completed the study and 2 (12.5%) subjects are still on study.

Table 11. Subject disposition (Study SHP677-304) by paediatric OD Cohort 5 and age group

	Pediatric (<6 years) n (%)	Pediatric (≥6 to <12 years) n (%)	Pediatric (≥12 to ≤18 years) n (%)	Total n (%)
All enrolled set	3	6	10	19
Not yet dosed	0	1	2	3
Screen failures	0	0	0	0
SAF	3 (100)	5 (100)	8 (100)	16 (100)
FAS	3 (100)	5 (100)	8 (100)	16 (100)
Received at least 1 dose of vonicog alfa	3 (100)	5 (100)	8 (100)	16 (100)
Received at least 1 dose of ADVATE	1 (33.3)	2 (40.0)	5 (62.5)	8 (50.0)
Completed study	3 (100)	4 (80.0)	7 (87.5)	14 (87.5)
Still on study	0	1 (20.0)	1 (12.5)	2 (12.5)
Discontinued study	0	0	0	0

Source: SHP677-304 iCSR (Pediatric subjects), Table 10.b.

The percentage of subjects is relative to the number of subjects in the SAF.

The ENR includes subjects who signed informed consent. Not yet dosed row includes subjects who enrolled in this study but did not receive vonicog alfa because they did not need treatment for BEs or management of surgical bleeding.

Recruitment

Between 01 April 2019 (i.e. the date the first subject signed informed consent form) and 26 January 2024 (i.e. the DCO of the presented analysis), a total of 19 subjects transitioned from Study 071102 into the OD treatment cohort of Study SHP677-304.

Conduct of the study

The original study protocol dated 29 August 2018 was amended 4 times, as summarized in 9.8.1 of the CSR.

Up to the cut-off date of the presented interim analysis, there was 1 critical deviation and 26 major protocol deviations reported in 10 subjects in Cohort 5. The critical deviation refers to an injection of expired study drug (administration 2 days after the expiry date) without identified safety issues. Major protocol deviations involved deviations in study drug compliance (13 events in 6 [37.5%] subjects); study procedures criteria (10 events in 6 [37.5%] subjects); and informed consent criteria, laboratory assessment criteria and SAE criteria (1 event each in 1 [6.3%] subject). Four major protocol deviations in study procedures criteria occurred due to COVID-19.

Baseline data

The mean (SD) age of subjects included in the OD Cohort 5 was 10.4 (5.40) years (range: 2-18 years); 3 subjects were aged <6 years, 5 subjects were aged ≥6 to <12 years, and 8 subjects were aged ≥12 to ≤ 18 years. In this cohort, 4 (25.0%) subjects had type 1 VWD, 1 (6.3%) subject had type 2A VWD, 3 (18.8%) subjects had type 2B VWD, and 8 (50.0%) subjects had type 3 VWD.

Numbers analysed

As of the DCO date for the presented interim analysis, a total of 164 BEs treated with vonicog alfa occurred in the 16 (100%) subjects who transitioned from Study 071102 and continued to receive OD treatment in Study SHP677-304.

Table 12. Treated BEs (Study SHP677-304) by paediatric OD Cohort 5 and age group

Characteristics	Pediatric (<6 years) (N=3)	Pediatric (≥6 to <12 years) (N=5)	Pediatric (≥12 to ≤18 years) (N=8)	Total (N=16)
Total number of subjects with BEs	3	5	8	16
Total number of BEs	35	46	83	164
Cause of BE, n (%)				
Spontaneous [a]	1 (2.9)	17 (37.0)	54 (65.1)	72 (43.9)
Injury	34 (97.1)	26 (56.5)	23 (27.7)	83 (50.6)
Menstrual bleeding	0	0	5 (6.0)	5 (3.0)
Missing	-	3 (6.5)	1 (1.2)	4 (2.4)
Location of BE, n (%)				
Skin	15 (42.9)	3 (6.5)	3 (3.6)	21 (12.8)
Venipuncture site	0	0	0	0
Muscle	2 (5.7)	0	7 (8.4)	9 (5.5)
Soft tissue	2 (5.7)	10 (21.7)	1 (1.2)	13 (7.9)
Mucosal, nasal	0	4 (8.7)	38 (45.8)	42 (25.6)
Mucosal, oral	1 (2.9)	22 (47.8)	5 (6.0)	28 (17.1)
Joint	6 (17.1)	13 (28.3)	16 (19.3)	35 (21.3)
Body cavity	3 (8.6)	1 (2.2)	0	4 (2.4)
Hematuria	0	0	1 (1.2)	1 (0.6)
Gastrointestinal	0	0	0	0
Central nervous system	3 (8.6)	0	0	3 (1.8)
Menstrual/heavy menstrual	0	0	9 (10.8)	9 (5.5)
Other	20 (57.1)	18 (39.1)	10 (12.0)	48 (29.3)
Severity, n (%)				
Mild	25 (71.4)	24 (52.2)	41 (49.4)	90 (54.9)
Moderate	10 (28.6)	20 (43.5)	36 (43.4)	66 (40.2)
Severe/major	0	1 (2.2)	4 (4.8)	5 (3.0)
Missing	-	1 (2.2)	2 (2.4)	3 (1.8)

Outcomes and estimation

Haemostatic efficacy of OD treatment

The overall haemostatic efficacy rating for the treated BEs was "Excellent" in 160 (97.6%) BEs, "Good" in 2 (1.2%) BEs, and was missing in 2 (1.2%) BEs. No significant differences were observed across age groups.

Table 13. Haemostatic efficacy (Study SHP677-304) by paediatric OD Cohort 5 and age group

Characteristics	Pediatric (<6 years) (N=3)	Pediatric (≥6 to <12 years) (N=5)	Pediatric (≥12 to ≤18 years) (N=8)	Total (N=16)
Efficacy rating [n (%)][a]				
Excellent	34 (97.1)	44 (95.7)	82 (98.8)	160 (97.6)
Good	1 (2.9)	1 (2.2)	0	2 (1.2)
Fair	0	0	0	0
None	0	0	0	0
Missing	0	1 (2.2)	1 (1.2)	2 (1.2)

Endpoints related to vonicog alfa infusions and weight-based consumption

Overall drug consumption is presented in Table 14. As of the DCO date for the presented interim analysis, a mean (SD) of 1.1 (0.36) and a median (min, max) of 1.0 (1.0, 5.0) vonicog alfa infusions were used per BE, with a mean (SD) total of 53.43 (19.88) IU/kg infused per bleed. Seven (43.8%) subjects had a total of 43 BEs treated with ADVATE in addition to vonicog alfa. A mean (SD) of 1 (0.15) ADVATE infusion was used per BE, with a mean total (SD) of 37.42 (6.45) IU/kg infused per bleed.

Table 14. Consumption data (Study SHP677-304) by paediatric OD Cohort 5 and age group

Characteristics	Pediatric (<6 years) (N=3)	Pediatric (≥6 to <12 years) (N=5)	Pediatric (≥12 to ≤18 years) (N=8)	Total (N=16)
Number of vonicog alfa Infusions to Treat BE [b]				
n	35	46	83	164
Mean (SD)	1.0 (0.17)	1.0 (0.15)	1.1 (0.48)	1.1 (0.36)
95% CI [c]	1.0, 1.1	1.0, 1.1	1.0, 1.2	1.0, 1.1
Median	1.0	1.0	1.0	1.0
Min, max	1, 2	1, 2	1, 5	1, 5
Number of subjects with ADVATE-treated bleeds	1 (33.3)	1 (20.0)	5 (62.5)	7 (43.8)
Number of ADVATE infusions to treat BE [b]				
n	1	1	41	43
Mean (SD)	1.0 (-)	1.0 (-)	1.0 (0.16)	1.0 (0.15)
95% CI [c]	-, -	-, -	1.0, 1.1	1.0, 1.1
Median	1.0	1.0	1.0	1.0
Min, max	1, 1	1, 1	1, 2	1, 2
Total vonicog alfa infused per bleed (IU/kg) [b]				
n	33	46	83	162
Mean (SD)	56.35 (15.03)	50.72 (10.65)	53.78 (24.85)	53.43 (19.88)
95% CI [b]	51.01, 61.68	47.56, 53.88	48.35, 59.20	50.35, 56.52
Median	53.33	47.62	50.22	49.72
Min, max	46.15, 98.63	38.71, 96.50	5.07, 250.30	5.07, 250.30
Total ADVATE infused per bleed (IU/kg) [b]				
n	1	1	41	43
Mean (SD)	35.85 (-)	47.98 (-)	37.21 (6.39)	37.42 (6.45)
95% CI [c]	-, -	-, -	35.19, 39.22	35.44, 39.41
Median	35.85	47.98	37.04	37.04
Min, max	35.85, 35.85	47.98, 47.98	20.62, 70.26	20.62, 70.26

Ancillary analyses

Exposure-response analysis

ER analysis of efficacy:

The population PK/PD models were used to predict the levels of VWF:RCo and FVIII:C at the start and end of each BE by taking into account the actual number of doses, and dose (IU/kg) of vonicog alfa and ADVATE for each BE.

At the end of BE treatment, the model predicted an increase in both VWF:RCo and FVIII:C levels as compared to BE start. At the end of BE treatment, the median (range) levels for VWF:RCo were 52.8 (0.501, 153), 46 (0.500, 114) and 35.6 (9.17, 97.8) IU/dL; and for FVIII:C were 74.5 (3.88, 176), 36.3 (3.15, 124) and 25.9 (3.57, 78.6) IU/dL, for paediatric subjects aged 12 to <18 years, 6 to <12 years and <6 years, respectively. By the end of BE treatment, all subjects achieved targeted exposure levels of VWF and FVIII needed to achieve bleeding control, corresponding to the clinical efficacy ratings (all excellent except for 1 subject, and good for 1 subject).

Summary of main studies

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

Table 15. Summary of efficacy for trial 071102

Title: A Phase 3, prospective, multicenter, uncontrolled, open-label clinical study to determine the efficacy, safety, and tolerability of rVWF with or without ADVATE in the treatment and control of bleeding episodes, the efficacy and safety of rVWF in elective and emergency surgeries, and the pharmacokinetics (PK) of rVWF in children diagnosed with severe von Willebrand disease	
Study identifier	071102; EudraCT Number: 2016-001477-33

Design	This is an ongoing, phase 3, open-label, uncontrolled, multicenter study designed to evaluate the efficacy, safety, and tolerability of vonicog alfa with or without ADVATE in the treatment and control of nonsurgical BEs and bleeding associated with elective and emergency surgeries, as well as the PK of vonicog alfa in paediatric subjects with severe VWD. The study consists of 3 treatment arms: on-demand (OD), elective surgery, and emergency surgery. Subjects in the OD treatment arm received vonicog alfa treatment for nonsurgical BEs over a 12-month period (up to 18 months for some subjects who were waiting to enter the continuation study [SHP677304]). Vonicog alfa was to be evaluated for haemostatic efficacy and safety in at least 24 subjects for OD treatment of BEs and at least 10 subjects undergoing elective or emergency surgery/a surgical procedure/an invasive procedure, including oral/dental procedures. The PK of vonicog alfa was assessed in paediatric subjects following an infusion of 50 ± 5 IU/kg von Willebrand factor (VWF): ristocetin cofactor (RCo). Sparse sampling approach was taken to reduce the burden of frequent blood sampling on the paediatric subjects, with only 3 post-infusion PK blood draws collected per subject. Any bleeding episodes requiring replacement therapy with VWF concentrate to control bleeding were to be treated with vonicog alfa with or without ADVATE. The dose was to be determined according to the bleeding type and severity, and it was to be adjusted based on the subject's clinical response. Paediatric subjects undergoing a minor or major surgical/invasive procedure were treated with vonicog alfa both preoperatively and postoperatively, as needed. After completing the study, subjects had the option to rollover into Continuation Study SHP677304 during where they could continue receiving OD treatment with vonicog alfa. This summary of efficacy provides results only for subjects who received OD therapy.	
	Duration of main phase: Duration of run-in phase: Duration of extension phase:	12 to 18 months Not applicable Not applicable
Hypothesis	No formal hypothesis testing was performed.	
Treatment groups	**OD treatment of nonsurgical BEs** Paediatric subjects with a diagnosis of severe VWD (defined as VWF:RCo <20%). Including previously untreated subjects who had not received VWF replacement and previously treated subjects who were unable to tolerate or were inadequately responsive to DDAVP, and had a minimum of 1 documented bleed requiring VWF coagulation factor replacement therapy during the previous 12 months prior to enrolment, and overall, 3 or more exposure days historically to VWF replacement therapy.	An initial dose of 40 to 60 IU/kg vonicog alfa was to be infused, along with 30 to 45 IU/kg ADVATE unless the subject had a haemostatically effective baseline FVIII level. In case of major BEs, a dose of vonicog alfa up to 80 IU/kg could be used. Subsequent doses were to be administered every 8 to 24 hours, with or without additional ADVATE, in order to maintain VWF:RCo and FVIII levels for as long as deemed necessary by the investigator. Number of subjects enrolled who received any infusion of study drug: 25 Number of subjects enrolled who met all eligibility criteria, had received any amount of study drug, and had provided at least 1 haemostatic assessment within 24 hours of a study drug infusion with or without ADVATE: 18

Endpoints and definitions	Primary endpoint	Treatment success	Number and percentage of paediatric subjects with treatment success for vonicog alfa-treated nonsurgical BEs (using a 4point scale). BE treatment success was defined as a mean efficacy rating score of <2.5. If a subject experienced only 1 study drug-treated BE, the rating score for the single bleed was used to determine treatment success. The individual haemostatic efficacy rating for each bleed was assigned scores as follows: Excellent = 1, Good = 2, Moderate = 3, and None = 4. A point estimate and corresponding 2-sided exact 95% CIs for the proportion of subjects with treatment success were calculated using the Clopper-Pearson method.
	Secondary endpoint	BEs with an efficacy rating of "excellent" or "good"	Number and percent of treated nonsurgical BEs with efficacy rating of "excellent" or "good" for OD treatment arm, presented overall and repeated by age cohort and VWD type.
	Secondary endpoint	Drug consumption	Number of infusions, vonicog alfa units, and ADVATE units (if needed), per BE.
Database lock	01 December 2023 (interim analysis cutoff date)		

Results and Analysis

Analysis description	**Primary Efficacy Analysis**								
Analysis population	FAS: All subjects who signed an informed consent form, were enrolled, met all inclusion and none of the exclusion criteria, had received any amount of study drug, and had provided at least 1 haemostatic assessment within 24 hours of a study drug infusion with or without ADVATE.								
Descriptive statistics and estimated variability	Treatment group	OD treatment							
		Age groups (years)			VWD types/subtypes				Overall
		<6	≥6-<12	≥12-<18	1	2A	2B	3	
	Number of subjects with treated BEs [a]	3	9	6	2	3	2	11	18
	Number of treated nonsurgical BEs [a]	10	37	57	12	37	5	50	104
	Treatment success								
	Number of subjects with treatment success, n (%) (95% CI)	3 (100.0) (29.2, 100.0)	9 (100.0) (66.4, 100.0)	6 (100.0) (54.1, 100.0)	2 (100.0) (15.8, 100.0)	3 (100.0) (29.2, 100.0)	2 (100.0) (15.8, 100.0)	11 (100.0) (71.5, 100.0)	18 (100.0) (81.5, 100.0)

Analysis description	**Secondary Efficacy Analysis**								
Descriptive statistics and estimated variability	Treatment group	OD treatment							
		Age groups (years)			VWD types/subtypes				Overall
		<6	≥6-<12	≥12-<18	1	2A	2B	3	
	BEs with an efficacy rating of "excellent" or "good"								
	Number of treated nonsurgical BEs with known efficacy rating	10	36	52	12	32	5	49	98
	Number of treated nonsurgical BEs with an efficacy rating of excellent/ good, n (%) (95% CI)	10 (100.0) (69.2, 100.0)	36 (100.0) (90.3, 100.0)	52 (100.0) (93.2, 100.0)	12 (100.0) (73.5, 100.0)	32 (100.0) (89.1, 100.0)	5 (100.0) (47.8, 100.0)	49 (100.0) (92.7, 100.0)	98 (100.0) (96.3, 100.0)
	Drug consumption								
	Number of vonicog alfa infusions per BE, n (%)								
	1	8 (80.0)	28 (77.8)	44 (84.6)	9 (75.0)	31 (88.6)	4 (80.0)	36 (78.3)	80 (81.6)
	2	0	5 (13.9)	7 (13.5)	2 (16.7)	3 (8.6)	0	7 (15.2)	12 (12.2)
	3	0	3 (8.3)	1 (1.9)	1 (8.3)	1 (2.9)	1 (20.0)	1 (2.2)	4 (4.1)
	>5	2 (20.0)	0	0	0	0	0	2 (4.3)	2 (2.0)
	Missing	0	1	5	0	2	0	4	6
	Number of ADVATE infusions per ADVATE-treated BE, n (%)								
	1	4 (100.0)	9 (100.0)	15 (100.0)	7 (100)	0	0	21 (100)	28 (100.0)
	Total vonicog alfa dose per bleed (IU/kg)								
	Mean (SD)	110.51 (124.704)	62.61 (32.195)	56.78 (22.629)	66.89 (36.742)	55.12 (22.082)	76.66 (52.164)	69.49 (63.141)	64.40 (48.349)
	Average vonicog alfa dose per infusion per bleed (IU/kg)								

	Mean (SD)	49.43 (7.954)	48.06 (9.014)	48.35 (7.545)	49.59 (10.608)	48.16 (6.536)	54.02 (3.540)	47.57 (8.669)	48.36 (8.079)
	Total ADVATE dose per bleed (IU/kg)								
	Mean (SD)	32.79 (1.508)	27.48 (9.687)	32.17 (8.804)	24.73 (8.032)	- (-)	- (-)	32.76 (7.938)	30.75 (8.576)
	Average ADVATE dose per infusion per bleed (IU/kg)								
	Same as the total dose								
Effect estimate per comparison	Not applicable; efficacy analyses were descriptive only.								
Notes	A total of 24 subjects completed the study after a treatment period of approximately 12 to 17 months. One subject in the OD treatment arm discontinued the study per physician decision (to start prophylaxis) 319 days after the baseline PK dose of vonicog alfa (last dose was received on Day 313). The primary endpoint analysis was repeated for the PPAS with one subject in FAS excluded; similar results were observed.								

BE: bleeding episode; DDAVP: desmopressin; FAS: full analysis set; FVIII: factor VIII; OD: on demand; PPAS: per protocol analysis set; RCo: ristocetin cofactor; rFVIII: recombinant factor VIII; rVWF: recombinant von Willebrand factor; VWD: von Willebrand disease; VWF: von Willebrand factor; VWF:RCo: von Willebrand factor ristocetin cofactor

Table 16. Summary of efficacy for Study SHP677-304

Title: A Phase 3b, prospective, open label, uncontrolled, multicenter study on long-term safety and efficacy of rVWF in paediatric and adult subjects with severe von Willebrand disease	
Study identifier	SHP677-304; EudraCT Number: 2018-003453-16
Design	This is a phase 3b, prospective, open-label, uncontrolled, nonrandomized, multicenter study evaluating long-term safety and efficacy of vonicog alfa for prophylaxis and OD treatment of BEs in paediatric and adult subjects with severe VWD. The study includes 6 cohorts in total: 4 prophylactic treatment cohorts and 2 on-demand (OD) treatment cohorts. However, only 1 of the cohorts (Cohort 5) is relevant for the efficacy analyses of OD treatment in paediatric subjects, included in the current application. This cohort include paediatric subjects rolled over from Study 071102 who continued receiving OD treatment in this continuation study. The minimum observation time for this study was 12 months. After this initial 12-month period, subjects could continue to be enrolled in the study until vonicog alfa was commercially available in their respective countries, or until subjects had been treated in the study for a maximum of 3 years, whichever occurred first. Any BE requiring treatment with VWF concentrate was to be treated with vonicog alfa, with or without ADVATE. Dose was determined based on bleeding type and severity and adjusted based on the subject's clinical response.
	Duration of main phase: Minimum 12 months; maximum 3 years Duration of run-in phase: Not applicable

	Duration of extension phase: Not applicable		
Hypothesis	Descriptive statistics only		
Treatment groups	**Cohort 5** Paediatric subjects of all ages from Study 071102 who continued receiving OD treatment in this continuation study		In general, an initial dose of 40 to 60 IU/kg vonicog alfa, with or without ADVATE was recommended. In cases of major BE, a dose of up to 80 IU/kg vonicog alfa could be infused. If necessary, subsequent doses of 40 to 60 IU/kg vonicog alfa could be administered every 8 to 24 hours with or without ADVATE for as long as deemed necessary by the investigator. Number of subjects enrolled in Cohort 5 (rollover over from 071102): 19 Number of subjects who received OD treatment of BEs: 16
Endpoints and definitions related to the OD treatment of BEs	Primary endpoint	Spontaneous annualized bleeding rate during prophylaxis treatment with vonicog alfa over 12 months	The primary endpoint will not be described in this summary of efficacy results as it is not relevant for the efficacy analyses of OD treatment in paediatric subjects.
	Secondary endpoint	Haemostatic efficacy rating for OD treatment of BEs	Overall haemostatic efficacy rating (defined as in Study 071102) at the resolution of bleed with respect to the treatment of BEs for the initial 12 months on study treatment. Rating was assessed by investigator per Efficacy Rating Scale in the protocol.
		Drug consumption	Number of infusions of vonicog alfa and ADVATE utilized for OD treatment of BEs. Weight-adjusted dose of vonicog alfa and ADVATE for OD treatment of BEs.
Database lock	26 January 2024 (interim analysis cutoff date)		

Results and Analysis

Analysis description	**Secondary Efficacy Analysis**				
Analysis population and time point description	FAS: all subjects who satisfied all entry criteria and received any amount of study drug. The data presented in the current application are for the subjects from the FAS belonging to Cohort 5 because these were the paediatric subjects who received OD treatment with vonicog alfa. Similarly, the primary endpoint and other secondary endpoints are not described if they are not relevant for the efficacy analyses of OD treatment in paediatric subjects. The haemostatic efficacy ratings were analysed based on the first 12 months and the entire study period. The number of infusions and consumption of vonicog alfa and ADVATE were analysed based on the entire study period.				
Descriptive statistics and estimated variability	Treatment group	Cohort 5			
		Age groups (years)			Overall
		<6	≥6-<12	≥12-<18	

	Number of subjects with treated BEs [a]	3	5	8	16
	Number of treated BEs [a]	35	46	83	164
	Number of subjects with ADVATE -treated BEs	1	1	5	7
	Number of ADVATE-treated BEs	1	1	41	43
	Efficacy rating [n (%)]				
	Excellent	34 (97.1)	44 (95.7)	82 (98.8)	160 (97.6)
	Good	1 (2.9)	1 (2.2)	0	2 (1.2)
	Fair	0	0	0	0
	None	0	0	0	0
	Missing	0	1 (2.2)	1 (1.2)	2 (1.2)
	Number of Infusions				
	Number of vonicog alfa infusions per BE				
	Mean (SD)	1.0 (0.17)	1.0 (0.15)	1.1 (0.48)	1.1 (0.36)
	Number of ADVATE infusions per BE				
	Mean (SD)	1.0 (-)	1.0 (-)	1.0 (0.16)	1.0 (0.15)
	Consumption				
	Total vonicog alfa infused per bleed (IU/kg)				
	Mean (SD)	56.35 (15.03)	50.72 (10.65)	53.78 (24.85)	53.43 (19.88)
	Total ADVATE infused per bleed (IU/kg)				
	Mean (SD)	35.85 (-)	47.98 (-)	37.21 (6.39)	37.42 (6.45)
Effect estimate per comparison	Not applicable; efficacy analyses were descriptive only.				
Notes	As of the interim analysis cutoff date, none of the 16 OD Cohort 5 subjects included in the FAS had discontinued the study. 14 (87.5%) subjects have completed the study, and 2 (12.5%) subjects are still on study. For these subjects, the study participation period ranged from 421 to 1163 days.				

BE: bleeding episode; FAS: full analysis set; OD: on demand; rVIII: recombinant factor VIII; rVWF: recombinant von Willebrand factor; VWD: von Willebrand disease; VWF: von Willebrand factor

[a] Treated BEs include all BEs treated with vonicog alfa, with or without ADVATE.

Analysis performed across trials (pooled analyses and meta-analysis)

Integrated efficacy analysis: Studies 071102/SHP677-304

For subjects who completed Study 071102 and entered Study SHP677-304, the MAH performed an integrated analysis of efficacy and safety combining data across both studies from the subset of paediatric subjects who received OD treatment with vonicog alfa any time from Day 1 in Study

071102 through the DCO dates for each study (01 December 2023 for Study 071102 and 26 January 2024 for Study SHP677-304).

The integrated analyses of efficacy included the following endpoints:

- Haemostatic efficacy defined by the number and percentage (with corresponding 95% CI) of paediatric subjects with treatment success for treated nonsurgical BEs.
- Number and percentage (with corresponding 95% CI) of treated nonsurgical BE with efficacy rating of 'excellent' or 'good' for OD arm.
- Characteristics of nonsurgical BE treated with vonicog alfa by bleeding location, cause and severity, respectively. Such characteristics include haemostatic efficacy at resolution of bleed; total number and weight-adjusted dose of vonicog alfa and ADVATE, respectively; as well as average dose of vonicog alfa and ADVATE, respectively, per BE.
- Other BE information, including number and percent of subjects having any treated BE as well as total number of BE, location of bleed, cause of bleed, and severity of bleed.

Analysis set:

The OD FAS included 21 paediatric subjects initially enrolled in Study 071102 who received OD treatment with the study drug in either Study 071102 (OD treatment arm) or SHP677-304 (OD Cohort 5) or both and had at least 1 efficacy rating scale assessment available. Overall, 2 subjects of the OD FAS are still ongoing in the continuation study as of the DCO, 1 subject of OD FAS discontinued the Study 071102, and 1 rollover subject of OD FAS who completed 071102 withdrew from Study SHP677-304 without being dosed in this continuation study. Subject disposition across the two studies is summarized in the Table 17.

Table 17. Subject disposition (integrated analysis of Study 071102 and SHP677-304)

Characteristic	Study 071102 OD Cohort (N=25) n (%)	Study SHP677-304 [a] Cohort 5 (N=16) n (%)	Overall OD (N=25) n (%)
Allocated to analysis set, n (%)			
SAF	25 (100)	16 (100)	25 (100)
OD FAS	18 (72.0)	16 (100)	21 (84.0)
Completed study	24 (96.0)	14 (87.5)	20 (80.0)
Still on study [b]	0	2 (12.5)	3 (12.0)
Discontinued [c]	1 (4.0)	0	2 (8.0)
Primary reason for discontinuation			
Physician decision	1 (4.0)	0	1 (4.0)
Withdrawal by subject	0	0	1 (4.0) [c]

[a] Only including pediatric subjects who received OD treatment.

[b] One subject completed Study 071102, enrolled in Study SHP677-304 but was not treated during Study SHP677-304 as DCO of 26 January 2024. This subject was not included in the SAF in Study SHP677-304 but included in the SAF in ISS (Study 071102/SHP677-304) for being treated during Study 071102 and was only summarized in the last Overall column for the still on study.

[c] One subject completed Study 071102, enrolled in Study SHP677-304 but discontinued without being dosed in Study SHP677-304 (withdrawal by subject) and was not included in Study SHP677-304 safety population. This subject was only summarized in the last overall column for the discontinuations.

Out of the 21 subjects in the OD FAS:

- Five (23.8%) subjects were aged <6 years (2 subjects were aged 1 year, 2 subjects were aged 3 years, and 1 subject was aged 5 years).
- Nine (42.9%) subjects were aged ≥6 to <12 years.
- Seven (33.3%) subjects were aged ≥12 to <18 years.

The mean (SD) age at study entry was 9.9 (5.44) years (range: 1-17 years). Most subjects were White, not Hispanic or Latino, and resided in the Europe. The number of males and females was approximately the same. Of these 21 subjects, 4 (19%) had type 1 VWD, 6 (28.6%) had type 2, and 11 (52.4%) had type 3 VWD.

Haemostatic efficacy of OD treatment

A total of 268 nonsurgical BEs were treated with the study drug in the 21 subjects of the OD FAS (n=47 in the 5 subjects aged <6 years, n=132 in the 9 subjects aged ≥6 to <12 years, n=89 in the 7 subjects aged ≥12 to <18 years). These BEs were characterized as follows

- Severity: minor (138 BEs), moderate (97 BEs), severe/major (7 BEs), and unknown severity (26 BEs).
- Cause: injury (135 BEs), spontaneous (105 BEs), menstrual bleeding (16 BEs), and unknown cause (12 BEs).
- Location: mucosal (110 BEs), joint (54 BEs), skin (25 BEs), menstrual (21 BEs), muscle (18 BEs), soft tissue (18 BEs), central nervous system (5 BEs), body cavity (4 BEs), haematuria (1 BE), unknown (1 BE), and other (65 BEs).

The treatment success for subjects with treated nonsurgical BEs in the OD FAS is summarised in Table 18.

Table 18. Treatment success (integrated analysis of Study 071102 and SHP677-304)

Parameter Response or statistic	Overall (N=21)
Number of treated nonsurgical BEs, n	268
Number of treated nonsurgical BEs with known hemostatic efficacy rating, n	260
Number of treated nonsurgical BEs with excellent or good treatment outcome [a,b]	
n (%)	260 (100)
95% CI	[98.6, 100.0]
Hemostatic efficacy ratings by episode, n (%)	
1: Excellent	256 (95.5)
2: Good	4 (1.5)
3: Moderate	0
4: None	0
Missing	8 (3.0)
Number of episodes per subject	
n	21
Mean (SD)	12.8 (11.28)
Median	9.0
Min, max	2.0, 44.0
Mean efficacy rating per subject	
n	21
Mean (SD)	1.0 (0.06)
Median	1.0
Min, max	0.8, 1.1
Number of subjects with treatment success	
n (%)	21 (100)
95% CI	83.9, 100.0

Regardless of the subjects' age group, VWD type, or severity of BEs, the majority of the nonsurgical BEs (237 [88.4%]) were treated with 1 infusion of vonicog alfa. Eighteen (6.7%) BEs were treated with 2 infusions, 4 (1.5%) BEs required 3 infusions, 1 (0.4%) BE required 5 infusions, and 2 (0.7%) BEs required >5 infusions of vonicog alfa. The mean (SD) total dose of vonicog alfa per bleed was 57.6 (33.90) IU/kg, and the mean (SD) average dose per infusion per bleed was 49.7 (8.83) IU/kg (Table 19).

ADVATE was administered in 10 subjects, in addition to vonicog alfa, for 71 BEs; all but 1 required 1 infusion. The mean (SD) total dose of ADVATE per bleed for was 34.8 (8.01) IU/kg (Table 19).

Table 19. Efficacy outcome (integrated analysis of Study 071102 and SHP677-304) by age groups

Parameter	Age group <6 years					Age group ≥6 to <12 years					Age group ≥12 to <18 years				
		Severity					Severity					Severity			
Response or statistic	Minor	Moderate	Severe/Major	Unknown	All	Minor	Moderate	Severe/Major	Unknown	All	Minor	Moderate	Severe/Major	Unknown	All
Number of treated nonsurgical BEs	27	20	0	0	47	81	45	2	4	132	30	32	5	22	89
Vonicog alfa infusions per bleed															
Mean (SD)	1.0 (0)	1.8 (2.31)	-	-	1.3 (1.54)	1.1 (0.31)	1.1 (0.40)	2.0 (1.41)	1.0 (0)	1.1 (0.38)	1.1 (0.32)	1.1 (0.36)	2.0 (1.73)	1.2 (0.51)	1.2 (0.54)
Median	1.0	1.0	-	-	1.0	1.0	1.0	2.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Min, max	1.0, 1.0	1.0, 9.0	-	-	1.0, 9.0	1.0, 3.0	1.0, 3.0	1.0, 3.0	1.0, 1.0	1.0, 3.0	1.0, 2.0	1.0, 2.0	1.0, 5.0	1.0, 3.0	1.0, 5.0
Number of actual vonicog alfa infusions per bleed, n (%) *															
1	27 (100.0)	17 (85.0)	-	-	44 (93.6)	75 (92.6)	40 (88.9)	1 (50.0)	4 (100)	120 (90.9)	24 (80.0)	28 (87.5)	3 (60.0)	18 (81.8)	73 (82.0)
2	0	1 (5.0)	-	-	1 (2.1)	4 (4.9)	4 (8.9)	0	0	8 (6.1)	3 (10.0)	3 (9.4)	1 (20.0)	2 (9.1)	9 (10.1)
3	0	0	-	-	0	1 (1.2)	1 (2.2)	1 (50.0)	0	3 (2.3)	0	0	0	1 (4.5)	1 (1.1)
4	0	0	-	-	0	0	0	0	0	0	0	0	0	0	0
5	0	0	-	-	0	0	0	0	0	0	0	0	1 (20.0)	0	1 (1.1)
>5	0	2 (10.0)	-	-	2 (4.3)	0	0	0	0	0	0	0	0	0	0
Missing	0	0	-	-	0	1 (1.2)	0	0	0	1 (0.8)	3 (10.0)	1 (3.1)	0	1 (4.5)	5 (5.6)
Hemostatic efficacy ratings by episode *															
1: Excellent	27 (100)	19 (95.0)	-	-	46 (97.9)	81 (100)	42 (93.3)	2 (100)	2 (50.0)	127 (96.2)	30 (100.0)	31 (96.9)	5 (100.0)	17 (77.3)	83 (93.3)
2: Good	0	1 (5.0)	-	-	1 (2.1)	0	3 (6.7)	0	0	3 (2.3)	0	0	0	0	0
3: Moderate	0	0	-	-	0	0	0	0	0	0	0	0	0	0	0
4: Nine	0	0	-	-	0	0	0	0	0	0	0	0	0	0	0
Missing	0	0	-	-	0	0	0	0	2 (50.0)	2 (1.5)	0	1 (3.1)	0	5 (22.7)	6 (6.7)
Total dose per bleed for vonicog alfa (IU/kg)															
n	26	19	-	-	45	80	45	2	4	131	27	31	5	21	84
Mean (SD)	54.6 (14.77)	83.7 (93.43)	-	-	68.0 (62.27)	53.0 (17.29)	54.3 (18.15)	110.0 (84.55)	56.0 (5.53)	54.4 (19.94)	53.1 (17.58)	54.9 (16.80)	96.4 (88.52)	58.6 (25.02)	57.1 (28.86)
Median	53.7	49.3	-	-	53.0	49.2	50.3	110.0	55.0	50.3	49.4	50.0	58.7	48.3	49.7
Min, max	41.2, 98.6	42.1, 365.9	-	-	41.2, 365.9	18.3, 156.7	5.1, 113.7	50.2, 169.8	51.2, 63.0	5.1, 169.8	17.6, 94.9	36.5, 118.9	36.5, 250.3	46.9, 145.5	17.6, 250.3
Missing	1	1	-	-	2	1	0	0	0	1	3	1	0	1	5
Average dose per infusion per bleed for vonicog alfa (IU/kg)															
n	26	19	-	-	45	80	45	2	4	131	27	31	5	21	84
Mean (SD)	54.6 (14.77)	49.0 (5.36)	-	-	53.4 (12.25)	49.3 (7.62)	48.4 (9.60)	53.4 (4.56)	56.0 (5.53)	49.3 (8.09)	48.1 (10.36)	50.0 (5.36)	47.4 (8.14)	49.2 (3.94)	48.4 (7.20)
Median	53.7	48.1	-	-	49.7	48.5	49.8	53.4	55.0	49.8	47.0	49.5	47.0	48.5	48.5
Min, max	41.2, 98.6	40.7, 82.4	-	-	40.7, 98.6	18.3, 79.8	5.1, 66.7	50.2, 56.6	51.2, 63.0	5.1, 79.8	17.6, 59.7	36.5, 61.8	36.5, 58.7	46.9, 55.6	17.6, 61.8
Missing	1	1	-	-	2	1	0	0	0	1	3	1	0	1	5
ADVATE infusions per bleed															
Mean (SD)	-	1.0 (0)	-	-	1.0 (0)	1.0 (0)	1.0 (0)	-	1.0 (0)	1.0 (0)	1.0 (0)	1.1 (0.3)	1.0 (-)	-	1.0 (0.22)
Median	-	1.0	-	-	1.0	1.0	1.0	-	1.0	1.0	1.0	1.0	1.0	-	1.0
Min, max	-	1.0, 1.0	-	-	1.0, 1.0	1.0, 1.0	1.0, 1.0	-	1.0, 1.0	1.0, 1.0	1.0, 1.0	1.0, 2.0	1.0, 1.0	-	1.0, 2.0
Number of actual ADVATE infusions per bleed, n(%) *															
1	0	5 (25.0)	-	-	5 (10.6)	37 (45.7)	6 (13.3)	0	2 (50.0)	45 (34.1)	9 (30.0)	10 (31.3)	1 (20.0)	0	20 (22.5)
2	0	0	-	-	0	0	0	0	0	0	0	1 (3.1)	0	0	1 (1.1)
3	0	0	-	-	0	0	0	0	0	0	0	0	0	0	0
4	0	0	-	-	0	0	0	0	0	0	0	0	0	0	0
5	0	0	-	-	0	0	0	0	0	0	0	0	0	0	0
>5	0	0	-	-	0	0	0	0	0	0	0	0	0	0	0
Total dose per bleed for ADVATE (IU/kg)															
n	0	5	-	-	5	37	6	0	2	45	9	11	1	0	21
Mean (SD)	-	33.4 (3.89)	-	-	33.4 (3.89)	34.5 (6.41)	37.9 (4.15)	-	42.1 (8.25)	35.3 (6.38)	29.9 (10.46)	37.2 (12.24)	38.5 (-)	-	34.1 (11.51)
Median	-	32.9	-	-	32.9	37.0	37.4	-	42.1	37.0	30.3	35.4	38.5	-	35.4
Min, max	-	30.8, 35.9	-	-	30.8, 35.9	9.1, 39.2	32.1, 43.0	-	36.3, 48.0	9.1, 48.0	18.0, 42.7	18.0, 70.3	38.5, 38.5	-	18.0, 70.3
Average dose per infusion per bleed for ADVATE (IU/kg)															
n	0	5	-	-	5	37	6	0	2	45	9	11	1	0	21
Mean (SD)	-	33.4 (3.89)	-	-	33.4 (3.89)	34.5 (6.41)	37.9 (4.15)	-	42.1 (8.25)	35.3 (6.38)	29.9 (10.46)	34.0 (5.47)	38.5 (-)	-	32.4 (8.02)
Median	-	32.9	-	-	32.9	37.0	37.4	-	42.1	37.0	30.3	35.1	38.5	-	35.1
Min, max	-	30.8, 35.9	-	-	30.8, 35.9	9.1, 39.2	32.1, 43.0	-	36.3, 48.0	9.1, 48.0	18.0, 42.7	18.0, 38.7	38.5, 38.5	-	18.0, 42.7

Efficacy outcomes related to vonicog alfa OD treatment in paediatric subjects are compared across the ISE (Studies 071102 and SHP677-304) and respective individual studies in Table 20.

Table 20. Comparison of efficacy outcomes across studies

Outcome	ISE (Studies 071102/SHP677-304) (OD N=21)	Study 071102 (N=18)	Study SHP677-304 (OD N=16)
Timeframe	**From Study 071102 Day 1 Through DCO in Study 071102 (01 December 2023) or Study SHP677-304 (26 January 2024)**	**From Study 071102 Day 1 Through DCO (01 December 2023)**	**From Study SHP677-304 Day 1 Through DCO (26 January 2024)**
Number of nonsurgical treated BEs	268	104	164
Number of subjects achieving treatment success in nonsurgical bleedings, n (%) [95% CI]	21 (100.0%) [83.9, 100.0]	18 (100.0%) [81.5, 100.0]	NA
Hemostatic efficacy rating for nonsurgical bleedings	260 episodes had a known hemostatic efficacy rating, and all had an 'excellent' (256 BEs) or 'good' (4 BEs) treatment outcome.	98 episodes had a known hemostatic efficacy rating, and all had an 'excellent' (97 BEs) or 'good' (1 BE) treatment outcome.	162 episodes had a known hemostatic efficacy rating, and all had an 'excellent' (160 BEs) or 'good' (2 BEs) treatment outcome.
Total dose of vonicog alfa (IU/kg) per nonsurgical bleed, mean (SD)	57.6 (33.90)	64.40 (48.349)	53.43 (19.88)

2.4.2. Discussion on clinical efficacy

Design and conduct of clinical studies

The requested extension of indication is supported by efficacy data obtained in study 071102 and its continuation study SHP677-304.

Study 071102 is part of the agreed PIP for Veyvondi and on 13 December 2024, PDCO confirmed that the OD arm of the study was compliant with the latest PIP as set out in the EMA's Decision dated 18 July 2024 (P/0236/2024).

Overall, the design of the study, the number and type of enrolled subjects and the duration of follow-up are largely compliant with the requirements set forth in the EMA guideline on clinical investigation of plasma-derived VWF products (CPMP/BPWG/220/02). Dosing guidance for the on-demand treatment of nonsurgical bleeds were in line with the currently approved posology in adults and justified by references to alternative (plasma-derived) VWF products.

Endpoints and the employed rating scale for the assessment of haemostatic efficacy are similar to the pivotal study of on-demand treatment in adults submitted for initial MA (study 071001). The rating scale has already been discussed and considered acceptable during the initial MA procedure. Nevertheless, the inherent limitations of the mainly subjective criteria, which are likely to be significantly impacted by physicians' experiences and the difficulty of making accurate prospective estimations of treatment requirements, are recognised. In addition, the applied method to determine efficacy can be criticised due to the lack of a pre-specified time point for assessment, as the rating was performed "after resolution of each bleed". Rapid treatment success would be important to reduce or prevent potential sequelae of bleeding episodes. However, the secondary endpoint of number of infusions with vonicog alfa provides relevant complementary information to assess the treatment success. For example, for BEs with an efficacy rating of "excellent" which required only 1 infusion, immediate treatment success could be assumed, also considering that subsequent doses every 8 to 24 hours were possible, if deemed necessary.

Of note, with a total of only five children aged <6 years and only two type 3 VWD subjects aged <6 years, the studied population does not fulfil the EMA guideline requirement of at least 8 children under the age of 6 years, including at least 3 children who suffer from hereditary type 3 VWD. However, it is acknowledged that, in addition to the two type 3 VWD children <6 years of age, the study population included an infant suffering from an apparently severe form of type 1 disease with

a VWF:RCo activity of <8 IU/kg. Furthermore, it is acknowledged that the requested EOI is limited to OD treatment (i.e. excluding the use of Veyvondi in children for prophylaxis or in the context of surgical procedures) and that the total numbers of patients per age cohort comply with the key binding elements of the latest PIP as agreed by PDCO.

The original study protocol was amended 9 times, including 3 global amendments. However, none of the introduced changes affected key determinates of the study's design or its scientific integrity. In Study 071102, only one subject had to be excluded from the PPAS due to major protocol deviations (lack of source documentation and high volume of missing efficacy data) and only one subject discontinued from the study (due to the physician's decision to start prophylactic treatment).

The open label and non-randomized (uncontrolled) design of the study represent potential sources of bias. Additional limitations are the exploratory design without prespecified hypotheses and the small sample size. Nevertheless, particularly in view of (i) the rarity of the targeted disease, (ii) the strong therapeutic rationale aimed at replacing a missing coagulation factor, (iii) the close link between measurable plasma levels of VWF and FVIII and clinical efficacy, and (iv) the standards set forth by the EMA clinical guideline for plasma-derived VWF (CPMP/BPWG/220/02), the design of study 071102 (and its continuation SHP677-304), as well as the overall type and amount of clinical efficacy data is considered acceptable.

Efficacy data and additional analyses

Across both studies (Study 071102 and its continuation SHP677-304), a total of 268 nonsurgical BEs in 21 subjects (n=104 in 18 subjects in study 071102 and n=164 in 16 subjects in SHP677-304) were treated with vonicog alfa. These events included 47 BEs in 5 subjects aged <6 years, 132 BEs in 9 subjects aged ≥6 to <12 years and 89 BEs in 7 subjects aged ≥12 to <18 years and a total of 7 severe/major BEs (n=2 in subjects aged ≥6 to <12 years and n=5 in subjects aged ≥12 to <18 years).

In both studies, the rate of treatment success (defined as a mean efficacy rating score of <2.5) was 100% and haemostatic efficacy ratings of "excellent" or "good" (secondary endpoint) were achieved for 100% of treated bleeding events. In studies 071102 and SHP677-304, there were 6 (5.8%) and 2 (1.2%) BEs with missing ratings, respectively. Subgroup analysis by age groups (<6 years, ≥6 to <12 years, and ≥12 to <18 years) showed consistent results. All subjects achieved treatment success irrespective of age group; VWD type; and cause, severity, and location of BEs. Most notable, separate analysis of the subset of type 3 VWD subjects showed results consistent with the overall reported outcomes.

Study protocols permitted the concomitant use of alternative haemostatic products (i.e. gelatin sponges, topical thrombin, fibrin sealants, absorbable collagen preparations, or antifibrinolytics). Of note, there was no reported concomitant use of DDAVP across Study 071102 and SHP677-304. Overall, the potential impact of concomitant use of antifibrinolytics on the reported efficacy outcomes was considered negligible.

Data obtained in Study 071102 are supported by an interim analysis of study SHP677-304, which provides further evidence of persistent clinical efficacy of Veyvondi beyond the 12-month duration of the pivotal trial. The value of these additional data is underscored by a total of 164 additional bleeding events, including 5 severe/major BEs and bleeding data for 3 additional subjects (including 2 subjects <6 years of age) who did not experience any BE requiring treatment during the course of Study 071102.

For all severe/major BEs treated in studies 071102 and SHP677-304 haemostatic efficacy of Veyvondi was rated "excellent". However, the total number of severe/major bleeds across both studies was low (n=7), suggesting a study population with rather mild bleeding phenotypes (i.e. low disease severity). Still, the definition of severe VWD used in the studies' eligibility criteria (i.e. VWF:RCo <20%) complies with the definition used in the EMA clinical guideline and the studied population includes a substantial number of patients suffering from type 3 VWD (n=11). In addition, the EMA clinical guideline does not specify a minimum requirement of treated severe/major bleeds for children. Upon request, the MAH discussed the apparent limitation of efficacy assessments for only two cases of treated severe/major BEs in children aged <12 years with no cases in children <6 years of age. Compared to adults who have more diverse bleeding complications and a higher incidence of severe and life-threatening bleeds, paediatric VWD patients rarely experience severe bleeds. Thus, the limited sample of severe BEs in children can be considered consistent with the age-related differences in disease phenotypes.

With regard to the treatment of children aged <6 years in study SHP677-304, it is further noted that a relatively high proportion of the treated BEs (n=15, 42.9%) were skin bleeds. By contrast, only few skin bleeds were treated in older children (n=6 for remaining age subgroups combined) and in Study 071102 (n=4 in 3 participants). This suggests a potentially different (more cautious) decision making during the continuation study, which is relevant for interpretation of the efficacy data in the youngest age group, considering that skin bleeds are usually less problematic to treat than other types of bleeds.

Of note, the efficacy dataset does not include any OD treatment of gastrointestinal (GI) bleeds. However, the expectation of efficacy of vonicog alfa in treating and controlling paediatric GI bleeds is supported by its mechanism of action and product characteristics, as well as the available data from former studies of vonicog alfa in adults.

Apart from the absence of GI bleeds, the dataset includes a sufficient number of clinically diverse bleeding types reflecting typical bleeding events in patients with VWD. Across both studies (071102 and SHP677-304) vonicog alfa demonstrated to be highly effective in the treatment of paediatric mucosal bleeds (including nasal, mouth, and gum mucosal bleeds).

Regardless of the subjects' age group, VWD type, or severity of BEs, the vast majority of BEs (237 [88.4%]) were treated with a single infusion of vonicog alfa. The mean (SD) total dose of vonicog alfa per bleed was 57.6 (33.90) IU/kg, and the mean (SD) average dose per infusion per bleed was 49.7 (8.83) IU/kg and largely comparable in all age groups. Hence, the administered doses generally aligned with the proposed posology and fell within the typical range for VWF products (as also specified in the respective Core SmPC). Only a minority of the BEs (n=71) were treated with a combination of Veyvondi and FVIII.

Of note, two bleeding episodes in a <6-year-old participant required >5 vonicog alfa infusions. The participant experienced one traumatic and one spontaneous left ankle bleeds that were respectively treated with 9 and 8 infusions of vonicog alfa. In 12 cases the reason of treatment/infusion was stated "to maintain haemostasis", which may suggest that the high number of infusions were administered out of caution to prevent joint damage. This was the only participant who was discontinued from the study (started prophylaxis due to physician decision, Day 319).

Results of the exploratory ER analysis using population PK/PD data indicate a considerable age-related drop in VWF:RCo and FVIII:C levels at the end of treatment. This appeared to be particularly pronounced in children <6 years of age and the predicted median values for VWF:RCo (35.6 IU/dL) and FVIII:C (25.9 IU/dL) fall clearly below the recommended target thresholds of 60 IU/dL (for VWF:RCo) and 40 IU/dL (for FVIII:C) to achieve haemostasis . However, upon request,

the MAH emphasised the limited informative value of these exploratory predictions of VWF:RCo and FVIII:C levels at the end of BE treatment and pointed out that, since haemostasis-related plasma levels are unlikely to be required throughout the entire course of BE treatment, they are better reflected by either C_{max} or C_{ave} which can be expected to be much higher than the levels determined at the end of treatment. In addition, to further support the adequacy of the proposed dosage recommendations for children, the MAH conducted a set of Monte Carlo simulations of VWF:RCo and FVIII:C exposure levels using the final PPK and PK/PD models in a virtual paediatric population. Indeed, the results of these simulations support the expectation that target haemostatic exposure levels can be achieved for both minor and major BEs in all paediatric age groups via dosage individualization (i.e. adjustments of dose levels, dosing intervals and/or number of infusions) within the dosage recommendations in SmPC section 4.2 (spanning initial doses of 40-80 IU/kg, repeated at intervals of 8-24 hours).

2.4.3. Conclusions on the clinical efficacy

Overall, efficacy data obtained in studies 071102 and SHP677-304 support the use of vonicog alfa in the on-demand treatment of nonsurgical haemorrhage in children with VWD.

2.5. Clinical safety

Introduction

The current application includes safety data for paediatric subjects exposed to vonicog alfa across studies 071102 and SHP677-304. The potential risks or adverse effects characteristic of this pharmacological class are thrombosis / thromboembolic events, immunogenicity / development of neutralizing antibodies, and hypersensitivity / allergic reactions.

Safety data for Study 071102 are presented with a DCO date of 01 December 2023 for the SAF which included 26 subjects, of whom 25 subjects were included in the OD treatment arm and 1 subject was included in the elective surgery arm. Of the 25 subjects in OD treatment arm, 1 subject was included in both OD treatment and emergency surgery arms. Study 071102 analyses are interim because as of the DCO the study remains ongoing for the surgery arm only. For Study SHP677-304, safety data are presented for the OD treatment arm (Cohort 5) only. This included 16 subjects in the SAF (DCO date of 26 January 2024). In addition, the MAH performed an integrated analysis of safety for the 25 unique paediatric subjects who were exposed to vonicog alfa in the OD treatment arms across both studies.

For detailed descriptions of Study 071102 and SHP677-304 and subject disposition across the two studies reference is made to section 2.4. and Table 17.

Safety was assessed in terms of TEAE and clinically significant abnormal laboratory test results on the basis of the following evaluations:

- TEAEs, TEAEs related to vonicog alfa, study procedures, and temporally associated with vonicog alfa, as well as serious TEAEs.
- TEAEs leading to study drug withdrawal, AEs resulting in study discontinuation, and AEs resulting in death.
- TEAESIs: hypersensitivity, anaphylactic and severe hypersensitivity reactions, and thromboembolic events.
- Neutralizing and binding antibodies to VWF.

- Neutralizing and binding antibodies to FVIII.
- Binding antibodies to Chinese hamster ovary (CHO) proteins, murine IgG, and rFurin.

Patient exposure

In Study 071102, for the subjects in the OD treatment arm with available data (N=20), a total of 151 infusions of vonicog alfa were administered. The mean (SD) vonicog alfa per subject dose was 358.42 (314.668) IU/kg; the mean (SD) number of units administered was 17088.0 (19303.31) IU. A total of 33 infusions of ADVATE were administered to 7 subjects for OD treatment. The mean (SD) dose received was 143.30 (90.865) IU/kg and the mean (SD) number of units was 6463.9 (5179.58) IU. Overall, the mean (SD) total dose of vonicog alfa administered per bleed was 64.40 (48.349) IU/kg, and the mean (SD) total dose of ADVATE administered per bleed was 30.75 (8.576) IU/kg.

In Study SHP677-304, for the subjects in OD Cohort 5 (n=16), a total of 164 BEs were treated with vonicog alfa up to the DCO of 26 January 2024. Overall, the mean (SD) total vonicog alfa dose administered for OD treatment per bleed was 53.432 (19.8772) IU/kg. A total of 43 BEs in 7 subjects were also treated with ADVATE. The mean (SD) total ADVATE dose administered for OD treatment per bleed was 37.424 (6.4492) IU/kg.

In the integrated safety analysis, for subjects in the OD arm (n=25), a total of 377 infusions of vonicog alfa were administered; 292 (77.5%) infusions were administered to treat BEs, 58 (15.4%) to maintain haemostasis, 25 (6.6%) were PK infusions, and 2 (0.5%) infusions had a missing reason to be administered. The mean (SD) vonicog alfa dose per subject for OD treatment was 738.34 (733.422) IU/kg, and the mean (SD) number of units administered was 34922.2 (40673.21) IU. A total of 81 infusions of ADVATE were administered to 11 subjects, including 10 subjects who received Advate, in addition to vonicog alfa, to treat BEs. The mean (SD) ADVATE dose per subject was 248.22 (402.699) IU/kg, and the mean (SD) number of units administered was 12891.6 (20082.38) IU.

Adverse events

In Study 071102, 122 TEAEs were reported in 23 (92.0%) subjects in the OD treatment arm. The SOC with the most TEAEs reported was infections and infestations (32 events in 13 [52.0%] subjects). The most frequently reported TEAEs (occurring in ≥4 subjects) were pyrexia (9 events in 4 [16.0%] subjects), upper respiratory tract infection (6 events in 4 [16.0%] subjects), and vomiting (5 events in 4 [16.0%] subjects).

In Study SHP677-304, 111 TEAEs were reported in 15 (93.8%) subjects in the OD Cohort 5. The SOC with the most TEAEs reported was infections and infestations (38 events in 13 [81.3%] subjects). The most frequently reported TEAEs (occurring in ≥20% subjects) were COVID-19 (8 events in 8 [50%] subjects), upper respiratory tract infection (8 events in 5 [31.3%] subjects), cough (7 events in 4 [25.0%] subjects), and vomiting (6 events in 4 [25.0%] subjects).

In the integrated safety analysis, 228 TEAEs were reported in 24 (96.0%) subjects who received vonicog alfa with or without ADVATE in the OD treatment arm (Table 21). Of these 228 TEAEs, 1 TEAE of moderate nausea (reported in a male in Study 071102) was considered related to vonicog alfa. 17 TEAEs reported in 11 (44.0%) subjects were considered temporally associated with vonicog alfa treatment. With the exception of fall (2 events), which was reported in 2 (8.0%) subjects, the temporally associated TEAEs were reported by 1 subject each. Most TEAEs were mild or moderate in severity; 4 TEAEs in 3 (12.0%) subjects were considered severe (pyrexia,

respiratory tract congestion, urinary tract infection, and traumatic haematoma). A total of 10 SAEs were reported in 6 (24.0%) subjects. These were coronavirus infection, urinary tract infection, vascular device infection, Yersinia infection, fall, traumatic haematoma, medical device site extravasation, pyrexia, obsessive-compulsive disorder, and hypotension. None of the reported SAEs were considered related to vonicog alfa. None of the subjects discontinued treatment or the study due to a TEAE. Overall, 2 TEAEs (conjunctivitis allergic and dermatitis) were identified by SMQ as potential hypersensitivity reactions in 2 (8.0%) subjects. No thromboembolic or anaphylactic events were identified by SMQ during the studies.

Table 21. Summary of TEAEs (integrated analysis of Study 071102 and SHP677-304)

Characteristic	OD (N=25) n (%) m
Any TEAE	24 (96.0) 228
TEAE related to study procedure	0
TEAE related to study drug	1 (4.0) 1
TEAE temporally associated to study drug	11 (44.0) 17
Severe TEAE	3 (12.0) 4
Severe TEAE related to study procedure	0
Severe TEAE related to study drug	0
Severe TEAE temporally associated to study drug	0
Serious TEAE	6 (24.0) 10
Serious TEAE related to study procedure	0
Serious TEAE related to study drug	0
Serious TEAE temporally associated to study drug	1 (4.0) 2
TEAEs leading to discontinuation of vonicog alfa	0
TEAEs leading to discontinuation of ADVATE	0
TEAEs leading to discontinuation from study	0
TEAEs leading to death	0
AESIs	2 (8.0) 2
Thromboembolic TEAE	0
Hypersensitivity TEAE	2 (8.0) 2
Hypersensitivity TEAE related to study drug	0
Hypersensitivity serious TEAE	0
Anaphylactic TEAE	0
Severe hypersensitivity TEAE	0

Percentage of subjects (n) who had a number of events in each category (m) were based on all subjects in the analysis set (N).
TEAEs were defined as any AE that starts during or after first administration of study drug for each study. A related TEAE was defined as any TEAE indicated as 'possibly related' or 'probably related' on the eCRF. Seriousness and severity were as recorded on the eCRF. A temporally associated TEAE was defined as an AE that began during infusion or within 24 hours after completion of infusion.
All AESIs were derived from SMQ query search.

Adverse events of special interest

In Study 071102, the investigator did not report any TEAESI of thromboembolic events, allergic reactions or severe hypersensitivity reactions. One mild, nonserious TEAE of pruritus, which was identified per broad SMQ as a potential hypersensitivity reaction was reported in 1 (4.0%) subject. The event was considered not related to the study drug, resolved within 1 day, and was specified by the investigator as "skin sensitivity to mediport dressing".

In Study SHP677-304, no thromboembolic events, allergic reactions, or severe hypersensitive reactions were reported by the investigator during the study.

Among subjects in the ISS (Studies 071102 and SHP677-304) who received OD treatment, no TEAESI of thromboembolic events, severe hypersensitivity reactions, or anaphylactic reactions were identified. Two TEAEs of mild conjunctivitis allergic and moderate dermatitis reported in 2 (8.0%) subjects were identified by narrow SMQ as potential hypersensitivity reactions; both events were nonserious.

Immunogenicity

Subjects were tested for the development of antibodies to VWF and FVIII, and to trace proteins that might be found in the vonicog alfa drug product (i.e. murine immunoglobulin [from the immunoaffinity purification], host-cell proteins, and rFurin [used to further process vonicog alfa]).

In Study 071102, no subjects developed neutralizing or binding antibodies to VWF, no subjects developed neutralizing antibodies to FVIII, and no subjects developed antibodies to murine IgG, CHO proteins, or rFurin.

Similarly, in OD Cohort 5 of Study SHP677-304, none of the subjects developed binding antibodies to VWF or to murine IgG, CHO protein, and/or rFurin. No confirmed neutralizing antibodies against VWF or FVIII were reported. However, 1 subject tested positive for binding IgG antibody to FVIII at month 18 and month 21 that were prior to the first study drug treatment in SHP677-304 and 756 and 861 days after the previous vonicog alfa dose in Study 071102, respectively. The positive results were at months 36, 39, 42, 48, and 51 after the baseline visit of Study 071102. Of note, the subject received a total of 7 vonicog alfa infusions without ADVATE during Study 071102 and 2 doses of vonicog alfa without ADVATE in the continuation study. There was no observation of treatment-boosted antibody response as seen by antibody titers.

Laboratory findings

In both studies, no clinically significant changes in laboratory parameters were considered related to the study drug.

Safety in special populations

Sex: There were no obvious differences in the AE profiles between male and female subjects in the ISS (Studies 071102 and SHP677-304).

Paediatric age groups: There were no obvious differences in the AE profiles of paediatric subjects by age groups in the ISS (Studies 071102 and SHP677-304).

VWD Type: There was no obvious difference in the AE profiles between subjects with type 1, type 2, or type 3 VWD in the ISS (Studies 071102 and SHP677-304).

Post marketing experience

As of 31 December 2024, the global cumulative post marketing subject exposure to vonicog alfa since launch is estimated to be approximately 600,773,687 IU corresponding to 47,834 patient-years.

The following ADRs have been identified during post approval use of vonicog alfa: anaphylactic reaction, infusion-related reactions (IRR, which may be clinically manifested by symptoms such as tachycardia, flushing, rash, dyspnoea, and blurred vision), and deep vein thrombosis (DVT).

- A total of 9 cases of anaphylactic reactions were reported with the use of Veyvondi in the post marketing setting in a total of 4 adult patients, 2 paediatric patients, and 3 patients

with unknown age. The cases reported by all the adult patients were considered related, the cases reported by the paediatric patients were both considered not related, and the cases reported by the patients with unknown age were considered related to Veyvondi. This ADR has never been observed in clinical studies.

- A total of 4 cases (3 from spontaneous and 1 from post marketing study sources) of IRR were reported with the use of Veyvondi in the post marketing setting. The cases were reported by 2 adult patients, 1 elderly patient, and 1 patient with unknown age. The cases reported by both the adult patients and the patient with unknown age were considered related and the case reported by the elderly patients was considered not related to Veyvondi.
- A total of 5 cases (2 from post marketing study sources, 2 literature-spontaneous, and 1 spontaneous) of DVT were reported with the use of Veyvondi in the post marketing setting. Of these, 2 cases (1 in adult and 1 in patient with unknown age) were considered related to Veyvondi and 3 in adult patients were considered not related to Veyvondi.

2.5.1. Discussion on clinical safety

The safety of Veyvondi in the on-demand treatment of bleeding in children was assessed in 25 unique subjects <18 years of age (including 5 subjects aged <6 years, 11 subjects aged ≥6 to <12 years and 9 subjects aged ≥12 years), who received infusions of Veyvondi either alone or in combination with ADVATE (i.e. a recombinant FVIII) in studies 071102 and its continuation study SHP677-304.

Across both studies, subjects received a total of 377 infusions of vonicog alfa. 292 (77.5%) infusions were administered to treat BEs, 58 (15.4%) to maintain haemostasis and 25 (6.6%) were PK infusions. Two infusions (0.5%) had a missing reason for administration.

The mean (SD) vonicog alfa dose per subject for OD treatment was 738.34 (733.422) IU/kg, and the mean (SD) number of units administered was 34922.2 (40673.21) IU. A total of 81 infusions of ADVATE were administered to 11 subjects, including 10 subjects who received ADVATE, in addition to vonicog alfa, to treat BEs. The mean (SD) ADVATE dose per subject was 248.22 (402.699) IU/kg, and the mean (SD) number of units administered was 12891.6 (20082.38) IU. Of note, the combined administration of Veyvondi and ADVATE in approximately 30% of infusions complicates the assessment of possible ADRs specific to Veyvondi.

Given the known safety profile of VWF-containing products (including products already approved for the use in paediatrics) and the orphan nature of severe VWD, the small sample size of only 25 subjects is considered acceptable.

With a total of only five children aged <6 years and only two type 3 VWD subjects aged <6 years, the studied population does not fulfil the EMA guideline requirement of at least 8 children under the age of 6 years, including at least 3 children who suffer from hereditary type 3 VWD. However, it is acknowledged that, in addition to the two type 3 VWD children <6 years of age, the study population included an infant suffering from an apparently severe form of type 1 disease with a VWF:RCo activity of <8 IU/kg. Furthermore, it is acknowledged that the requested EOI is limited to OD treatment (i.e. excluding the use of Veyvondi in children for prophylaxis or in the context of surgical procedures) and that the total numbers of patients per age cohort comply with the key binding elements of the latest PIP as agreed by PDCO.

Safety aspects of particular importance to this class of drug include the risk of hypersensitivity reactions, thrombogenicity and the development of binding and/or neutralizing anti-drug

antibodies. All of these potential and/or identified risks were tightly monitored and captured as adverse events of special interest (AESI).

Overall, safety data obtained in the context of on-demand treatment of nonsurgical BEs in children (up to the data cut-off date of the presented study reports of studies 071102 and SHP677-304) are considered consistent with previous clinical studies of vonicog alfa in adults and do not raise concerns regarding potential age-related differences.

In both studies, there were no fatal or life-threatening adverse events. Most TEAEs were non-serious and there were no TEAEs leading to discontinuation. No thromboembolic events, allergic reactions, or severe hypersensitivity reactions were reported by the investigators. SMQ analyses by the MAH identified the potential hypersensitivity reactions of mild conjunctivitis allergic, moderate dermatitis, and mild pruritus. However, these TEAEs were seemingly not temporally related to administration of study drug. No subject developed anti-drug antibodies (binding or neutralizing) to vonicog alfa.

The finding of sporadic positive tests for FVIII binding (non-neutralising) antibodies in a single subject who did not receive any concomitant treatment with ADVATE during the studies remains inconclusive. Of note, antibody titers remained in the low range, were contrasted with negative results and did not have any notable impact on efficacy and safety responses. Overall, a connection to the treatment with vonicog alfa appears highly unlikely and this finding does not raise concerns regarding the product's immunogenicity.

Four severe TEAEs of pyrexia, respiratory tract congestion, urinary tract infection, and traumatic haematoma were reported (considered not related). The severe event of pyrexia was reported 27 days after last IP administration, which indeed makes relatedness unlikely.

A total of 10 SAEs were reported in 6 participants: coronavirus infection, urinary tract infection, vascular device infection, Yersinia infection, fall, traumatic haematoma, medical device site extravasation, pyrexia, obsessive-compulsive disorder, and hypotension. All 10 SAEs were considered not related to vonicog alfa. The SAE of medical device site extravasation (described as infiltrated mediport) occurred during vonicog alfa infusion and resolved in 2 days. Thus, it seems reasonable to assume that the event was likely related to the administration procedure.

Clinical laboratory evaluations did not reveal clinically significant changes that were considered related to study drug. Some events of iron deficiency and anaemia were likely related to the von Willebrand disease itself and not the study drug.

Across both studies, only a single adverse event was considered related to Veyvondi. This was an event of moderate nausea which was reported in a boy in Study 071102. The adverse drug reaction of nausea is not considered remarkable for this class of product and is already included in section 4.8 of the SmPC with a frequency of "common".

An event of temporally associated infusion-related reaction occurred during administration and was considered "unlikely" related to vonicog alfa. The adverse drug reaction of infusion-related reaction (including tachycardia, flushing, rash, dyspnoea, blurred vision) is already represented in section 4.8 of the SmPC.

The frequency, type and severity of adverse reactions in children receiving Veyvondi for the treatment of haemorrhage are expected to be the same as in adults. Of note, the inclusion of paediatric data to the tabulated list of adverse reactions (Table 4 of SmPC section 4.8) led to a change of most frequencies from 'common' to 'uncommon' (Dysgeusia, Tremor, Tachycardia, Deep venous thrombosis, Hot flush, Chest discomfort, Infusion site paraesthesia, Electrocardiogram T wave inversion, Heart rate increased). This is considered acceptable.

All listed safety concerns for vonicog alfa are to be further characterised through routine pharmacovigilance as well as the category 3 study based on the EUHASS registry, with a protocol to be submitted as separate procedure (as previously agreed in procedure EMEA/H/C/004454/II/0030).

2.5.2. Conclusions on clinical safety

Overall, the safety data submitted with this application are considered consistent with previous clinical studies of vonicog alfa in adults, do not indicate any adverse events specific to the paediatric population, and support its safe and well tolerated use for the on-demand treatment of nonsurgical BEs in children with VWD (i.e. patients <18 years of age).

The protocol for the category 3 study based on the EUHASS registry should be submitted in a separate post authorisation measure procedure.

2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.6. Risk management plan

The MAH submitted/was requested to submit an updated RMP version with this application.

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 6.0 is acceptable.

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

Pharmacovigilance plan

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

Study Status	**Summary of objectives**	**Safety concerns addressed**	**Milestones**	**Due dates**
Category 3 - Required additional pharmacovigilance activities				
Participation in registries (e.g., EUHASS	The EUHASS registry serve to collect further safety information in	• Hypersensitivity reactions • Thromboembo	Regular updates	Data are reviewed on an

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
registry) and review of the data provided by the registries to further characterise the safety concerns for long-term safety follow-up. Ongoing	patients with VWD.	lic 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.		ongoing basis as part of signal detection and reported within PSUR/ PBRERs when available.

Risk minimisation measures

Routine risk minimisation activities are sufficient to manage the safety concerns of the medicinal product.

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.8, 5.1 and 5.2of the SmPC have been updated. The Package Leaflet has been updated accordingly.

Changes were also made to the PI to bring it in line with the current Agency/QRD template, SmPC guideline and other relevant guideline(s) [e.g. Excipients guideline, storage conditions, Braille, etc…], which were accepted by the CHMP.

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons:

- The PIL design and content were tested for readability in 2023, with positive results.
- The current proposed changes to the PIL are minor. The adjustments to the indication and paediatric population wording are straightforward.
- Based on clinical and PK/PD data, same dosing instructions for adults and paediatric patients are applicable with no age restriction. The safety profile in the paediatric population is comparable to that observed in adults.

- There is no change in legal status and no new presentation. Moreover, the design, layout and writing style remain unchanged in comparison to the current approved PIL, which underwent a full readability user test in 2023.
- Paediatric patients receiving Veyvondi are likely to be assisted by adults (care givers or parents) and the PIL has already been tested in this population.

Taken together, as there are no changes implemented that affect the readability of the PIL, the conduction of a user consultation on the PIL in the course of the current procedure is not considered necessary.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The MAH applied for an extension of the therapeutic indication for vonicog alfa to expand the use of Veyvondi to treat haemorrhage in children with VWD aged less than 18 years.

The agreed indication is stated below in bold:

*"Prevention and treatment of haemorrhage or surgical bleeding in adults (age**d** 18 years and older) with von Willebrand disease (VWD), when desmopressin (DDAVP) treatment alone is ineffective or contraindicated.*

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."

Von Willebrand disease (VWD) is a hereditary bleeding disorder caused by a loss or defective function of von Willebrand factor (VWF). VWF serves essential functions during haemostasis by promoting platelet adhesion to subendothelial collagen at sites of vascular damage and by protecting the critical coagulation factor VIII from degradation. Clinical presentation of VWD varies considerably among patients and depends critically on the amount and functionality of residual VWF, as well as the patient's age and sex. The main burden of the disease results from bleeding symptoms which are primarily caused by defective platelet adhesion and aggregation in mucosa-associated bleedings like for instance epistaxis and menorrhagia. In general, bleeding symptoms are more severe in type 2 and type 3 than in type 1 VWD. Disease subtypes with markedly reduced FVIII levels (type 2N and type 3 VWD) are further complicated by ''haemophilia-type'' joint and deep subcutaneous tissue bleeds eventually leading to long-term damages and disabilities. The majority of patients (60-80%) experience excessive bleeding after surgery or dental extractions. A well-known, serious, and possibly life-threatening complication affecting patients with severe disease phenotypes is gastrointestinal bleeding resulting from angiodysplasia.

3.1.2. Available therapies and unmet medical need

Treatment of VWD largely depends on the type and severity of the disease. The mainstay of treatment is on-demand therapy to control spontaneous bleeding or to prevent excessive bleeding during surgical procedures. Currently, several plasma-derived VWF/FVIII concentrates (containing different amounts and ratios of VWF and FVIII) are available for VWD treatment in children in the

EU. Besides the problem of varying composition and overall plasma donor availability, drawbacks of plasma-derived VWF/FVIII products include a risk for excessive plasma FVIII levels upon repeated administrations (which may lead to thrombogenesis), a theoretical risk of pathogen transmission and the presence of extraneous plasma proteins which may trigger allergic responses.

3.1.3. Main clinical studies

Study 071102: A Phase 3, prospective, multicenter, uncontrolled, open-label clinical study to determine the efficacy, safety, and tolerability of rVWF with or without ADVATE in the treatment and control of bleeding episodes, the efficacy and safety of rVWF in elective and emergency surgeries, and the pharmacokinetics (PK) of rVWF in children diagnosed with severe von Willebrand disease.

Study SHP677-304: A Phase 3b, prospective, open-label, uncontrolled, multicenter study on long-term safety and efficacy of rVWF in paediatric and adult subjects with severe von Willebrand disease (VWD).

Across both studies (Study 071102 and its continuation SHP677-304), a considerable number of clinically diverse nonsurgical bleeding events (n=268) were evaluated. Bleeding events were well distributed across the different paediatric age groups (n=47 BEs in 5 subjects aged <6 years, n=132 BEs in 9 subjects aged ≥6 to <12 years and n=89 BEs in 7 subjects aged ≥12 to <18 years) and included clinically diverse types reflecting typical bleeding events in patients with VWD.

3.2. Favourable effects

In both studies, the rate of treatment success (defined as a mean efficacy rating score of <2.5) was 100% and haemostatic efficacy ratings of "excellent" or "good" (secondary endpoint) were achieved for 100% of treated bleeding events. There were no BEs with "moderate" or "none" efficacy ratings but 8 (3.0%) BEs with missing rating. Subgroup analysis by age groups (<6 years, ≥6 to <12 years, and ≥12 to <18 years) showed consistent results. All subjects achieved treatment success irrespective of age group; VWD type; and cause, severity, and location of BEs. Most notable, separate analysis of the subset of type 3 VWD subjects showed results consistent with the overall reported outcomes.

Regardless of the subjects' age group, VWD type, or the severity of BEs, the vast majority of BEs were successfully treated with a single infusion of vonicog alfa at doses consistent with the proposed posology and the typical/expected range for VWF products.

Interim data from the continuation study SHP677-304 extend the dataset beyond the 12-month duration of Study 071102 and provide additional evidence of consistency and long-term clinical efficacy of vonicog alfa in the on-demand treatment of haemorrhage in children. The value of these additional data is further underscored by the contribution of a total of 164 additional treated bleeding events, including 5 severe/major BEs, and bleeding data for 3 additional subjects (including 2 subjects <6 years of age) who did not experience any BE requiring treatment during the course of Study 071102.

3.3. Uncertainties and limitations about favourable effects

The open-label and non-randomized (uncontrolled) design of the study represent potential sources of bias. Additional limitations are the exploratory design without prespecified hypotheses and the small sample size. However, in view of (i) the rarity of the targeted disease, (ii) the aimed replacement of a missing coagulation factor following a strong therapeutic rationale, (iii) the close

link between measurable plasma levels of VWF and FVIII and clinical efficacy and (iv) the standards set forth by the EMA clinical guideline for plasma-derived VWF (CPMP/BPWG/220/02), the design of study 071102 (and its continuation SHP677-304) and the overall type and amount of clinical efficacy data provided to support the requested EOI are considered acceptable.

The endpoints and the rating scale used for the assessment of haemostatic efficacy reflect current standards in the field of coagulation factor replacement therapy and are considered acceptable. Nevertheless, the subjective component of the assessment and the difficulty of making accurate, prospective estimations of treatment requirements are recognised as sources of uncertainty.

With a total of only five children <6 years of age and only two type 3 VWD subjects <6 years of age, the studied population does not fulfil the EMA guideline requirement of at least 8 children under the age of 6 years, including at least 3 children who suffer from hereditary type 3 VWD. However, it is acknowledged that, in addition to the two type 3 VWD children <6 years of age, the study population included an infant suffering from an apparently severe form of type 1 disease with a VWF:RCo activity of <8 IU/kg. Furthermore, it is acknowledged that the requested EOI is limited to OD treatment (i.e. excluding the use of Veyvondi in children for prophylaxis or in the context of surgical procedures) and that the total numbers of patients per age cohort comply with the key binding elements of the latest PIP as agreed by PDCO.

The total number of treated severe/major bleeds was low (n=7 across both studies), suggesting a study population with rather mild bleeding phenotypes (i.e. low disease severity). However, the definition of severe VWD used in the studies' eligibility criteria (i.e. VWF:RCo <20%) complies with the definition used in the EMA clinical guideline and the studied population includes a substantial number of patients suffering from type 3 disease (n=11). In addition, the EMA clinical guideline does not specify a minimum requirement of evaluated severe/major bleeds for children. Nevertheless, the low number of treated major/severe BEs in children aged <12 years (n=2) and the complete absence of such bleeds in children <6 years of age cause uncertainty and hamper the evaluation of haemostatic efficacy. In addition, the efficacy dataset does not include any cases of treated GI-bleeds

As study protocols permitted the concomitant use of alternative haemostatic products (i.e. gelatin sponges, topical thrombin, fibrin sealants, absorbable collagen preparations, or antifibrinolytics), a potential contribution of these treatments to the reported efficacy outcomes cannot be excluded.

Reported PK/PD data for the newly requested target population (i.e. children <18 year of age) are based on sparse sampling and model-based predictions. PK model-based covariate analysis suggests an inverse relationship between age and clearance of vonicog alfa. Furthermore, an exploratory exposure-response analysis indicates insufficient plasma levels of VWF:RCo and FVIII:C activities at the end of treatment, raising some uncertainties regarding the adequacy of the proposed posology, particularly for children aged <6 years. On the other hand, a potentially higher clearance in younger age groups is not unexpected and it also needs to be considered that dosing is mainly based on clinical response.

3.4. Unfavourable effects

Veyvondi represents a purified recombinant VWF. Safety aspects of particular importance to the class of VWF products include the risk of hypersensitivity reactions, thrombogenicity and the development of binding and/or neutralizing anti-drug antibodies. The risk management plan (RMP) for Veyvondi describes hypersensitivity reactions and thromboembolic events (particularly in patients with low ADAMTS13 levels as well as other risk factors, and concomitant overuse of FVIII) as important identified risks whereas inhibitor formation is listed as an important potential risk.

As of the cut-off date of the submitted study reports, no ADRs related to these key risks (identified or potential) were observed in the context of OD treatment of children in studies 071102 and SHP677-304. Most TEAEs were mild to moderate in severity and were assessed by the investigator as not related to the study drug.

The only TEAE which was considered related to Veyvondi was an event of moderate nausea reported in a boy in Study 071102. Nausea is already included as an ADR in section 4.8 of the SmPC.

Overall, safety data obtained in the OD treatment of haemorrhage in studies 071102 and SHP677-304 are considered consistent with previous clinical studies of Veyvondi in adults and do not raise concerns regarding potential age-related differences.

3.5. Uncertainties and limitations about unfavourable effects

Uncertainties about the reported unfavourable effects arise from the non-controlled design of studies 071102 and SHP677-304 and the small number of recruited participants, especially in subgroups (age groups, VWD types), which may have been too small to detect rare adverse events like e.g. thrombotic events in subjects with known risk factors for thrombosis.

3.6. Effects Table

Table 22. Effects table for Veyvondi in the on-demand treatment of haemorrhage in children with severe VWD (Study 071102 and IA of SHP677-304 with data cut-off: 26 January 2024)

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects						
Number of subjects with treatment success	Mean efficacy rating score <2.5 on a 4-point rating scale	n (%) [95% CI]	18 (100.0) [81.5, 100.0]	N/A	Mean (SD) efficacy rating score of 1.01 (0.039) Supported by: Consistent results across (i) different types and severities of BEs, (ii) age groups, and (iii) types of VWD; IA of continuation study SHP677-304; Strong mechanistic rationale of substitution therapy; Number and proportion of treated nonsurgical BEs with an efficacy rating of excellent or good (n (%) [95% CI] = 98 (100.0) [96.3, 100.0]. Uncertainties relate to: Open-label, non-randomised study design;	Study 071102

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
					Small sample sizes in subgroups; Permitted concomitant use of alternative haemostatic products; Subjective component of assessment; Few treated severe/major BEs (n=7 across both studies); No treated severe/major BEs in children <6 years; No treated GI bleeds; Limitations of PK/PD data (sparse sampling & model-based predictions) with only limited support for the proposed posology for children <6 years.	
Unfavourable Effects						
Hypersensitivity reactions	May manifest as anaphylactic shock, angioedema, chest tightness, hypotension, lethargy, nausea, vomiting, paraesthesia restlessness or rash	n (%)	None	N/A	Important identified risk as per Veyvondi RMP. No events observed due to the small sample size.	Section 2.5 and RMP
Thrombembolic events	Clinical signs of thrombosis	n (%)	None	N/A	Important identified risk as per Veyvondi RMP. No events observed due to the small sample size.	Section 2.5 and RMP
Inhibitor formation	Development of neutralizing antibodies to VWF	n (%)	None	N/A	Important potential risk as per Veyvondi RMP. No events observed due to the small sample size.	Section 2.5 and RMP

Abbreviations: BE= Bleeding episode, CI= confidence interval, ER=Exposure-response, GI= gastrointestinal, IA=interim analysis, n=number, N/A=not applicable, RMP=Risk management plan, VWD=von Willebrand disease, VWF=von Willebrand factor

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The efficacy data from both submitted studies indicates that vonicog alfa is efficacious for on-demand treatment of bleeding episodes in children with different types of VWD. For paediatric patients with VWD, cessation of BEs, along with the potential avoidance of serious complications and sequelae associated with chronic BEs, represent substantial clinical benefits. Symptomatic relief is considered an important benefit that is likely to lead to improved functional outcomes and quality of life.

Safety data submitted with this application were consistent with previous clinical studies of Veyvondi in adults and do not raise concerns regarding potential age-related differences. The only reported adverse event considered related to Veyvondi was an event of moderate nausea in a boy, which is not considered an important identified risk.

3.7.2. Balance of benefits and risks

Based on the totality of data submitted with this application, the benefits of on-demand treatment of hemorrhage with Veyvondi in children with VWD are considered sufficient to outweigh the reported and expected risks.

3.7.3. Additional considerations on the benefit-risk balance

None.

3.8. Conclusions

The overall B/R of Veyvondi is positive for the treatment of haemorrhage in children (aged less than 18 years) with von Willebrand disease (VWD), when desmopressin (DDAVP) treatment alone is ineffective or contraindicated.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following changes:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a Addition of a new therapeutic indication or modification of an approved one	Type II	I, IIIA, and IIIB

Extension of indication to include treatment of haemorrhage in children aged less than 18 years for Veyvondi, based on results from studies 071102 and SHP677-304. As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 6.0 of the RMP has also been submitted. In addition, the MAH took the opportunity to bring the PI in line with the latest QRD template version 10.4, to update the PI in accordance with the latest EMA excipients guideline, and to implement editorial changes. Version 6.0 of the RMP has been accepted.

The variation leads to amendments to the annexes I, IIIA and IIIB and to the Risk Management Plan (RMP).

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annexes I, IIIA and IIIB and to the Risk Management Plan are recommended.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk management plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

In addition, an updated RMP should be submitted:

At the request of the European Medicines Agency;

Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Paediatric data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0236/2024 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the "EPAR- Procedural steps taken and scientific information after authorisation" will be updated as follows:

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion 'Veyvondi-H-C-004454-II-EMA/VR/0000264863'.

Attachments

1. Product information (changes highlighted) as adopted by the CHMP.