12 October 2023
EMA/505160/2023
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

VEYVONDI

International non-proprietary name: Vonicog alfa

Procedure No. EMEA/H/C/004454/0000

Note

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

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List of abbreviations

ABR - annualized bleeding rate

ADAs – anti-drug antibodies

AEs - adverse events

AESIs - adverse events of special interest

ALT - alanine aminotransferase

BEs - bleeding episodes

CNS - central nervous system

DDAVP - desmopressin

ePRO- electronic patient reported outcomes

FAS - full Analysis Set

FVIII - factor VIII

GI - gastrointestinal

IR - incremental recovery

IRR - infusion-related reactions

ISS - Integrated Summary of Safety

mFAS - modified Full Analysis Set

OD - on-demand

PD - pharmacodynamics

pdVWF - plasma-derived von Willebrand factor

PK – pharmacokinetics

rVWF – recombinant von Willebrand factor

sABR - spontaneous annualized bleeding rate

SAEs - serious adverse events

SD - standard deviation

SDV - Source data verification

TEAEs - treatment emergent adverse events

UTI - urinary tract infection

VWD - von Willebrand disease

VWF - von Willebrand factor

VWF:CB - von Willebrand factor:collagen binding

VWF:RCo - von Willebrand factor Ristocetin Cofactor activity

1. 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 6 March 2023 an application for a variation.

The following variation was requested:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include "prophylactic treatment to prevent or reduce the frequency of bleeding episodes" for VEYVONDI based on final results from study 071301 and interim results from study SHP677-304. Study 071301 is a prospective, phase 3, open-label, international multicenter study on efficacy and safety of prophylaxis with rVWF in severe von Willebrand disease; while study SHP677-304 is 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. As a consequence, sections 4.1, 4.2, 5.1 and 5.2 of the SmPC are updated. In addition, changes to sections 4.4, 6.2 and 6.6 were made. The Package Leaflet is updated in accordance. Version 4.0 of the RMP has also been submitted.

The requested variation proposed amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision (EMA Decision P/0363/2022) on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0363/2022 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

On 22 May 2014, the Marketing Authorisation holder (MAH) obtained CHMP protocol assistance (EMEA/H/SA/1378/2/FU/1/2014/PA) on the design of the Phase 3 Study 071301 for the prophylactic use of rVWF to prevent or reduce the frequency of bleeding episodes (BEs) in patients with von Willebrand disease (VWD).

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: N/A

Timetable	Actual dates
Submission date	6 March 2023
Start of procedure:	25 March 2023
CHMP Rapporteur Assessment Report	22 May 2023
PRAC Rapporteur Assessment Report	26 May 2023
Updated PRAC Rapporteur Assessment Report	2 June 2023
PRAC Outcome	8 June 2023
CHMP members comments	12 June 2023
Updated CHMP Rapporteurs' Joint Assessment Report	15 June 2023
Request for supplementary information (RSI)	22 June 2023
CHMP Rapporteur Assessment Report	13 September 2023
PRAC Rapporteur Assessment Report	13 September 2023
PRAC Outcome	28 September 2023
CHMP members comments	02 October 2023
Updated CHMP Rapporteur Assessment Report	05 October 2023
Opinion	12 October 2023

2. Scientific discussion

2.1. Introduction

The purpose of this application is to seek approval for the expanded use of vonicog alfa (VEYVONDI) for prophylactic treatment to prevent or reduce the frequency of bleeding episodes in adults with severe von Willebrand disease (VWD).

2.1.1. Problem statement

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 represents the most common inherited human bleeding disorder with a prevalence of 0.6-1.3%. 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 von Willebrand's disease is rare (<5% of cases, approx. 1 in 1 million people) and represents is the most severe form caused by an almost complete loss of circulating VWF.

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.

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 to control spontaneous bleeding or to prevent excessive bleeding during surgical procedures. However, a subset of patients with severe VWD (i.e. suffering from frequent and severe BEs) may benefit from long-term prophylactic treatment as also acknowledged by the wording in section 4.1 of the Core SmPC for human plasma derived VWF (CPMP/BPWG/278/02) *("Prevention and treatment of haemorrhage or surgical bleeding in von Willebrand disease (VWD), when desmopressin (DDAVP) treatment alone is ineffective or contra-indicated")* and the recently published ASH ISTH NHF WFH 2021 guideline on the management of VWD (Connell et al. 2021).

State the claimed the therapeutic indication

With this application, the MAH applied for an extension of indication for VEYVONDI to include prophylactic treatment in adults with severe VWD to prevent or reduce the frequency of bleeding episodes as follows:

VEYVONDI is indicated in adults (age 18 and older) with von Willebrand Disease (VWD), when desmopressin (DDAVP) treatment alone is ineffective or not indicated for the

- Treatment of haemorrhage and surgical bleeding

- Prevention of surgical bleeding

- Prophylactic treatment to prevent or reduce the frequency of bleeding episodes.

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 18 years and older) with von Willebrand disease (VWD), when desmopressin (DDAVP) treatment alone is ineffective or contraindicated. ~~*VEYVONDI is indicated in adults (age 18 and older) with von Willebrand Disease (VWD), when desmopressin (DDAVP) treatment alone is ineffective or not indicated, for the*~~

- ~~*Treatment of haemorrhage and surgical bleeding*~~
- ~~*Prevention of surgical bleeding.*~~

VEYVONDI should not be used in the treatment of Haemophilia A."

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.

Vonicog alfa is authorised for marketing in the United States (US), Canada, and Japan (under the trade name VONVENDI), and the European Union, United Kingdom, Switzerland, and Australia (under the trade name VEYVONDI), and is indicated for on-demand treatment and control of bleeding events as well as perioperative management of bleeding in adults (age 18 years and older) diagnosed with VWD. In addition, vonicog alfa is approved in the US for routine prophylaxis to reduce the frequency of bleeding events in adult patients with severe type 3 VWD receiving on-demand therapy; and in Japan for prophylactic treatment for suppression of bleeding tendency in adults with VWD.

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

On 22 May 2014, the Marketing Authorisation holder (MAH) obtained CHMP protocol assistance (EMEA/H/SA/1378/2/FU/1/2014/PA) on the design of the Phase 3 Study 071301 for the prophylactic use of rVWF to prevent or reduce the frequency of BEs in patients with VWD. According to the MAH, the final design of Study 071301 including inclusion/exclusion criteria, primary endpoint, secondary outcomes, observation time, and the statistical plan has been aligned with this advice.

2.1.4. General comments on compliance with GCP

As requested during the EMA pre-submission meeting held on 29 June 2022, the MAH provided the GCP inspection reports already conducted in relation to study 071301 from both the FDA (1 sponsor report and 3 site inspection reports) and PMDA (1 site inspection report). None of the previous inspections revealed major issues requiring further regulatory actions.

Table 1. Study 071301 Sites Audited by Regulatory Authorities

Site (Full Address)	Country	Date of Inspection	Regulatory Agency	Findings
Site 109 Indiana Hemophilia & Thrombosis Center, Inc. 8326 Naab Rd Indianapolis, IN 46260-1920	United States	17 Sep 2021	FDA	None. Inspection Report available upon request.
Site 192 Hamilton Health Sciences Centre 1200 Main St. W. Hamilton, Ontario, L8N 3Z5	Canada	05-06 Oct 2021	FDA	None. Inspection Report available upon request.
Site 400 Erasmus University Medical Center S Gravendijkwal 230 3015 CE Rotterdam	Netherlands	18-19 Oct 2021	FDA	None. Inspection Report available upon request.
Site 463 Ege University Medical Faculty Hematology Ege Universitesi Tip Fakultesi Ic Hastaliklari Anabilim Dali Hematoloji Bilim Dali Ismir	Turkey	16 Dec 2021 EST / 17 Dec 2021 JPT	PMDA	None. Inspection Report available upon request. The PMDA reviewed site-specific documents as part of a virtual Sponsor inspection. Because no concerns were raised in the virtual inspection, no on-site inspection was required.

FDA=Food and Drug Administration; PMDA=Pharmaceuticals and Medical Devices Agency

2.2. Non-clinical aspects

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

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

2.3. Clinical aspects

2.3.1. Introduction

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

Table 2. Clinical Studies of Vonicog alfa prophylaxis for VWD

Study Number and Status	Description	Sample Size	Main Criteria for Inclusion	Dose Range and Frequency
071301 Completed	Phase 3 Prophylaxis A prospective, Phase 3, open-label, international multicenter study on efficacy and safety of prophylaxis with rVWF in severe VWD	23 (13 Prior OD; 10 Switch)	≥18 years with severe VWD (VWF:RCo <20%) who previously received VWF for OD treatment and prophylactic treatment was recommended or who had been receiving prophylactic treatment with a pdVWF product	PK assessments: 50±5 IU/kg VWF:RCo at initial assessment in Prior OD subjects; prophylaxis dose after 5 to 6 infusions in Switch subjects and at end of study in all subjects. Prophylaxis: Subjects previously OD (Prior OD): twice-weekly doses of 50±10 IU/kg VWF:RCo or individualized doses based on PK, type and severity of past BEs, and clinical and laboratory data Subjects switching from pdVWF prophylaxis (Switch): rVWF dose equivalent to weekly dose of VWF (±10%) in the pdVWF concentrate divided into 2 infusions or individualized dose/dosing frequency Treatment of BEs: individualized based on weight, VWD type, and severity of BE and monitoring of appropriate clinical and laboratory measures, with or without ADVATE® Perioperative management of bleeding: Priming dose (generally 40 to 60 IU/kg) on the day before surgery to allow endogenous FVIII activity to reach at least 30 IU/dL (minor, oral surgery), or 60 IU/dL (major surgery) by 3 hours before surgery. Preoperative loading dose, with or without ADVATE, based on the 3-hour presurgical FVIII activity, to get the subject to targeted VWF:RCo and FVIII activities at initiation of the surgery. After surgery, additional vonicog alfa infusions were given to maintain targeted VWF:RCo and FVIII activities. Maximum dose per infusion: up to 80 IU/kg VWF:RCo.
SHP677-304 Ongoing	Phase 3b Continuation A Phase 3b, prospective, open-label, uncontrolled, multicenter study on long-term safety and efficacy of rVWF in pediatric and adult subjects with severe VWD	Planned: up to 71 subjects with severe VWD transitioning from previous studies or newly enrolled (including at least 5 subjects with type 3 VWD on prophylaxis regimen).	Pediatric and adult subjects with severe VWD (VWF:RCo <20%) requiring replacement therapy to control bleeding	PK assessments: 50 (±5) IU/kg VWF:RCo before prophylaxis initiation for newly enrolled subjects (Cohort 4) and for all subjects in prophylaxis cohorts (Cohorts 1-4) at the end of the study. Prophylaxis: dose/dosing frequency depending on previous treatment (prophylaxis) and BEs in the past 6 months; for prophylactic treatment cohort open to new subjects, initiation dosing frequency is 50±10 IU/kg once weekly prophylactic infusion 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 management of 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

ADVATE=recombinant factor VIII (octocog alfa); BE=bleeding episode; FVIII=factor VIII; IU=International Unit; OD=on-demand; pdVWF=plasma-derived von Willebrand factor; PK=pharmacokinetic(s); rVWF=recombinant von Willebrand factor (vonicog alfa); VWD=von Willebrand disease; VWF=von Willebrand factor; VWF:RCo=von Willebrand factor:ristocetin cofactor

2.3.2. Pharmacokinetics

Study 071301

For a detailed description of study 071301, reference is made to section 2.4.1 below.

During Study 071301, two PK/PD assessments using a full PK sampling collection scheme were conducted. For Prior OD (on-demand) subjects, an initial PK assessment and a steady-state PK assessment at the end of studywere performed. The rVWF infusion for the initial PK assessment for Prior OD subjects only was to be administered during the baseline visit, which had to take place within 42 days after the completion of screening procedures and upon confirmation of eligibility. A washout period of at least 5 days since the last pre-study VWF dose was required prior to infusion of rVWF for PK assessment. Subjects received 50 ±5 IU/kg rVWF for the initial PK assessment. Blood samples were to be drawn within 30 minutes pre-infusion, and at 11 time points post-infusion (15, 30, and 60 [±5] minutes; 3, 6, 12, and 24 [±0.5] hours; and 30, 48, 72, and 96 [±2] hours).

For patients who had been receiving prophylactic treatment with a plasma-derived VWF "Switch subjects", 2 steady state PK assessments were performed. The first PK assessment was performed shortly after reaching steady state, which was expected to be around prophylactic dose #5 or #6 following the 1st prophylactic dose received, for majority of the subjects, and a second PK assessment was performed at the EOS; however, one Switch subject had the initial PK assessment done at the first dose.

For steady state PK assessments (second PK assessment for all subjects and initial PK assessment for Switch subjects), the rVWF dose was to be given for prophylaxis at the time, and blood samples were be drawn within 30 minutes pre-infusion, and at 11 time points post-infusion (15, 30, and 60 [±5] minutes; 3, 6, 12, and 24 [±0.5] hours; and 30, 48, 72, and 96 [±2] hours) as long as it did not interfere with subject's scheduled regular prophylactic dosing regimen, otherwise the sampling at 96 ±2 hours was to be omitted, but it was critical that the assessments were at the same partial interval, thereby including the same number of sampling timepoints for the 1st and 2nd PK assessments for an individual Switch subject. The final sample for PK assessment had to be drawn before the next scheduled prophylactic dose was administered.

PK/PD parameters were derived using noncompartmental methods using actual elapsed time from the start of infusion rather than scheduled sampling times, wherever possible, and actual infusion duration.

In addition, pre-dose and 30-minute post-dose samples were taken at Months 1, 2, 3, 6, and 9 to assess incremental recovery (IR, postdose value minus pre-dose value divided by rVWF dose) of PK and PD measures over time. The EOS IR information was obtained from the PK assessment at the end of study using C_{max} samples.

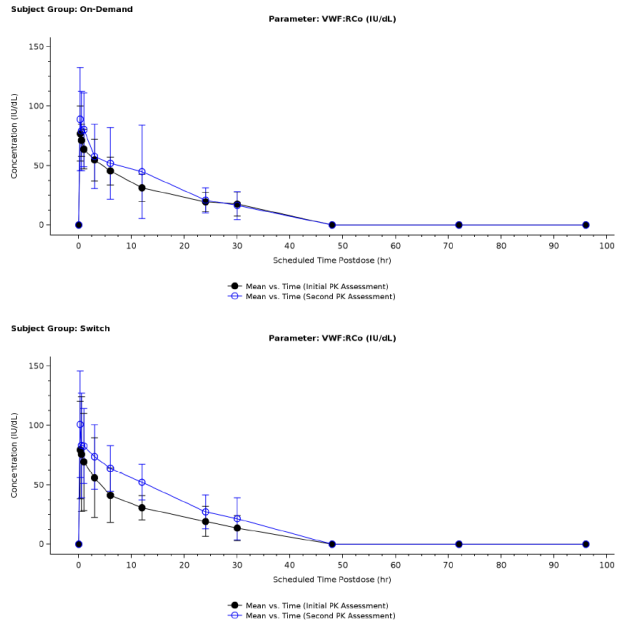
Results:

In the PK FAS, 22 subjects (12 Prior OD subjects and 10 Switch subjects) completed the initial PK/PD assessments. Among these subjects, 9 Prior OD subjects who completed the study had a full PK assessment at the EOS; and 7 out of 8 Switch subjects who completed the study had a full PK assessment at the EOS (1 subject completed the study but did not have a PK assessment at the EOS).

The Prior OD and Switch groups' plasma concentration–time profiles for VWF:RCo at the initial and second/final (Month 12) assessment are shown in the Figure below. Following the initial PK vonicog alfa dose, VWF:RCo peaked at 0.25 hours with 77.3 IU/kg (median) and 77.01 (23.04) IU/kg (mean [standard deviation (SD)]) for Prior OD subjects, and at 0.5 hours with 73.0 IU/kg (median) and 75.79 (48.28) IU/kg (mean [SD]) for Switch subjects, which then declined and was below the lower limit of quantification at 48 hours and beyond for both groups. Following the final EOS PK vonicog alfa dose, the

concentration-time profiles followed a similar trend, with median VWF:RCo peaks at 0.25 hours with 89.40 IU/kg (median) and 89.18 (43.32) IU/kg (mean [SD]) for Prior OD subjects. The VWF:RCo peak concentration for Switch subjects at the EOS analysis occurred at 0.25 hours for the mean (SD), with 101.11 (44.85) IU/kg, and at 0.5 hours for the median, with 95.30 IU/kg.

Figure 1. Initial vs Final Assessment of VWF:RCo Activity



The error bars show mean ± SD.
CSR=clinical study report; LLOQ=lower limit of quantification; OD=On-demand;
PK=pharmacokinetic; VWF:RCo=von Willebrand factor ristocetin cofactor
Values <LLOQ (8.0 IU/dL for VWF:RCo) were considered as zero in descriptive statistics.
Source: Study 071301 revised CSR Listing 16.2.6.22; Table 14.2.8.1, and Table 14.2.8.7.

Key PK parameters for the Prior OD subjects at the initial PK assessment, a summary of the VWF:RCo PK profile at steady state (i.e. initial and EOS PK assessments for Switch subjects and EOS PK for Prior OD subjects), and statistical comparisons of final vs. initial parameters are summarized below (tables 3-6):

Table 3. Descriptive Statistics for Selected Parameters for VWF:RCo After a Single Dose of Vonicog Alfa (Initial Assessment for the Prior On-demand Group) (PK Analysis Set)

Variable PK Parameter	Initial Assessment (Prior OD Group)		
	N=12[a]		
VWF:RCo	**Median**	**Arithmetic Mean (SD)**	**(Min, Max)**
CL (dL/kg/h)	0.04331	0.0477 (0.0162)	(0.0237, 0.0709)
C_{max} (IU/dL)	75.7	74.6 (16.1)	(37.3, 106)
C_{max}/Dose ([IU/dL]/[IU/kg])	1.48	1.49 (0.316)	(0.833, 2.12)
$AUC_{0\text{-}inf}$ (IU·h/dL)	1178	1199 (468)	(631, 2150)
$AUC_{0\text{-}inf}$/Dose ([IU·h/dL]/[IU/kg])	23.09	23.6 (9.04)	(14.1, 42.1)
T_{max} (h)	0.54	ND	(0.27, 1.02)
$t_{1/2}$ (h)	15.98	17.2 (10.1)	(9.01, 45.8)
IR at C_{max} ([IU/dL]/[IU/kg])	1.44	1.46 (0.321)	(0.830, 2.12)

AUC=area under the plasma concentration–time curve; $AUC_{0\text{-}inf}$=AUC from time 0 to infinity; CL=clearance; C_{max}=maximum plasma concentration; CSR=clinical study report; IR=incremental recovery; Max=maximum; Min=minimum; ND=not derived; OD=on-demand; PK=pharmacokinetic; SD=standard deviation; $t_{1/2}$=terminal elimination half-life; T_{max}=time to reach the maximum plasma concentration; VWF:RCo=von Willebrand factor ristocetin cofactor activity
[a] N is the number of subjects who had the assessment, but not all parameters could be calculated for all subjects.
For the initial PK assessment, all Prior OD subjects received vonicog alfa doses between 44 and 55 IU/kg. This assessment was done after a washout and with the first dose of vonicog alfa.

Table 4. Descriptive Statistics for Selected Parameters for Steady State von Willebrand Factor Ristocetin Cofactor Activity (Final Assessment for the Prior On-demand Group and Both Assessments for the Switch Group) (PK Analysis Set)

Variable PK Parameter	Prior OD Group		Switch Group			
	EOS		Initial Assessment		EOS	
	N=9[a]		N=10[a]		N=7[a]	
	Mean[b] (SD)	(Min, Max)	Mean[b] (SD)	(Min, Max)	Mean[b] (SD)	(Min, Max)
VWF:RCo						
C_{max} (IU/dL)	92.6 (37.1)	(41.6, 148.7)	85.3 (40.9)	(35.6, 167.4)	102.9 (44.7)	(46.7, 176.6)
C_{max}/Dose ([IU/dL/[IU/kg])	1.87 (0.624)	(0.889, 2.68)	1.63 (0.357)	(1.21, 2.25)	1.88 (0.291)	(1.57, 2.28)
$AUC_{0\text{-}96\ hours}$ (IU·h/dL)	1561 (1298)	(460, 4460)	1242 (800.5)	(692, 2950)	1662 (675.0)	(1230, 2440)
$AUC_{0\text{-}96\ hours}$/Dose ([IU·h/dL]/[IU/kg])	30.9 (23.4)	(9.83, 83.4)	23.7 (9.21)	(13.3, 39.6)	27.5 (9.74)	(21.7, 38.7)
T_{max} (h)	0.330[c]	(0.25, 1.25)	0.470[c]	(0.28, 1.07)	0.40[c]	(0.33, 0.52)
IR at C_{max} ([IU/dL]/[IU/kg])	1.75 (0.548)	(0.890, 2.68)	1.61 (0.336)	(1.21, 2.13)	1.88 (0.289)	(1.57, 2.28)

AUC=area under the plasma concentration–time curve; $AUC_{0\text{-}96\ hours}$=AUC from time 0 to 96 hours after the dose (which is approximately the dosing interval tau for the majority of subjects); C_{max}=maximum plasma concentration; EOS=end of study; IR=incremental recovery; Max=maximum; Min=minimum; OD=on-demand; PK=pharmacokinetic; SD=standard deviation; T_{max}=time to reach the maximum plasma concentration; VWF:RCo=von Willebrand factor ristocetin cofactor activity

[a] N is the number of subjects who had the assessment but not all parameters could be calculated for all subjects.

[b] Arithmetic means reported.

[c] Value is median.

For the final PK assessment, all 9 Prior OD subjects were on the twice weekly regimen and received vonicog alfa doses between 41 and 56 IU/kg.

For the initial and final PK assessments, the Switch subjects received vonicog alfa doses ranging from 24 to 75 IU/kg and from 24 to 78 IU/kg, respectively. At the initial assessment, Switch subjects were taking vonicog alfa doses twice weekly (8 of 10 subjects), once a week (1 subject), and 3 times a week (1 subject).

Not all subjects reached C_{max} at the same time after the dose; therefore, the PK parameters and the mean concentration-time curves may appear to be mismatched even though both are correct.

Mean values are arithmetic means.

Table 5. Statistical Comparison of Key Pharmacokinetic Parameters Between VWF:RCo Initial Assessment and Study Completion for Prior On-demand Subjects

Parameter (unit)	Time Point	n	Geo LS Mean	95% CI of Geo LS Mean	Study Completion vs Initial Assessment (V2/V1)		
					Ratio (%)	90% CI of Ratio (%)	p-value
$AUC_{0\text{-}inf}$ (IU·h/dL)	Initial	11	1113	(796.6, 1554)	107.28	(72.27, 159.24)	0.7546
$AUC_{0\text{-}tau,}$72hr (IU·h/dL)	EOS	9	1194	(821.3, 1735)	-	-	-
$AUC_{0\text{-}inf}$/D (kg·IU·h/dL/IU)	Initial	11	22.09	(16.16, 30.18)	110.92	(77.27, 159.22)	0.6163
$AUC_{0\text{-}tau,72hr}$/D (kg·IU·h/dL/IU)	EOS	9	24.50	(17.29, 34.70)	-	-	-
$AUC_{0\text{-}inf}$ (IU·h/dL)	Initial	11	1113	(787.0, 1575)	109.36	(72.23, 165.56)	0.7051
$AUC_{0\text{-}tau,96hr}$ (IU·h/dL)	EOS	9	1218	(825.5, 1796)	-	-	-
$AUC_{0\text{-}inf}$/Dose (kg·IU·h/dL/IU)	Initial	11	22.09	(15.97, 30.57)	113.10	(77.29, 165.51)	0.5727
$AUC_{0\text{-}tau,}$96hr/Dose (kg·IU·h/dL/IU)	EOS	9	24.99	(17.39, 35.91)	-	-	-
C_{max} (IU/dL)	Initial	12	72.74	(59.39, 89.09)	115.34	(91.56, 145.30)	0.2854
	EOS	9	83.90	(66.26, 106.2)	-	-	-
C_{max}/Dose (kg·IU/dL/IU)	Initial	12	1.454	(1.210, 1.747)	117.52	(97.55, 141.57)	0.1463
	EOS	9	1.709	(1.388, 2.105)	-	-	-

AUC=area under the plasma concentration–time curve; $AUC_{0\text{-}inf}$=AUC from time 0 to infinity; $AUC_{0\text{-}tau}$=AUC over the dosing interval; CI=confidence interval; C_{max}=maximum plasma concentration; CSR=clinical study report; EOS=end of study; Geo=geometric; LS=least squares; OD=on demand; V=visit

Notes: The log-transformed PK parameter estimates were analyzed using a linear mixed-effect model with time point as an independent fixed effect and subject as a random effect. The model estimates of the LS means, difference between LS means, and corresponding CIs were exponentiated to get the geometric LS means, paired ratio, and corresponding CIs shown on the table. Only PK parameters with n≥3 for both time points were included in the analysis.

Table 6. Statistical Comparison of Key Pharmacokinetic Parameters Between VWF:RCo Initial Assessment and Study Completion for Switch Subjects

Parameter (unit)	Time Point	n	Geo LS Mean	95% CI of Geo LS Mean	Study Completion vs Initial Assessment (V2/V1)		
					Ratio (%)	90% CI of Ratio (%)	p-value
$AUC_{0\text{-}tau,72hr}$ (IU·h/dL)	Initial	10	1073	(738.1, 1559)	106.40	(93.37, 121.23)	0.3697
	EOS	5	1141	(780.2, 1669)			
$AUC_{0\text{-}tau,72hr}$/Dose (kg·IU·h/dL/IU)	Initial	10	22.23	(17.51, 28.21)	101.09	(88.52, 115.45)	0.8720
	EOS	5	22.47	(17.47, 28.90)			
$AUC_{0\text{-}tau,96hr}$ (IU·h/dL)[a]	Initial	7	1090	(716.7, 1659)	144.96	(78.16, 268.88)	0.2962
	EOS	3	1581	(832.7, 3001)			
$AUC_{0\text{-}tau,96hr}$/Dose (kg·IU·h/dL/IU)	Initial	7	23.11	(17.38, 30.72)	109.14	(83.66, 142.39)	0.2857
	EOS	3	25.22	(18.58, 34.24)			
C_{max} (IU/dL)	Initial	10	76.83	(54.68, 107.9)	112.29	(95.81, 131.60)	0.2061
	EOS	7	86.27	(60.89, 122.2)			
C_{max}/D (kg·IU/dL/IU)	Initial	10	1.592	(1.391, 1.822)	111.32	(99.86, 124.10)	0.1037
	EOS	7	1.772	(1.529, 2.054)			

AUC=area under the plasma concentration–time curve; $AUC_{0\text{-}tau}$=AUC over the dosing interval; CI=confidence interval; C_{max}=maximum plasma concentration; CSR=clinical study report; EOS=end of study; Geo=geometric; LS=least-squares; PK=pharmacokinetic; V=visit

[a] For these parameters, subject was removed from the originally defined model due to estimation issue.

Notes: The log-transformed PK parameter estimates were analyzed using a linear mixed-effect model with time point as an independent fixed effect and subject as a random effect. The model estimates of the LS means, difference between LS means, and corresponding CIs were exponentiated to get the geometric LS means, paired ratio, and corresponding CIs shown on the table. Only PK parameters with n≥3 for both time points were included in the analysis.

The absence of statistically significant differences between the initial and EOS PK assessments for any of the VWF:RCo PK parameters analysed (geometric LS means) supports the MAH's notion of temporal consistency of vonicog alfa PK properties.

Considering the differences in sample sizes (with a lower number of available PK assessments at EOS) and to better address the issue of intra-subject consistency of PK parameters over time, the MAH was requested to provide summary tables for final versus initial PK parameters for VWF:RCo and FVIII:C considering only the subset of subjects with available PK data from both PK visits (baseline and EOS). Together, the newly provided data further support the MAH's claim of a lack of statistically significant differences in PK properties of vonicog alfa during long-term prophylactic treatment.

Median VWF:RCo IR for both groups was similar and relatively constant over the assessment time course. The medians ranged from 1.276 (prophylaxis visit) to 1.793 (Month 9) for the Prior OD subjects and from 1.280 (prophylaxis visit) to 1.718 (Month 6) for Switch subjects.

Table 7. Summary of VWF:RCo Incremental Recovery

Group Characteristic	Prophylaxis Visit	Month 1	Month 2	Month 3	Month 6	Month 9
Prior OD						
n	6	9	9	8	9	7
Mean (SD)	1.161 (0.611)	1.586 (0.742)	1.706 (0.459)	1.581 (0.375)	1.626 (0.491)	1.698 (0.494)
Median	1.276	1.496	1.768	1.492	1.521	1.793
Q1, Q3	1.13, 1.58	1.08, 2.13	1.40, 1.88	1.43, 1.83	1.44, 1.76	1.22, 2.11
Min, Max	0.00[a], 1.70	0.310, 2.64	0.965, 2.54	0.998, 2.14	1.08, 2.64	0.955, 2.33
Switch						
n	7	5	7	10	9	8
Mean (SD)	1.419 (0.524)	1.591 (0.219)	1.390 (0.337)	1.530 (0.490)	1.596 (0.619)	1.645 (0.363)
Median	1.280	1.489	1.476	1.705	1.718	1.665
Q1, Q3	0.985, 1.85	1.48, 1.78	1.31, 1.59	1.20, 1.93	1.59, 1.93	1.39, 1.91
Min, Max	0.900, 2.39	1.35, 1.86	0.702, 1.75	0.654, 2.04	0.561, 2.41	1.08, 2.14

C_{max}=maximum plasma concentration; CSR=clinical study report; IR=incremental recovery; Max=maximum; Min=minimum; n=number of subjects in each category; OD=on demand; PK=pharmacokinetic; Q1=first quartile; Q3=third quartile; SD=standard deviation; VWD=von Willebrand disease

[a] One subject in the Prior OD group with Type 3 VWD [redacted], had an IR of 0 for the prophylaxis visit and an IR of 0.310 at the Month 1 visit; no further IR assessments were performed for this subject.

Notes: Non-PK infusion PK samples were used to calculate IR as follows: (30 min Postdose - Predose)/Actual Dose in IU/kg.
IR at C_{max} on Month 12 included in separate PK Infusion Parameter summary tables.

Study SHP677-304

For a detailed description of the continuation study SHP677-304, reference is made to section 2.4.1 below.

Study SHP677-304 is still ongoing. The present submission is supported by an interim analysis performed with a data cut-off of 30 Jun 2022. The interim analysis included PK data for a total of 11 subjects who completed the parent study 071301 and continued prophylactic treatment in study SHP677-304.

PK data in the interim analysis are limited to an analysis of incremental recovery (IR) of vonicog alfa for subjects receiving prophylaxis. IR was determined for VWF:RCo, VWF:Ag, and VWF:CB for the initial continuation study prophylaxis visit, as well as for follow-up visits at Months 1, 2, 3, 6, 9, and 12.

As noted by the MAH, the IR at 30 minutes postdose was generally >1 and consistent over time for the majority of subjects for VWF:RCo, VWF:Ag, and VWF:CB, which demonstrates sustainable exposure for continued prophylactic dosing of vonicog alfa. Additionally, the ranges of the mean values of IR over time from Month 1 to Month 12 for VWF:RCo were consistent with values observed in the parent study.

Table 8. Summary of VWF:RCo IR [(IU/dL)/(IU/kg)], Cohorts 1 and 2

Cohort Subject	Prophylaxis Visit	Month 1	Month 2	Month 3	Month 6	Month 9	Month 12
Cohort 1							
	2.06	2.75	2.17	2.40	2.26	ND	ND
	ND	ND	ND	ND	1.02	0.346	1.05
	0.744	1.48	0.624	1.58	0.404	1.42	1.56
	ND	2.21	ND	ND	ND	2.10	2.07
	ND	0.987	ND	ND	ND	2.02	1.60
	ND	1.50	ND[a]	0.921	1.50	1.68	1.39
	ND	1.32	ND	ND	1.02	1.03	1.23
	ND	1.69	ND	1.75	1.53	1.73	1.73
	1.26	1.51	ND	1.47	1.42	1.39	1.50
	ND	1.52	0.611	1.62	1.36	1.70	ND
Cohort 2							
	1.59	1.67	1.37	ND	0.952	ND	0.796

IR=incremental recovery; IU=international unit(s); ND=not derived; VWF:RCo=von Willebrand factor: Ristocetin cofactor

[a] Negative IR calculated; excluded from descriptive statistics.

2.3.3. Pharmacodynamics

Mechanism of action

Vonicog alfa is a recombinantly produced VWF intended to replace endogenous VWF. VWF functions at two steps of haemostasis. First, VWF facilitates primary haemostasis by its ability to associate to subendothelial collagen as well as platelet adhesion receptor GP1. This effect occurs immediately and is known to depend to a large extent on the degree of VWF multimerisation. In addition, VWF indirectly promotes secondary haemostasis by protecting the critical coagulation factor VIII from degradation. Because of this, administration of vonicog alfa restores the FVIII:C level to normal as a secondary effect. As noted in section 5.1 of the currently approved SmPC, after administration of vonicog alfa, the FVIII:C level rises above 40% within 6 hours and peaks within 24 hours in the majority of patients.

Primary and secondary pharmacology

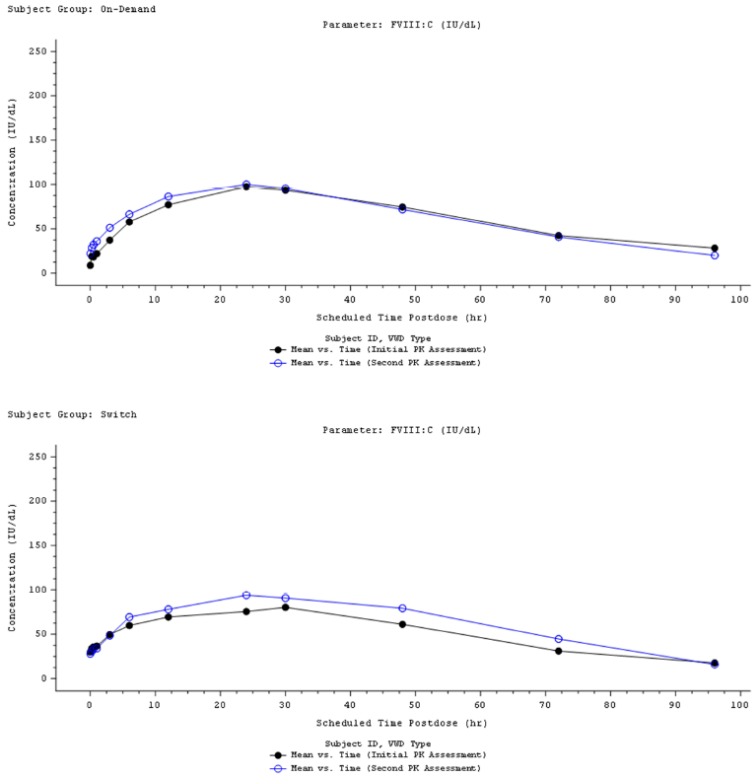
Both prophylaxis studies (Study 071301 and SHP677-304) included assessments of plasma FVIII activity as a measure of vonicog alfa PD.

Study 071301

Factor VIII:C

The Prior OD and Switch groups' plasma concentration–time profiles for FVIII activity at the initial and second/final (Month 12) assessment are shown in the Figure below. For Prior OD subjects, the mean (SD) and median pre-dose concentrations of FVIII:C for the initial PK assessment was 8.8 (14.9) and 2.0 IU/dL, respectively. Following the initial vonicog alfa dose (which ranged from 44.78 to 54.73 IU/kg), mean (SD) and median FVIII:C peaked at 24 hours at 97.4 (23.6) and 91.5 IU/dL, respectively, which then declined over time to a mean (SD) and median of 28.3 (26.6) and 18.0 IU/dL, respectively, by 96 hours. The initial pre-dose FVIII:C concentrations for Switch subjects were a mean (SD) and median of 30.0 (21.6) and 24.0 IU/dL, respectively. The PD concentration over time curve for Switch subjects followed a similar trend as the Prior OD subjects; after the initial vonicog alfa dose (range of 24.38 IU/kg to 74.48 IU/kg), mean (SD) and median FVIII:C peaked at 30 and 24 hours, respectively, at 80.2 (25.4) and 85.5 IU/dL, respectively, which then declined over time to a mean (SD) and median of 17.7 (16.1) and 13.0 IU/dL, respectively, by 96 hours.

Figure 2. Initial vs Final Assessment of FVIII Activity (Prior OD [Top] and Switch [Bottom] Groups)



Key FVIII:C PD parameters for the Prior OD subjects at the initial PK assessment, a summary of FVIII:C PD at VWF:RCo steady state (i.e. initial and EOS PK assessments for Switch subjects and EOS PK for Prior OD subjects), and statistical comparisons of final vs. initial PD parameters of FVIII:C are summarized in the below tables 9-12.

Table 9. Descriptive Statistics for Selected Parameters for Factor VIII Activities After a Single Dose of Vonicog Alfa (Initial Assessment for the Prior On-demand Group) (PK Analysis Set)

	Initial Assessment (Prior OD Group)		
	N=12[a]		
Parameter (units)	Median	Arithmetic Mean (SD)	(Min, Max)
C_{max} (IU/dL)	87.0	90.8 (32.1)	(46, 158)
C_{max}/Dose ([IU/dL]/[IU/kg])	1.838	1.81 (0.628)	(0.926, 3.10)
$AUC_{0\text{-tlast}}$ (IU·h/dL)	4524	4949 (2436)	(1670, 11300)
$AUC_{0\text{-tlast}}$/Dose ([IU·h/dL]/[IU/kg])	94.64	98.6 (47.5)	(33.8, 221)
$C_{predose}$ (IU/dL)	2.0	8.8 (14.9)	(2, 45)
T_{max} (h)	24.055	ND	(12.0, 46.3)

AUC=area under the plasma concentration-time curve; $AUC_{0\text{-tlast}}$=AUC from time 0 to the last measurable concentration; CSR=clinical study report; C_{max}=maximum plasma concentration; $C_{predose}$=plasma concentration before the vonicog alfa infusion; Max=maximum; Min=minimum; OD=on-demand; PK=pharmacokinetic; SD=standard deviation; T_{max}=time to reach the maximum concentration

[a] N is the number of subjects that had the assessment, but not all parameters could be calculated for all subjects.
For the initial PK assessment, all Prior OD subjects received vonicog alfa doses between 44 and 55 IU/kg.

Similar to the PK data, the reported single dose PD data (i.e. vonicog alfa-induced rise of plasma FVIII:C levels) are considered largely consistent with the know PK/PD behaviour of VEYVONDI as e.g. reflected in the EPAR.

Table 10. Descriptive Statistics for Selected Parameters for Steady State Factor VIII:C (Final Assessment for the Prior OD Group and Both Assessments for the Switch Group) (PK Analysis Set)

	Prior OD Group			Switch Group					
	Final Assessment			Initial Assessment			Final Assessment		
	N=9			N=10			N=10[a]		
Parameter (units)	Median	Mean (SD)	(Min, Max)	Median	Mean (SD)	(Min, Max)	Median	Mean (SD)	(Min, Max)
C_{max} (IU/dL)	97.0	104.1 (35.1)	(63, 169)	89.0	85.6 (21.5)	(53, 118)	80.0	75.7 (37.3)	(22, 112)
C_{max}/Dose ([IU/dL/[IU/kg])	1.84	2.14 (0.738)	(1.22, 3.65)	1.71	1.76 (0.423)	(1.28, 2.50)	1.38	1.33 (0.394)	(0.744, 1.78)
$AUC_{0\text{-}96\ hours}$ (IU·h/dL)	5752	5984 (2490)	(2870, 11400)	4327	4621 (1161)	(3530, 6890)	6175	5836 (1735)	(3960, 7380)
$AUC_{0\text{-}96\ hours}$/Dose ([IU·h/dL]/[IU/kg])	116.1	121.8 (45.35)	(55.7, 205)	88.5	94.8 (26.72)	(63.1, 145)	101.8	96.6 (23.57)	(70.8, 117)
$C_{predose}$ (IU/dL)	11.0	22.1 (23.5)	(6, 81)	24.0	30.0 (21.6)	(2, 67)	21.0	28.0 (21.2)	(1, 70)
T_{max} (h)	24.5	NA	(6.17, 29.3)	24.2	NA	(9.78, 30.0)	24.1	NA	(1.08, 30.0)

AUC=area under the plasma concentration-time curve; $AUC_{0\text{-}96\ hours}$=AUC from time 0 to 96 hours after the dose (which is approximately the dosing interval tau for the majority of subjects); C_{max}=maximum plasma concentration; $C_{predose}$=plasma concentration before the vonicog alfa infusion; CSR=clinical study report; Max=maximum; Min=minimum; N=number of subjects who had the assessment, though not all parameters could be calculated for all subjects; OD=on-demand; PK=pharmacokinetic; SD=standard deviation; T_{max}=time to reach the maximum concentration

[a] N=7 for $AUC_{0\text{-}96\ hours}$ and $AUC_{0\text{-}96\ hours}$/Dose for the Final Assessment in the Switch Group.

For the final PK assessment, all 9 Prior OD subjects were on the twice weekly regimen and received vonicog alfa doses between 41 and 56 IU/kg.

For the initial and final PK assessments, the Switch subjects received vonicog alfa doses ranging from 24 to 75 IU/kg and from 24 to 78 IU/kg, respectively. At the initial assessment, Switch subjects were taking vonicog alfa doses twice weekly (8 of 10 subjects), once a week (1 subject), and 3 times a week (1 subject).

Not all subjects reached C_{max} at the same time after the dose; therefore, the PK parameters and the mean concentration-time curves may appear to be mismatched even though both are correct.

Mean values are arithmetic means.

Table 11. Statistical Comparison of Key Pharmacokinetic Parameters Between Initial Factor VIII:C Assessment and Study Completion for Prior On-demand Subjects

					Study Completion vs Initial Assessment (Initial/EOS)		
Parameter (unit)	Time point	n	Geo LS Mean	95% CI of Geo LS Mean	Ratio (%)	90% CI of Ratio (%)	p-value
$AUC_{0\text{-}tlast}$ (IU·h/dL)	Initial	12	4466	(3441, 5796)	109.41	(83.30, 143.70)	0.5634
$AUC_{0\text{-}tau,72hr}$ (IU·h/dL)	EOS	9	4886	(3627, 6581)	-	-	-
$AUC_{0\text{-}tlast}$/D (kg·IU·h/dL/IU)	Initial	12	89.28	(69.13, 115.3)	112.30	(86.90, 145.13)	0.4311
$AUC_{0\text{-}tau,}$72hr/D (kg·IU·h/dL/IU)	EOS	9	100.3	(75.05, 134.0)	-	-	-
$AUC_{0\text{-}tlast}$ (IU·h/dL)	Initial	12	4466	(3408, 5852)	122.11	(93.11, 160.16)	0.2114
$AUC_{0\text{-}tau,96hr}$ (IU·h/dL)	EOS	9	5453	(4015, 7407)	-	-	-
$AUC_{0\text{-}tlast}$/D (kg·IU·h/dL/IU)	Initial	12	89.28	(68.58, 116.2)	125.34	(97.51, 161.11)	0.1339
$AUC_{0\text{-}tau,}$96hr/D (kg·IU·h/dL/IU)	EOS	9	111.9	(83.27, 150.4)	-	-	-
C_{max} (IU/dL)	Initial	12	85.63	(68.88, 106.5)	109.34	(91.60, 130.53)	0.3773
	EOS	9	93.63	(73.93, 118.6)	-	-	-
C_{max}/D (kg·IU/dL/IU)	Initial	12	1.712	(1.375, 2.132)	112.11	(95.11, 132.14)	0.2329
	EOS	9	1.919	(1.517, 2.428)	-	-	-
$C_{predose}$ (IU/dL)	Initial	12	3.830	(1.961, 7.480)	489.07	(329.22, 726.52)	<0.0001
	EOS	9	18.73	(9.337, 37.57)	-	-	-

AUC=area under the plasma concentration–time curve; $AUC_{0\text{-}tau}$=AUC over the dosing interval; $AUC_{0\text{-}tlast}$=AUC from time 0 to the last measurable concentration; CI=confidence interval; C_{max}=maximum plasma concentration; $C_{predose}$=plasma concentration before the vonicog alfa infusion; CSR=clinical study report; EOS=end of study; Geo=geometric; LS=least squares; PK=pharmacokinetic

The log-transformed PK parameter estimates were analyzed using a linear mixed-effect model with time point as an independent fixed effect and subject as a random effect. The model estimates of the LS means, difference between LS means, and corresponding CIs were exponentiated to get the geometric LS means, paired ratio, and corresponding CIs shown on the table.

Only PK parameters with n≥3 for both timepoints were included in the analysis.

Upon request, the MAH presented a summary of cases of high pre-dose FVIII variability in relation to the preceding doses of vonicog alfa ± ADVATE that contributed to the observed pre-dose FVIII:C. Except for one case, all notable values could be reasonably explained by either the timing or the amount of preceding doses of vonicog alfa ± ADVATE.

Table 12. Statistical Comparison of Key Pharmacokinetic Parameters Between Initial Factor VIII:C Assessment and Study Completion for Switch Subjects

Parameter (unit)	Time point	n	Geo LS Mean	95% CI of Geo LS Mean	Study Completion vs Initial Assessment (V2/V1)		
					Ratio (%)	90% CI of Ratio (%)	p-value
$AUC_{0\text{-}tau,72hr}$ (IU·h/dL)	Initial	10	4166	(3386, 5125)	108.10	(86.80, 134.62)	0.4956
	EOS	5	4503	(3478, 5830)	-	-	-
$AUC_{0\text{-}tau,72hr}$/D (kg·IU·h/dL/IU)	Initial	10	86.32	(73.40, 101.5)	96.87	(84.36, 111.25)	0.6483
	EOS	5	83.62	(69.48, 100.6)	-	-	-
$AUC_{0\text{-}tau,96hr}$ (IU·h/dL)[a]	Initial	7	4510	(3604, 5645)	125.23	(90.01, 174.24)	0.2408
	EOS	3	5649	(4010, 7957)	-	-	-
$AUC_{0\text{-}tau,96hr}$/D (kg·IU·h/dL/IU)	Initial	7	93.19	(70.37, 123.4)	100.90	(53.15, 191.55)	0.9772
	EOS	3	94.03	(53.16, 166.3)	-	-	-
C_{max} (IU/dL)	Initial	10	83.01	(60.46, 114.0)	75.93	(52.40, 110.01)	0.2049
	EOS	7	63.03	(42.97, 92.45)	-	-	-
C_{max}/D (kg·IU/dL/IU)[a]	Initial	10	1.720	(1.429, 2.071)	74.09	(58.39, 94.00)	0.0432
	EOS	7	1.274	(1.021, 1.591)	-	-	-
C_{min} (IU/dL)	Initial	10	15.84	(7.346, 34.14)	100.95	(35.80, 284.65)	0.9869
	EOS	7	15.99	(6.141, 41.61)	-	-	-
C_{min}/D (kg·IU/dL/IU)	Initial	10	0.3281	(0.1534, 0.7017)	94.94	(34.96, 257.82)	0.9258
	EOS	7	0.3115	(0.1214, 0.7998)	-	-	-
$C_{predose}$ (IU/dL)	Initial	10	20.81	(9.313, 46.49)	86.38	(30.62, 243.70)	0.8005
	EOS	7	17.97	(6.652, 48.55)	-	-	-

AUC=area under the plasma concentration–time curve; $AUC_{0\text{-}tau}$=AUC over the dosing interval; CI=confidence interval; C_{max}=maximum plasma concentration; C_{min}=minimum plasma concentration; $C_{predose}$=plasma concentration before the vonicog alfa infusion; CSR=clinical study report; EOS=end of study; Geo=geometric; LS=least squares; PK=pharmacokinetic

The log-transformed PK parameter estimates were analyzed using a linear mixed-effect model with time point as an independent fixed effect and subject as a random effect. The model estimates of the LS means, difference between LS means, and corresponding CIs were exponentiated to get the geometric LS means, paired ratio, and corresponding CIs shown on the table. Only PK parameters with n≥3 for both time points were included in the analysis.

[a] For these parameters, subject was removed from the originally defined model due to estimation issue.

Statistical difference in Cmax/D was observed but can be explained by the impact of two subjects who contributed non-reliable Cmax estimates due to unavailable FVIII:C levels beyond the 1-hour time point of assessment. The MAH confirmed that if only reliable estimates of Cmax were considered, no significant changes between the two PK visits were found.

Study SHP677-304

Pre-dose Factor VIII activity

PD data in the interim analysis of Study SHP677-304 are limited to an evaluation of pre-dose plasma FVIII:C levels in the 11 subjects who completed Study 071301 and continued prophylactic treatment in Study SHP677-304 upon.

Table 13. Summary of Pre-dose FVIII Activity (IU/dL): FVIII:C, Cohorts 1 and 2

Cohort Subject	Prophylaxis Visit	Month 1	Month 2	Month 3	Month 6	Month 9	Month 12
Cohort 1							
	NA	127	120	4	79	NA	NA
	NA	NA	NA	64	4	9	81
	10	12	12	11	25	23	13
	11[a]	15	93[a]	NA	36[a]	NA	16
	9	3	NA	NA	4	17	6
	37[a]	29	35	29	19	34	32
	NA	6	59[a]	8[a]	52	16	3
	44	39	NA	33	81	77	35
	9	10	15[a]	12	11	6	21
	NA	2	10	37	41	13	4
Cohort 2							
	NA	NA	5	NA	5	5	5

FVIII:C=factor VIII clotting (activity); IU=international unit(s); NA=no sample or no result available

[a] Missing dose information; excluded from descriptive statistics

2.3.4. PK/PD modelling

To support prophylactic dosage (dose and dosing interval) of vonicog alfa in adult subjects with VWD, existing population PK and PK/PD models (previously established for clinical studies conducted in adult subjects with VWD for OD treatment and perioperative management of bleeding (i.e. Studies 070701, 071001, and 071101)) were updated by including the data collected in the prophylaxis studies 071301 and SHP677-304 (IA). In the population PK model, VWF:RCo was used to characterise the PK properties of VWF. In addition, the PK/PD relationship was assessed by linking VWF activity to FVIII activity.

Population PK

A total of 100 unique subjects with at least 1 measurable value of VWF:RCo had PK samples collected and were included in the population PK analysis. The population included a total of 50 (50.0%) male and 50 (50.0%) female subjects. The population included a total of 5 (5.0%) elderly subjects (≥65 years). The population included a total of 20 (20.0%) subjects with VWD Type 1 or 2 and 80 (80.0%) subjects with VWD Type 3. A total of 61 (61.0%) subjects received vonicog alfa, while a total of 31 (31.0%) subjects received vonicog alfa/ADVATE and a total of 8 (8.0%) subjects received pdVWF:pdFVIII. The population included a total of 86 (86.0%) subjects with normal renal function, 13 (13.0%) subjects with mild renal impairment, and 1 (1.0%) subject with moderate renal impairment. The median (range) age and body weight in the PK population were 36.0 years (18.0 to 77.0 years) and 72.5 kg (43.8 to 145 kg), respectively.

Results

Key findings of the population PK analyses are summarised as follows:

The PK of VWF:RCo was described by a 2-compartment model with linear elimination and baseline (endogenous) levels of VWF. For a typical adult subject with VWD type 3 (70 kg, 35 years, Study 071001) receiving vonicog alfa, the CL and Vc of VWF:RCo were 1.99 dL/h and 37.4 dL, respectively. The total volume of distribution of VWF:RCo was 53.0 dL, which is consistent with total blood volume in a 70-kg subject (52 dL), suggesting that distribution was limited to the vascular space. For a typical adult patient, the half-life of VWF:RCo associated with the distribution ($t_{1/2\alpha}$)and elimination ($t_{1/2\beta}$) phases were 1.90 and 19.4 h, respectively

Covariate analyses showed that the CL of VWF:RCo was dependent on body weight, age, the type of product (vonicog alfa versus pdVWF:pdFVIII), and study (prophylaxis). The exponent for the effect of body weight on CL was 0.611 [ie, $(WT/70)^{0.611}$], suggesting a faster CL of VWF:RCo in subjects with

higher body weight. The exponent for the effect of age on CL was -0.112 [i.e. (age/35) $^{-0.112}$]. These results suggest a slower CL of VWF:RCo in older subjects when considering subjects with similar body weight. The CL of VWF:RCo for the pdVWF:pdFVIII product was 59% faster than the CL of vonicog alfa in a prophylaxis setting. For a typical adult patient with type 3 VWD receiving pdVWF:pdFVIII, the $t_{1/2}$ of VWF:RCo associated with the distribution ($t_{1/2\alpha}$) and elimination ($t_{1/2\beta}$) phases were 1.84 and 12.6 hours, respectively. Subjects enrolled in the prophylaxis and continuation studies (071301 and SHP677-304) presented a CL of VWF:RCo 57% higher relative to that in Study 071001.

Based on the covariate analyses, race, sex, VWD type (VWD type 1-2 versus 3), and coadministration with rFVIII, did not affect the CL of VWF:RCo. Clearance and Vc were dose-independent for a dose range of 2.0 to 80 IU/kg. The effect of spontaneous bleeding on the CL and Vc of VWF:RCo in the OD study (Study 071001) and prophylaxis study (Study 071301), as well as both studies combined, was not statistically significant.

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 94 subjects with at least 1 measurable value of FVIII were included in the population PK/PD analysis (Studies 070701, 071001, 071101, and 071301). Of the 94 subjects included in the PK/PD analysis, 16 (17.0%) presented with VWD Type 1-2 and 78 (83.0%) presented with VWD Type 3

Results:

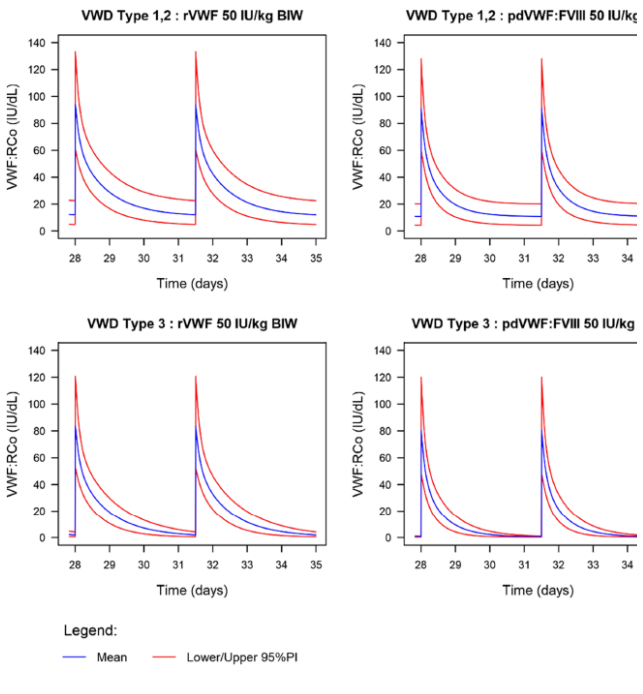
- The final PK/PD model shows that the K_{out} was 3.85 L/h; the volume of distribution of FVIII (V_{FVIII}) (34.0 dL), as part of the PK/PD model, was consistent with the volume of distribution of VWF:RCo estimated with the population PK model (37.4 dL). Likewise, the exponent for the effect of body weight on the volume of distribution of FVIII (i.e. 0.605) was consistent with the exponent for the effect of body weight of VWF:RCo estimated with the population PK model (i.e. 0.579).
- Based on Hill coefficient values from the model (indicating the steepness of the response slope), the PK/PD relationship in subjects with VWD type 3 (Hill=2.15) is suggested to be relatively steep compared with subjects with type 1-2, probably due to very low endogenous levels of VWF:RCo in subjects with type 3 and a rapid effect on FVIII observed soon after intravenous administration of vonicog alfa.
- Covariate testing showed that the study effect of prophylaxis was statistically significant on the mean rate constant of degradation of FVIII (K_{out}) and maximum inhibitory effect (I_{max}). The effect of bleeding and disease type on K_{out}, I_{max} were not statistically significant.
- At steady state, PK/PD parameters using simulated concentrations in Switch subjects were similar to those observed in Prior OD subjects.

Population PK/PD simulations (see Figure 3 below) suggest that following twice-weekly dosing with 50 IU/kg vonicog alfa, the FVIII:C in patients with type 3 at steady state is expected to be above 40 IU/dL for an average of 5.29 days over a weekly interval (76% of weekly time). As a comparison, the population PK/PD model analyses suggest that following twice-weekly dosing with pdVWF:pdFVIII, the FVIII:C in patients with type 3 is expected to be above 40 IU/dL for an average of 3.70 days over a weekly interval (53% of weekly time). Data for patients with type 1-2 are scarce, but modelling analyses suggest that patients with type 1-2 receiving vonicog alfa either once or twice weekly would, on average, have FVIII:C levels above 40 IU/dL over the 7 days of weekly time following both twice-weekly and once-weekly dosing.

The MAH confirmed that the clearance of VWF:RCo in the prophylaxis studies was higher than in previous trials and hypothesises that this difference may be attributed to differences in blood sample preparations and/or bioanalytical assays between the different studies. The observed differences in K_{out} and I_{max} in turn, were reasonably explained as a direct consequence of higher VWF:RCo clearance (resulting in lower levels of activity). Even though the MAH's explanation remains hypothetical, it is agreed that the observed impact of treatment (on-demand vs. prophylaxis) on VWF:RCo clearance is reasonably explained by a likely impact of methodological between-study differences.

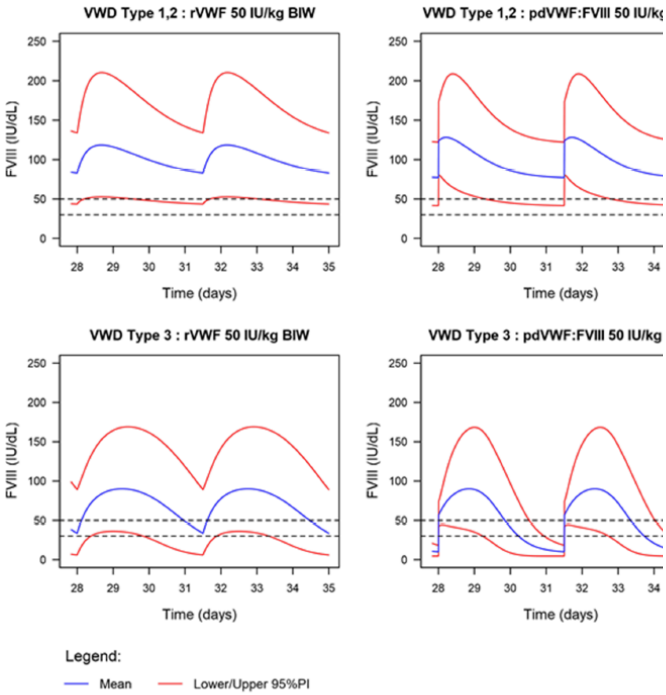
Figure 3. Simulated steady state VWF:RCo (A) and FVIII activity (B) profiles for twice weekly dosing

A



BIW=twice weekly; FVIII=factor VIII; pdVWF=plasma-derived von Willebrand factor; rVWF=recombinant von Willebrand factor (vonicog alfa); VWD=von Willebrand disease; VWF:RCo=von Willebrand factor ristocetin cofactor activity

B



BIW=twice weekly; FVIII=factor VIII; pdVWF=plasma-derived von Willebrand factor; rVWF=recombinant von Willebrand factor (vonicog alfa); VWD=von Willebrand disease

2.3.5. Discussion on clinical pharmacology

In Study 071301, non-compartmental analyses using rich samples were used to evaluate PK/PD properties of vonicog alfa after single and multiple doses under long-term prophylaxis. In Study SHP677-304, PK/PD analyses were limited to assessments of IR and pre-dose plasma FVIII activity. In addition to the PK/PD data observed in the clinical studies, population PK and PK/PD modelling was used to provide additional support for the adequacy of the proposed prophylactic dosing regimen.

Results obtained in the single dose PK/PD assessment in Prior OD subjects (C_{max} 75.7 IU/dL, T_{max} 0.54 hours, $t_{1/2}$ 15.98 hours, $AUC_{0\text{-}inf}$ 1178 IU·h/dL) were generally consistent with the known PK/PD behaviour of vonicog alfa as reflected in its EPAR and in sections 5.1 and 5.2 of its currently approved SmPC. With regards to the employed methodology, the spacing of sampling times, the use of pre-infusion concentration corrections and a washout period covering >4 half-times of VWF and FVIII for the first assessment in Prior OD subjects are acknowledged.

Additional steady state PK/PD assessments performed during prophylactic treatment (early after treatment initiation and at EOS in Switch subjects and at EOS in Prior OD subjects) essentially support the notion of a stable / consistent PK/PD behaviour of vonicog alfa over the duration of treatment, not only with regard to VWF:RCo PK but also with regard to the vonicog alfa-mediated upregulation of plasma FVIII activity with largely comparable peak levels (mean values ranging from 75.7 IU/dL to 104.1 dL reached approximately 24 hours after administration) not raising concerns regarding a possible exceeding of safety relevant thresholds. Furthermore, a comparison of PK assessments performed before and after initiation of prophylactic treatment confirms a statistically significant approximately 5-fold increase in FVIII:C levels from 3.83 IU/dL at baseline to 18.7 IU/dL under prophylaxis (geometric least squares means).

However, given a significant number of early discontinuations from study 071301, the actual degree of generalisability of the steady state PK data obtained at EOS remains debatable. In fact, results from this assessment were only available for 9 of the 13 Prior OD and 7 of the 10 Switch subjects, raising concerns with regards to a potential enrichment of favourable responders. Importantly, similar concerns apply to the Switch group of the study, which is considered likely to be enriched for subjects with a favourable response to prophylactic treatment.

In general (and as expected), the PK/PD data obtained in study 071301 show a high degree of interindividual heterogeneity and remain difficult to interpret in the context of the small sample size. However, in view of the available data, general conclusions of a therapy-induced increase in steady-state plasma FVIII:C levels upon initiation of prophylactic treatment and overall consistency of the PK/PD behaviour of vonicog alfa under the proposed prophylactic dosing regimen (without safety relevant increases in plasma FVIII:C levels) are considered sufficiently well-founded.

In view of the available PK/PD data obtained in Study 071301, the additionally presented model-based analyses are viewed as merely supportive. However, the population PK model appears sufficiently validated and by predicting plasma FVIII:C levels in type 3 VWD above 40 IU/dL for an average of 5.29 days (i.e. 76% of weekly time), PK/PD simulations provide further support for the proposed initiation of prophylactic treatment using individual doses of 40-60 IU/kg vonicog alfa and a BIW regimen. This is also reflected in section 4.2 of the SmPC.

2.3.6. Conclusions on clinical pharmacology

Outcomes of PK/PD assessments performed in the prophylaxis studies 071301 and SHP677-304 together with supportive evidence from population PK/PD modelling support the proposed posology for an initiation of prophylactic treatment (i.e. BIW 40-60 IU/kg).

2.4. Clinical efficacy

2.4.1. Main studies

Efficacy of prophylaxis with vonicog alfa in VWD was investigated in the completed Phase 3 clinical study 071301 and the ongoing long-term extension study SHP677-304. In addition, for subjects who completed Study 071301 and entered Study SHP677-304, the MAH performed an integrated analysis of efficacy data from the day of the first dose of prophylactic treatment in Study 071301 through the data cut-off date (30 Jun 2022) in Study SHP677-304.

Study 071301: A Prospective, Phase 3, Open-label, International Multicenter Study on Efficacy and Safety of Prophylaxis with rVWF in Severe von Willebrand Disease

Methods

Study 071301 was a prospective, open-label, uncontrolled, non-randomized, international, multicenter (32 sites in 9 countries) Phase 3 study to evaluate the efficacy and safety of prophylactic treatment with vonicog alfa in adult patients with severe VWD. The study included 2 groups of study subjects:

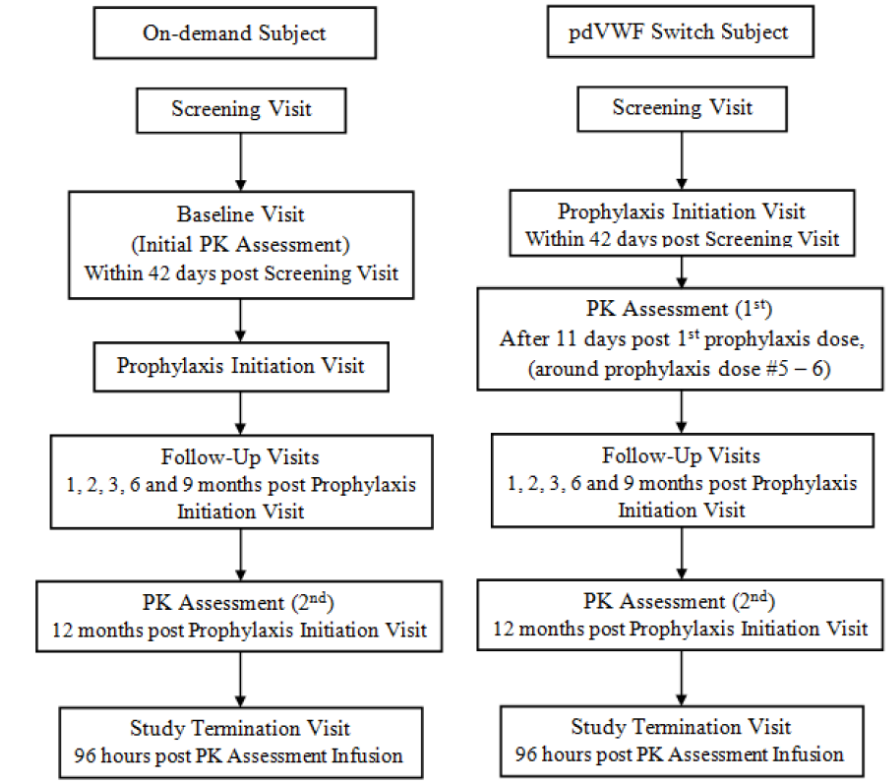
- "Prior OD subjects": Subjects who had been receiving OD (on-demand) treatment with a VWF product prior to Study 071301 and had ≥3 documented spontaneous bleeds (not including menorrhagia) requiring VWF treatment during the 12 months prior to Study 071301.
- "pdVWF Switch subjects" (referred to as "Switch subjects"): Subjects who had been receiving prophylactic treatment with a plasma-derived VWF (pdVWF) for at least 12 months prior to Study 071301.

The observation period for historical BEs was the 365 days prior to the first prophylactic dose of vonicog alfa.

The study aimed at an enrolment of ≥8 subjects into each of the 2 groups, with a total of at least 5 subjects with Type 3 VWD to be followed for 12 months. Both, Prior OD and Switch subjects were to receive prophylactic treatment with vonicog alfa for a 12-month period (longer for some subjects, depending on when the continuation study was initiated at the subjects' study sites).

During prophylactic treatment, any BEs (bleeding episodes) requiring rVWF therapy were to be treated with rVWF with or without ADVATE (recombinant Factor VIII [rFVIII], octocog alfa). In addition, subjects who required surgery or dental procedures were treated with investigational product (i.e. rVWF with or without ADVATE) to manage peri-operative bleeding. Efficacy and safety were assessed throughout the study. PK/PD were assessed twice with an initial assessment before the start of prophylactic rVWF treatment for Prior OD subjects and after the first 5 to 6 prophylactic rVWF doses (approximately after 11 days on rVWF prophylaxis) for Switch subjects. For both groups, a second or final PK/PD assessment was performed at study completion (last rVWF dose). After completing the study, subjects could continue into the Continuation Study SHP677-304, during which they could continue receiving prophylactic rVWF treatment or switch to only on-demand rVWF therapy.

Figure 4. Study 071301 Design



pdVWF=plasma-derived von Willebrand factor; PK=pharmacokinetic

Study participants

Subjects had to be adults (≥18 years of age, BMI ≥15 but <40 kg/m^2) with severe VWD (baseline VWF Ristocetin Cofactor activity [VWF:RCo] <20 IU/dL) and a history of BEs which required either OD or prophylactic VWF substitution treatment. Subjects with Type 2N VWD were formally excluded.

Prior OD subjects required a history of ≥3 documented spontaneous bleeds (not including menorrhagia) requiring VWF treatment during the past 12 months. Switch subjects had to receive prophylactic treatment with a pdVWF product for no less than 12 months prior to screening. Of note, subjects receiving prophylactic treatment with more than 5 infusions or a weekly dose exceeding 240 IU/kg at the time of screening were formally excluded.

Enrollment was restricted to subjects with available records to reliably evaluate type, frequency, and treatment of bleeding episodes during at least 12 months preceding enrollment. Availability of dosing and factor consumption during 12 months (up to 24 months) of treatment prior to enrollment was required for pdVWF Switch subjects and was desired (but not a requirement) for Prior OD subjects.

Treatments

Prophylaxis

Prior OD subjects started rVWF prophylactic treatment with the standard prophylactic dose within the range of 50 ±10 IU/kg rVWF per infusion with infusions given twice per week.

For Switch subjects, the total weekly dose (IU/kg) of rVWF for each subject was to be equivalent (±10%) to the weekly pdVWF dose received during prophylactic treatment before the study. The total weekly dose of IP was to be divided into 2 separate infusions given on 2 separate days of the week (Schedule A). Based on the total weekly dose or other clinical judgement, the total weekly dose may have been administered as 3 infusions (Schedule B; e.g. infusions on Monday, Wednesday and Saturday). A once weekly dose regimen was allowed only if the subject had been on a once weekly dose regimen with pdVWF. For all subjects, dose escalations (not exceeding an upper limit of 80 IU/kg rVWF per infusion) and increases of dosing frequency were allowed in case of insufficient therapeutic response as evidenced by breakthrough bleeding episodes. The criteria for dose and/or frequency escalation were specific to each bleeding indication but, overall, involved 1 significant breakthrough bleeding episode despite the subject being compliant with scheduled prophylaxis treatment. In general, the dose per infusion was escalated (up to a maximum of 80 IU/kg) before the dosing frequency was increased.

Bleeding episodes and surgery

In case of an acute bleeding episode, the subject was to be treated with rVWF with or without ADVATE. If endogenous FVIII was below 30% to 40% or was unknown and could not be estimated from the subject's PK study, an infusion of rVWF:ADVATE at an ratio of 1.3:1 ±0.2 was to be administered initially.

Subsequent infusions were to be with 40 to 60 IU/kg rVWF:RCo with or, in many cases, without 30 to 45 IU/kg ADVATE (only to be administered if plasma FVIII levels fell below 30 IU/L during the treatment period).

In case of surgery, 12 to 24 hours prior to the procedure, a priming dose with rVWF (based on the subject's IR and $t_{1/2}$) was to be infused to allow the endogenous FVIII levels to raise to at least 30 IU/dL (minor, oral surgery) or 60 IU/dL (major surgery) at the time the loading dose of rVWF was infused. VWF and FVIII levels were to be assessed within 3 hours prior to surgery initiation and results were to be available prior to administering the loading dose. If FVIII levels prior to the loading dose administration were not at least 30 IU/dL (minor, oral surgery) or 60 IU/dL (major surgery), ADVATE was to be administered in addition to rVWF in order to raise FVIII activity to the targeted levels. The preoperative loading dose was calculated as the difference in the target peak and baseline plasma VWF:RCo levels divided by the IR (ΔVWF:RCo x BW (kg) /IR) with IR at C_{max} defined as (C_{max}-$C_{pre\text{-}dose}$)/Dose. If the IR was not available, an IR of 1.7 IU/dL per IU/kg was to be assumed. For minor and oral surgery, the IR from the preoperative Priming Dose visit was to be used to guide dosing, and the target peak was 50-60 IU/dL VWF:RCo and 40-50 IU/dL FVIII. For major surgery, the target peak was 100 IU/dL VWF:RCo and 80-100 IU/dL FVIII.

Subjects undergoing minor surgery were to be infused with rVWF every 12 to 24 hours or every other day, targeting >30 IU/dL (rVWF and FVIII) for at least the first 48 hours. Subjects undergoing oral surgery were to be infused with rVWF at least once within the first 8 to 12 hours, targeting >30 IU/dL (rVWF and FVIII).

Subjects undergoing major surgery were to be infused with rVWF every 12 to 24 hours for at least the first 72 hours post-surgery, targeting a VWF:RCo and FVIII trough activity >50 IU/dL, followed by further treatment post-72 hours for as long as deemed necessary by the Investigator, targeting a VWF:RCo and FVIII trough activity of >30 IU/dL.

Objectives

To evaluate the efficacy and safety (including immunogenicity, thrombogenicity, and hypersensitivity reactions), as well as PK, PD, health-related quality of life, and pharmacoeconomics of prophylactic treatment with vonicog alfa in adult patients with severe VWD.

Outcomes/endpoints

Primary Endpoint:

- Annualized bleeding rate (ABR) for spontaneous (not related to trauma) BEs during prophylactic treatment with vonicog alfa

Secondary Endpoints:

- ABR percent reduction success for Prior OD subjects, defined as at least 25% reduction of ABR based on spontaneous BEs during vonicog alfa prophylaxis relative to the subject's own historical ABR during OD VWF treatment prior to this study
- ABR preservation success for Switch subjects, defined as achieving an ABR based on spontaneous BEs during vonicog alfa prophylaxis that was no greater than the subject's own historical ABR based on spontaneous BEs during prophylactic treatment with pdVWF prior to this study
- Categorized spontaneous ABR (sABR) defined as 0, >0 to 2, >2 to 5, or >5 during prophylactic treatment with vonicog alfa
- Total number of infusions and the average number of infusions per week during prophylactic treatment with vonicog alfa
- Total weight adjusted consumption of vonicog alfa during prophylactic treatment
- ABR for spontaneous BEs by location of bleeding (gastrointestinal [GI], epistaxis, joint bleeding, menorrhagia, oral and other mucosa, muscle, and soft tissue, etc) while on prophylactic treatment with vonicog alfa

Sample size

Approximately 22 adult subjects with severe VWD (baseline VWF:RCo <20 IU/dL) were planned to be included in the study. The aim was to have at least 8 subjects in each cohort (OD and switch). A total of at least 5 type 3 VWD subjects were planned to be followed for 12 months. The sample size was driven by practical considerations (primarily the enrollment of a rare patient population) and EMA Guideline on the 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

The primary outcome measure is ABR for spontaneous (not related to trauma) bleeding episodes during prophylactic treatment with rVWF (vonicog alfa). No formal statistical hypothesis test was planned for the analysis.

The primary efficacy analysis was planned to be based on the Full Analysis Set (FAS) and was planned to be summarized by the two cohorts: on-demand and switch subjects. As a supportive analysis, the same analysis was planned to be carried out on the Per-Protocol (PP) analysis set.

The FAS was planned to be composed of all subjects who receive prophylaxis IP treatment.

The PP Analysis Set was planned to be composed of subjects who are at least 70% compliant regarding the number of scheduled prophylactic infusions (as measured by the ratio of actual number of infusions to planned number of infusions). Only subjects who met all study entry criteria and who had no major protocol violations that might impact primary efficacy assessments were planned to be included in the PP analysis set.

The Modified Full Analysis Set (mFAS) consisted of all subjects who received prophylaxis treatment with IP and did not have data (entire infusion or bleed record[s]) identified to be removed due to lack of proper ALCOA-C (Attributable, Legible, Contemporaneous, Original, Accurate, and Complete; ICH E6 R2) compliant source documentation. This analysis set was used for supportive analyses of efficacy (not prespecified in the study protocol but introduced ad-hoc due to insufficient quality of source data).

The spontaneous ABR while treated with rVWF (vonicog alfa) for each cohort was planned to be estimated using a negative binomial regression. The prior ABR was planned to be based on historical data collected from each enrolled subject.

The two ABRs (prior to prophylaxis treatment and while on prophylaxis) for each cohort were planned to be compared within each subject using a generalized linear mixed-effects model (GLMM) (with a logarithmic link function, the default for the negative binomial distribution), accounting for the fixed effect of the two treatments. The follow-up time (in years) was planned to be specified as an offset. The ratio of ABR while in the study to historical ABR was planned to be estimated and reported together with the 95% confidence interval for each of the two cohorts.

The difference in on-study ABR relative to historical ABR was planned to be summarized descriptively.

Results

Participant flow

In Study 071301, 23 subjects were given at least one dose of prophylactic vonicog alfa as study treatment and 17 subjects completed the study. In the Prior OD group, 13 subjects started prophylactic vonicog alfa treatment, 4 subjects were early terminated (discontinued) from the study, and 9 subjects completed the study. In the Switch group, 10 subjects started prophylactic vonicog alfa, 2 subjects were early terminated (discontinued) from the study, and 8 subjects completed the study. No subject discontinued the study for lack of efficacy. One subject discontinued due to the non-serious adverse event (AE) of headache.

Table 14 – Subjects who terminated from the study (safety analysis set)

Listing 16.2.1.2
Subjects Who Terminated from the Study
(Safety Analysis Set)

Sex/ Age (years)/ Race	Group	Date of Informed Consent/ Study Day	Date of First Dose/ Study Day	Date of Last Dose/ Study Day	Date of Termination/ Study Day	Termination Stage	Duration of Exposure (Days)	Primary Reason for Discontinuation
	On-Demand						35	Adverse event: HEADACHE
	On-Demand						198	The subject is scheduled for an extended treatment period 3 months with equivalent to hydrocortisone greater than 10 mg per day
	On-Demand						72	Withdrawal by subject: subject refused to continue the study
	On-Demand						4	Withdrawal by subject: the patient moved and did not answer the phone for 2 weeks.
	Switch						110	Treatment with not permitted medication during the study: corticoids in high doses for an undetermined period of time due to patient starts with an arthritis rheumatoid during the study.
	Switch						267	Withdrawal by subject: for reasons of social status and personal

IP = Investigational product.
F = Female, M = Male.
A = Asian, B = Black or African American, M = Multiple, N = American Indian or Alaska Native, O = Other, P = Native Hawaiian or Other Pacific Islander, W = White.
Study day is calculated relative to the date of first dose of IP administered in the study.
Duration of exposure is calculated as (last dose date - first dose date + 1).

Conduct of the study

Changes to the study protocol:

Following the first version of the study protocol submitted to competent authorities (i.e. Amendment 1, dated 08 April 2016), there were 10 amendments. These included 2 global amendments which introduced the following major changes:

Major changes introduced with protocol Amendment 3 (global), dated 03 August 2017:

- Addition of an evaluation efficacy of the treatment of perioperative bleeding management, if surgery is required, as a secondary objective
- Introduction of a threshold of >25% defining a relevant ABR reduction
- Provision was made for a paper diary if it was not possible to use an electronic diary

Major changes introduced with protocol Amendment 6 (global), dated 12 March 2018:

- Addition of the pdVWF Switch cohort

- efficacy of BE treatment and perioperative management were moved from secondary to exploratory objectives
- addition of new steady-state PK parameters and PD parameters
- Redefinition of the FAS as all subjects who receive prophylaxis IP treatment
- Removal of the interim analysis

Protocol deviations:

One subject had a critical deviation related to eligibility: enrollment despite meeting exclusion criterion #7, a history of immune disorders. Of the 23 subjects in the SAF, 17 (73.9%) had at least one major protocol deviation. The most common major protocol deviations were related to IP administration and source documentation criteria (lack of ALCOA-C-compliant source documentation).

The eDiary did not function as intended. An eDiary was used to capture all bleeding and infusion events that occurred offsite (i.e. when the subject was not at the clinic). These data, entered directly into the eDiary by each subject, were considered source data. Some subjects did not or could not always use the eDiary device (due to technical issues and/or user errors) to report their bleed and infusion data and reported this information to the site staff, either during their next visit or over the phone. An eCRF page was developed to capture this bleed and infusion data not recorded in the eDiary. Ultimately, an internal audit of Study 071301 revealed that the mechanism of capturing these data by sites did not always meet proper ALCOA-C criteria for source documentation. A corrective and preventative action plan was implemented to ensure data integrity in the study. Study conduct improved post-audit, leading to improved compliance by subjects in recording bleed and infusion data in the eDiary from the use of more updated electronic patient reported outcomes (ePRO) technology.

Source data verification (SDV) was reperformed for all bleed and infusion data in the eCRF. Site queries were generated for all data that did not meet ALCOA-C criteria. Any instances for which a monitor was unsure if proper source documentation existed were reviewed by a Data Council, which completed their review of impacted data and issued queries requesting sites to remove data for which proper ALCOA-C-compliant source did not exist. Ten subjects from 8 sites had either infusion or bleed data identified to be removed due to lack of ALCOA-C-compliant source documentation. No bleeding data were removed from the database because one site did not agree to remove bleeding data for the 1 subject with BEs (16 of them) identified as lacking ALCOA-C-compliant source documentation. However, 10 subjects had one or more entire IP infusions removed from the database for lack of ALCOA-C-compliant source documentation. Because of this situation, the SAP included analyses of the primary and secondary efficacy endpoints in the mFAS, which excluded the 10 subjects with entire bleed or IP infusion record(s) identified to be removed due to lack of ALCOA-C-compliant source documentation.

The impact of the coronavirus disease 2019 (COVID-19) pandemic on study conduct was minimal. Subject enrollment ended before the pandemic started and subjects could self-administer study drug at home. By necessity, BEs that required in-clinic treatment or other medical attention still required such treatment/attention. There were some COVID-19 related protocol deviations but only 1 was a major protocol deviation.

The conduct of Study 071301 was strongly affected by a lack of ALCOA-C-compliant source documentation due to issues related to a malfunctioning eDiary device. During the pre-submission meeting held on 29 June 2022, the MAH presented the following tabular listing of subjects who had either infusion or bleed data affected by the lack of ALCOA-C-compliant source documentation.

In total, 10/23 subjects who received prophylactic treatment in Study 071301 had either infusion (all 10 subjects) or bleed (1 of 10 subject) records proposed to be queried for removal from the electronic data capture (EDC) sys... due to inadequate source documentation. Ultimately, only infusion records were removed from the databas... ported bleed records of a subject were retained by the site in the database due to th... con... that the written records provided by the subject, even without signature/date, we... till ... ent as source document verification. These records were included in the primary efficacy an...is.

Given the study's p...ary ...oint (i.e. sABR), the decision not to remove the impacted bleeding data (affecting 1 study subject) ... the primary analysis can be considered a conservative approach avoiding potential bias in favour of ...udy drug and hence appears acceptable. As a result, data removal had no impact on the study's prim... fficacy endpoint.

To allow for an assessmen... e impact of data removal on the efficacy results, the MAH defined and analysed a modified FAS (...) which includes only subjects who did not have data identified to be removed. As such, the mF... n be considered to represent a worst-case scenario providing a certain degree of reassurance.

In addition, in the integrated efficacy analyses, the MAH defined a rollover subset FAS (rollover sFAS), including all subjects whose data were identified for removal in Study 071301 and who rolled over to the continuation study SHP677-304 for continued prophylactic treatment (Cohorts 1 and 2). As such, for 4 of the 10 subjects affected by data removal, the rollover sFAS allows for a within subject comparison of efficacy results between Study 071301 and Study SHP677-304 (in which no data were removed) to demonstrate consistency (despite differences in compliance rates). Notably, 2 of the 3 subjects who had a considerable degree (i.e. >50%) of infusion data removed for ALCOA-C non-compliance in Study 071301 rolled over into Study SHP677-304. The third subject with >50% of infusion data removed from the EDC discontinued early from the study and contributed only a total of 5 on-study infusions to the FAS. For the remaining 7 subjects, the majority of infusion data were ALCOA-C compliant with proportions of non-compliance of 0.84%, 3.33%, 3.55%, 5.00%, 8.53%. 12.82% and 17.86%, respectively.

Baseline data

Subject demography and baseline characteristics for the 23 FAS subjects in Study 071301 are summarised in tables 14 and 15 below.

Table 14. Study 071301 Subject Demographics and VWD Type (Full Analysis Set)

Characteristic	Prior OD (N=13)	Switch (N=10)	Total (N=23)
Age (years)			
Mean (SD)	38.0 (17.6)	43.9 (21.8)	40.6 (19.3)
Min, Max	20, 67	18, 77	18, 77
Sex, n (%) of subjects			
Male	5 (38.5)	7 (70.0)	12 (52.2)
Female	8 (61.5)	3 (30.0)	11 (47.8)
Race, n (%) of subjects			
White	13 (100)	9 (90.0)	22 (95.7)
Not Reported	0	1 (10.0)	1 (4.3)
Ethnicity, n (%) of subjects			
Hispanic/Latino	0	2 (20.0)	2 (8.7)
Not Hispanic/Latino	13 (100)	7 (70.0)	20 (87.0)
Not Reported	0	1 (10.0)	1 (4.3)
Weight (kg)			
Mean (SD)	64.8 (8.9)	70.3 (13.6)	67.2 (11.3)
Min, Max	53.5, 84.2	47.4, 89.9	47.4, 89.9
VWD Type, n (%) of subjects			
Type 1	2 (15.4)	1 (10.0)	3 (13.0)
Type 2A	0	1 (10.0)	1 (4.3)
Type 2B	1 (7.7)	0	1 (4.3)
Type 3	10 (76.9)	8 (80.0)	18 (78.3)

CSR=clinical study report; Max=maximum; Min=minimum; n=number of subjects in each category; N=number of subjects in the full analysis set; OD=on-demand; SD=standard deviation; VWD=von Willebrand disease

Table 15. Study 071301 Historical bleeding during the prior 12 Month (Full Analysis Set)

Characteristic	Prior OD (N=13)	Switch (N=10)
Overall ABR		
Mean (SD)	16.1 (42.4)	5.3 (14.7)
Median (IQR)	5.0 (3.0, 5.0)	0 (0.0, 1.0)
Min, Max	3.0, 157.0	0, 47.0
sABR		
Mean (SD)	15.5 (42.0)	5.0 (14.4)
Median (IQR)	3.0 (3.0, 4.0)	0 (0.0, 1.0)
Min, Max	3.0, 155.0	0, 46.0
Number of BEs	209	53
Causes of Bleeding, n (%) of BEs		
Spontaneous	197 (94.3)	50 (94.3)
Injury	7 (3.3)	3 (5.7)
Surgery	1 (0.5)	0
Unknown	4 (1.9)	0
Severity of Bleeding, n (%) of BEs		
Minor	157 (75.1)	52 (98.1)
Moderate	42 (20.1)	1 (1.9)
Major	2 (1.0)	0
Missing	8 (3.8)	0
Anatomical Location of Bleeding, n (%) of BEs		
Hemarthrosis	10 (4.8)	1 (1.9)
Other (majority of these were mucosal)	193 (92.3)	52 (98.1)
Skin	6 (2.9)	0

ABR=annualized bleeding rate; BE=bleeding episode; CSR=clinical study report; FAS=full analysis set; IQR=interquartile range; Max=maximum; Min=minimum; n=number of subjects in each category; N=number of subjects in the full analysis set; OD=on-demand; sABR=spontaneous ABR; SD=standard deviation; VWF=von Willebrand factor
Note 1: ABR results are descriptive statistics.
Note 2: Historical BEs only include treated (with VWF) BEs. Historical bleeds were expected to be different for the two groups (Prior OD and Switch); therefore, data were not summarized overall (for the 23 subjects in the FAS).

Approximately half of the subjects were male, and half were female. The majority (i.e. 78%) of subjects had Type 3 VWD. Overall, composition of the study population is considered adequate and representative of the intended target population (i.e. adult patients suffering from severe VWD).

The subject's medical history included documented history of on-demand or pdVWF prophylaxis treatment for at least the past 12 months and documented history (e.g. patient charts and prescription information) of all bleeding episodes within the past 12 months (up to 24 months if available).

Numbers analysed

The FAS (i.e. the primary analysis set for efficacy) included 23 subjects who received prophylactic vonicog alfa treatment. The mFAS (i.e. subjects with no data identified to be removed for lack of ALCOA-C-compliant documentation) comprised 13 subjects (6 Prior OD and 7 Switch subjects). The PPAS (i.e. subjects who were ≥70% compliant with the planned prophylactic treatment regarding the number of scheduled prophylactic infusions and had no major protocol deviations that might impact primary efficacy assessments) comprised 16 subjects (8 Prior OD and 8 Switch).

Overall, mean duration of vonicog alfa prophylaxis was approximately 10.7 months (ranging from 0.1 to 16.3 months). Mean treatment compliance was >80% for both the Prior OD and Switch groups. Through Month 12, most (82.6%) FAS subjects were at least 70% compliant. In the mFAS, mean duration of vonicog alfa prophylaxis was approximately 9.7 months (ranging from 1.0 to 16.0 months); the decrease relative to the FAS was driven by the Prior OD group (mean duration of approximately 10.1 months in the FAS but only approximately 8.3 months in the mFAS). Mean treatment compliance was >90% for both the Prior OD and Switch groups. Through Month 12, all (100.0%) mFAS subjects were at least 70% compliant.

Endpoints Related to bleeding events:

For Study 071301, the primary analysis of the primary efficacy endpoint on-study sABR was performed with a generalized linear mixed model (GLMM) assuming a negative binomial distribution with a log link

function. The model-based comparison of on-study to historical sABR is presented for the FAS with on-study data through Month 12 in Table 16 below.

Table 16. Study 071301 Primary Efficacy Analysis: Comparison of On-Study sABR Through Month 12 vs Historical sABR Using a Negative Binomial Model (Full Analysis Set)

Time Period Statistic	Prior OD (N=13)	Switch (N=10)
Historical		
Number of Spontaneous Treated BEs	201	50
sABR (95% CI)	6.541 (2.516, 17.004)	0.514 (0.042, 6.307)
On-Study (while receiving prophylactic vonicog alfa)		
Number of Spontaneous Treated BEs	9	18
sABR (95% CI)	0.555 (0.150, 2.048)	0.283 (0.021, 3.851)
Comparison (On-Study vs Historical sABR)		
sABR on-study:historical ratio (95% CI)	0.085 (0.021, 0.346)	0.550 (0.086, 3.523)
sABR percent change from historical	91.5% reduction	45.0% reduction

BE=bleeding episode; CI=confidence interval; CSR=clinical study report; N=number of subjects in the full analysis set; OD=on-demand; sABR=spontaneous annualized bleeding rate
Note: The sABR was the number of spontaneous bleeds divided by the observation period in years. Only BEs treated with VWF infusions were included. Six BEs (4 historical [all in Prior OD group] and 2 on-study [Switch group]) of unknown cause were counted as spontaneous bleeds for this analysis.

For the Prior OD group, there was a 91.5% reduction in the sABR when comparing on-study sABR (mean sABR=0.555) to the historical sABR (mean sABR=6.541). The model-based mean sABR ratio (on-study:historical) was 0.085 (95% CI: [0.021, 0.346]) for the Prior OD group. For the Switch group, the model-based mean sABR ratio (on-study:historical) was 0.550 (95% CI: [0.086, 3.523]) which corresponded to a reduction of 45.0% from historical to on-study sABR. The same analysis of sABR was repeated for the mFAS, PPAS, and VWD Type 3 subjects in the FAS and the mFAS. These results were consistent in direction and magnitude with the results for the FAS through Month 12.

Table 17. Study 071301 Historical and On-Study sABR Through Month 12 Using a Negative Binomial Model (Various Analysis Sets)

Population Statistic	Prior OD	Switch
Type 3 VWD subjects in FAS	**N=10**	**N=8**
Number of Spontaneous Treated BEs	9	18
sABR (on-study) (95% CI)	0.681 (0.149, 3.116)	0.501 (0.042, 6.018)
sABR ratio (on-study:historical) (95% CI)	0.084 (0.016, 0.446)	0.530 (0.077, 3.623)
sABR, percent change from historical	91.6% reduction	47.0% reduction
Type 3 VWD subjects in mFAS	**N=5**	**N=5**
Number of Spontaneous Treated BEs	6	1
sABR (on-study) (95% CI)	1.473 (0.130, 16.745)	0.195 (0.007, 5.849)
sABR ratio (on-study:historical) (95% CI)	0.043 (0.002, 1.015)	0.244 (0.007, 8.083)
sABR, percent change from historical	95.7% reduction	75.6% reduction

BE=bleeding episode; CI=confidence interval; CSR=clinical study report; FAS=full analysis set; mFAS=modified FAS; N=number of subjects in the respective analysis set; OD=on-demand; PPAS=per protocol analysis set; sABR=spontaneous annualized bleeding rate; VWD=von Willebrand disease
Notes: The sABR was the number of spontaneous bleeds divided by the observation period in years. Only BEs treated with von Willebrand Factor infusions are included. Bleeding episodes of unknown cause were counted as spontaneous bleeds for this analysis.

Table 18. Study 071301 Descriptive Statistics for Historical and On-Study sABR Through Month 12 (Full Analysis Set and Modified Full Analysis Set)

Time Period Statistic	Prior OD	Switch
Full Analysis Set (FAS)	**N=13**	**N=10**
Historical sABR		
Mean (SD)	15.462 (41.9536)	5.000 (14.4222)
Median (Min, Max)	3.000 (3.00, 155.00)	0.000 (0.00, 46.00)
On-study sABR		
Mean (SD)	0.663 (1.7266)	1.692 (3.8467)
Median (Min, Max)	0.000 (0.00, 5.78)	0.000 (0.00, 12.08)
Change from historical		
Mean (SD)	-14.798 (42.1849)	-3.308 (10.8569)
Median (Min, Max)	-3.000 (-155.00, 2.78)	0.000 (-33.92, 3.85)
Modified Full Analysis Set (mFAS)	**N=6**	**N=7**
Historical sABR		
Mean (SD)	29.167 (61.6779)	0.571 (0.7868)
Median (Min, Max)	3.000 (3.00, 155.00)	0.000 (0.00, 2.00)
On-study sABR		
Mean (SD)	0.964 (2.3606)	0.140 (0.3701)
Median (Min, Max)	0.000 (0.00, 5.78)	0.000 (0.00, 0.98)
Change from historical		
Mean (SD)	-28.203 (62.2114)	-0.432 (0.7849)
Median (Min, Max)	-3.000 (-155.00, 2.78)	0.000 (-2.00, 0.00)

CSR=clinical study report; FAS=full analysis set; Max=maximum; mFAS=modified FAS; Min=minimum; N=number of subjects in the respective analysis set; OD=on-demand; SD=standard deviation; sABR=spontaneous annualized bleeding rate

Individual subject data for historical and on-study sABR are provided in Table 19 below.

Table 19. Study 071301 Individual Subject sABR Results (Full Analysis Set)

Subject	Historical sABR[a]	On-Study sABR[b]	Change from Historical	
			Absolute Change	% Change
Prior OD				
	3	0	-3	-100%
	8	0	-8	-100%
	155	0 (Day 37)	-155	-100%
	3	0 (Day 201)	-3	-100%
	4	0	-4	-100%
	3	0 (Day 80)	-3	-100%
	3	0	-3	-100%
	3	5.78	+2.78	+92.7%
	4	0 (Day 17)	-4	-100%
	3	0	-3	-100%
	6	2.84	-3.16	-52.7%
	3	0	-3	-100%
	3	0	-3	-100%
	1	0.98	-0.02	-2%
	2	0	-2	-100%
	46	12.08	-33.92	-73.7%
	1	0	-1	-100%
	0	0	0	undefined
	0	0 (Day 113)	0	undefined
	0	0	0	undefined
	0	3.85	+3.85	undefined
	0	0	0	undefined
	0	0 (Day 269)	0	undefined

BE=bleeding episode; CSR=clinical study report; OD=on-demand; sABR=spontaneous annualized bleeding rate; VWF=von Willebrand factor

[a] Based on spontaneous, treated (with VWF) BEs within the 12 months before Day 1.

[b] Based on data through Month 12.

Continued prophylaxis in Study SHP677-304

Switch back to OD in Study SHP677-304

Early discontinuation

Regardless of study analysis population/analysis subsets, >80% of Prior OD subjects achieved sABR reduction success (defined as ≥25% reduction in on-study sABR compared with historical sABR) and >90% of Switch subjects achieved sABR preservation success (defined as on-study sABR no greater than historical sABR). When only Type 3 VWD subjects were considered, regardless of study population/analysis subsets, >80% of Prior OD subjects achieved sABR reduction success and >87% of Switch subjects achieved sABR preservation success on study treatment through Month 12.

In the FAS, 5 subjects (2 Prior OD and 3 Switch) experienced on-study spontaneous BEs that were treated with VWF through Month 12 (summarized in the table below). None of the spontaneous treated BEs was fatal or life-threatening. None of the spontaneous treated BEs was a body cavity, GI, or central nervous system (CNS) bleed.

Two subjects, both with VWD Type 3, did not achieve on-study sABR reduction/preservation success through Month 12:

- Subject (Prior OD) did not achieve sABR reduction success with an on-study sABR approximately 93% higher than historical.
- Subject (Switch) did not achieve sABR preservation success with an on-study sABR of 3.85 compared with a historical sABR of zero.

Table 20. Study 071301 On-study and Historical Treated Spontaneous Bleeding Episodes and sABRs for Subjects with On-study Spontaneous Treated BEs (Full Analysis Set)

Subject ID (Age [years] / Sex / Race)	On-study (Through Month 12)[a]		Historical (Within the Year before Study 071301 Day 1)[b]		sABR %Change from Historical
	Number and Location of Spontaneous Treated BEs	sABR	Number and Location of Spontaneous Treated BEs	sABR	
Prior OD Group					
	2 mucosal (nose), 1 other (bleeding menses), 2 menorrhagia, and 1 menstrual bleeding	5.78	1 oral mucosa, 1 sclera of the right eye, 1 menorrhagia	3	+93%
	2 mucosal (gum), 1 mucosal (mouth)	2.84	4 right elbow, 1 right and left elbow, 1 inguinal area	6	-53%
Switch Group					
	1 right ankle	0.98	1 hemarthrosis	1	-2%
	10 mucosal (nose), 3 unknown	12.08	46 nasal mucosa	46	-74%
	2 mucosal (gum), 2 mucosal (nose)[d]	3.85	None	0	undefined

BE=bleeding episode; CSR=clinical study report; F=female; ID=identification; M=male; mFAS=modified full analysis set; OD=on-demand; VWD=von Willebrand disease; sABR=spontaneous annualized bleeding rate; VWF=von Willebrand factor

[a] On-study period through the Month 12 Visit was not exactly 1 year for any subject.

[b] Historical bleeds were collected over more than a year for some subjects, but the historical sABR was calculated as the number of treated BEs reported in the 12 months prior to the first dose of prophylactic vonicog alfa in this Study 071301.

[c] Excluded from the mFAS

[d] Unknown cause

Notes: All subjects in this table completed Study 071301. Table includes only spontaneous BEs treated with VWF. BEs of unknown cause were considered spontaneous for this presentation. All subjects with on-study treated spontaneous BEs had VWD Type 3.

did not have any on-study spontaneous treated BEs. Subjects marked with * rolled-over into Continuation Study SHP677-304.

Endpoints Related to Vonicog Alfa Infusions and Weight-based Consumption

Infusion and consumption data for prophylactic vonicog alfa through Study 071301 Month 12 are summarized for the FAS and mFAS in the table below. All Prior OD subjects started on a twice-a-week dosing regimen and all but 1 stayed on this regimen throughout the study. Most (80%) Switch subjects were also started on a twice-a-week dosing regimen and all but 2 stayed on this regimen throughout the study. Prior OD subjects received a mean of 1.88 prophylactic rVWF infusions per week. Switch subjects received a mean of 1.85 prophylactic rVWF infusions per week. Prior OD subjects received a mean of 98.6 IU/kg weight-adjusted prophylactic rVWF per week. Switch subjects received a mean of 94.0 IU/kg weight-adjusted prophylactic rVWF per week.

Table 21. Study 071301 Prophylactic Vonicog Alfa Infusions and Weight-based Consumption Through Month 12 (Full Analysis Set and Modified Full Analysis Set)

Parameter	Analysis Population			
	FAS		mFAS	
	Prior OD (N=13)	Switch (N=10)	Prior OD (N=6)	Switch (N=7)
Prophylactic Infusions per Subject				
Mean (SD)	65.1 (38.4)	87.8 (30.2)	64.8 (41.58)	82.1 (32.39)
Min, Max	2, 116	31, 116	12, 106	31, 107
Initial Prophylactic Regimen (Infusions per Week), n (%) of subjects				
1× per week	0	1 (10.0)	0	1 (14.3)
2× per week	13 (100)	8 (80.0)	6 (100)	6 (85.7)
3× per week	0	1 (10.0)	0	0
Anytime Prophylactic Regimen (Infusions per Week), n (%) of subjects[a]				
1× per week	0	1 (10.0)	0	1 (14.3)
2× per week	13 (100)	8 (80.0)	6 (100)	6 (85.7)
3× per week	1 (7.7)	2 (20.0)	1 (16.7)	0
Every 3 days	0	1 (10.0)	0	1 (14.3)
Weekly Number of Prophylactic Infusions per Subject				
Mean (SD)	1.88 (0.7)	1.85 (0.4)	2.11 (0.342)	1.77 (0.436)
Min, Max	0.7, 3.5	0.8, 2.1	1.8, 2.7	0.8, 2.0
Average Weight-adjusted Vonicog Alfa Dose Per infusion, IU/kg				
Mean (SD)	52.2 (3.8)	52.2 (16.2)	51.1 (4.4)	48.6 (18.3)
Min, Max	44.8, 58.8	24.4 (79.4)	44.8, 56.5	24.4, 79.4
Monthly Weight-adjusted (IU/kg) Prophylactic Dose Per Subject				
Mean (SD)	427.2 (175.9)	407.2 (131.8)	468.5 (98.3)	353.7 (120.2)
Min, Max	151.2, 813.6	207.9, 554.8	400.6, 665.7	207.9, 495.6
Dose Per BE				
Number of BEs	7[b]	17[b,c]	5[d]	1[c]
Mean (SD)	1.3 (0.49)	1.2 (0.66)	1.4 (0.55)	1.0 (--)
Median (Min, Max)	1.0 (1, 2)	1.0 (1, 3)	1.0 (1, 2)	1.0 (1, 1)

BE=bleeding episode; CSR=clinical study report; EOS=end of study; FAS=full analysis set; ICH=International Council for Harmonisation; IP=investigational product; Max=maximum; mFAS=modified FAS; Min=minimum; n=number of subjects in each category; N=number of subjects in the respective analysis set; OD=on-demand; SD=standard deviation

[a] Subjects could have used multiple regimens during the study.

[b] Two BEs for Prior OD subjects and 1 BE for Switch subjects were excluded from this table for lack of drug and/or dose information for infusions used to treat the BEs or use of Haemate P instead of vonicog alfa. All 3 subjects had other treated BEs included in this table.

[c] One BE of unknown cause was included.

[d] All BEs were for a single Prior OD subject. One BE for the Prior OD subject was excluded from this table for lack of drug and/or dose information for infusions used to treat the BE.

Study SHP677-304: A Phase 3b, Prospective, Open-label, Uncontrolled, Multicenter Study on Long-term Safety and Efficacy of rVWF in Pediatric and Adult Subjects with Severe von Willebrand Disease (VWD)

Methods

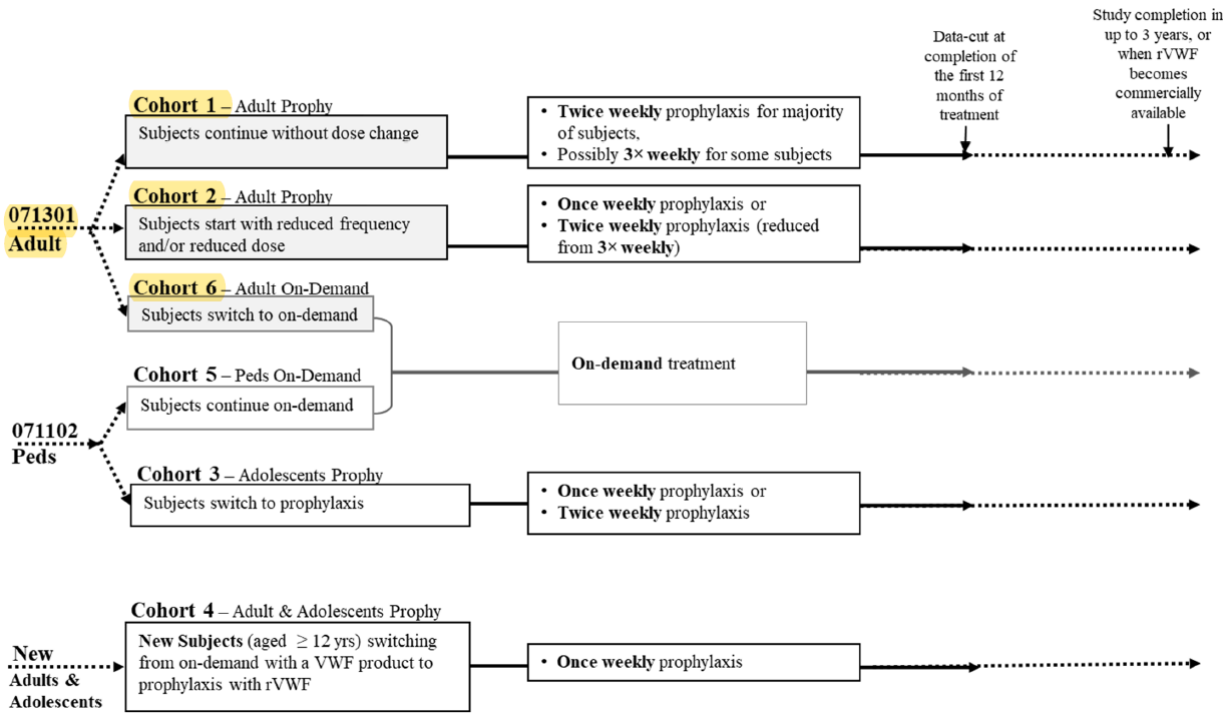
Study SHP677-304 is an ongoing, Phase 3b, prospective, open-label, uncontrolled, non-randomized, multicentre study evaluating long-term safety and efficacy of vonicog alfa for prophylaxis and OD treatment of BEs in paediatric and adult subjects with severe VWD. As part of the current submission, the MAH presents an interim analysis of data obtained in adults who rolled over from the parent Study 071301 to Study SHP677-304. Consequently, the presented interim analysis (with a data cut-off date of 30 Jun 2022) is limited to data obtained in Cohorts 1 and 2 for efficacy and Cohorts 1, 2, and 6 for safety.

- Cohort 1: Subjects transitioning from Study 071301 who were to remain on the same prophylactic dose as in Study 071301
- Cohort 2: Subjects transitioning from Study 071301, with no clinically significant BE within the past 6 months, who were to start Study SHP677-304 at a lower dose/frequency compared to the dose received in Study 071301
- Cohort 6: Adult subjects from Study 071301 who (based on medical assessment and/or subject's individual preference) switched back from prophylactic to OD treatment in Study SHP677-304.

For all cohorts, during the entire study observation period, any BE that required substitution therapy with VWF concentrate was to be treated with vonicog alfa with or without recombinant factor VIII (rFVIII). If surgery was needed, subjects received vonicog alfa, with or without rFVIII, for management of perioperative bleeding.

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.

Figure 5. Study SHP677-304 Design



Study participants

See Study 071301 above. The presented interim analysis is limited to data from adult subjects who rolled over from the parent study (071301) to this continuation study.

Treatments

See Study 071301 above. Treatment recommendations were consistent with the parent study 071301.

Objectives

To evaluate long-term safety and efficacy of vonicog alfa for prophylaxis and OD treatment of BE in paediatric and adult subjects with severe VWD.

Outcomes/endpoints

Primary Endpoint:

- sABR during prophylactic treatment with vonicog alfa based on the data collected during the first 12 months on study treatment

Secondary Endpoints:

- sABR under prophylactic treatment with vonicog alfa over the entire study period
- Categorized sABR (0, >0 to ≤2, >2 to ≤5, or >5 spontaneous treated BEs per year)
- sABR by bleeding location
- Categorized weekly number of infusions defined as 1, 2, or ≥3 during prophylactic treatment with vonicog alfa
- Total number of infusions and the average number of infusions per week during prophylactic treatment with vonicog alfa
- Total weight-adjusted consumption of vonicog alfa during prophylactic treatment
- Overall hemostatic efficacy rating at resolution of bleed
- Number of infusions of vonicog alfa and rFVIII (ADVATE) to treat BEs
- Weight-adjusted consumption of vonicog alfa and rFVIII (ADVATE) per BE while enrolled in the 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 prophylactic treatment (i.e. subjects belonging to Cohorts 1 and 2).

Results

Participant flow

Of the 17 subjects who completed Study 071301, 11 subjects (5 Prior OD and 6 Switch) continued prophylactic vonicog alfa treatment in Study SHP677-304. Of the 11 subjects, 10 subjects continued with their prophylactic treatment at the same dosing regimen as during Study 071301 (Cohort 1) and 1 subject decreased the dosing frequency level (Cohort 2): Eight (8) of the 10 subjects who rolled over from Study 071301 into Cohort 1 were receiving 2× weekly vonicog alfa infusions and 1 subject was receiving 1× weekly vonicog alfa infusions in Study 071301; these subjects continued these dosing frequencies in Study SHP677-304. One subject in Cohort 1 was receiving 3× weekly vonicog alfa infusions in Study 071301 and initially continued to do so in Study SHP677-304; this subject had a dosing interval

change from 3× weekly to 2× weekly on 19 Jul 2021, this change was not captured in the dose adjustment form but was reflected in the infusion records. One subject who rolled over into Cohort 2 had the dosing regimen reduced from 2× weekly in Study 071301 to 1× weekly in Study SHP677-304. The remaining 2 subjects did not continue prophylactic treatment and entered Cohort 6.

Up to the cut-off date of the presented interim analysis, 3 subjects in Cohort 1 and both subjects in Cohort 6 completed the study. No subjects had discontinued the study.

Conduct of the study

The original study protocol dated 29 August 2018 was amended 3 times. None of the introduced changes affected key determinates of the study's design or its scientific integrity.

Up to the cut-off date of the presented interim analysis, there were 20 major protocol deviations reported in 7 subjects. Major protocol deviations were reported in 6 subjects in Cohort 1 and 1 subject in Cohort 6 and involved deviations in IP compliance, study procedures criteria, laboratory assessment criteria, informed consent criteria, administrative criteria, efficacy criteria, other criteria, and SAE criteria.

Baseline data

Subject demography and baseline characteristics for the 11 FAS subjects in Study SHP677-304 are summarszed in table below.

Table 22. Study SHP677-304 Cohorts 1 and 2 Subject Demographics and Baseline Characteristics (Full Analysis Set)

Characteristics	Cohort 1 (N=10)	Cohort 2 (N=1)	Total (N=11)
Age (years)			
Mean (SD)	44.1 (20.30)	25.0 (-)	42.4 (20.10)
Median	39.5	25.0	32.0
Min, Max	19, 77	25, 25	19, 77
Sex [n (%)]			
Male	6 (60.0)	0	6 (54.5)
Female	4 (40.0)	1 (100)	5 (45.5)
Race [n (%)]			
White	9 (90.0)	0	9 (81.8)
Not Reported	1 (10.0)	1 (100)	2 (18.2)
Ethnicity [n (%)]			
Hispanic or Latino	1 (10.0)	0	1 (9.1)
Not Hispanic or Latino	8 (80.0)	0	8 (72.7)
Not Reported	1 (10.0)	1 (100)	2 (18.2)
VWD Type [n (%)]			
Type 2A	1 (10.0)	0	1 (9.1)
Type 3	9 (90.0)	1 (100)	10 (90.9)

iCSR=interim clinical study report; Max=maximum; Min=Minimum; n=number of subjects in each category; N=number of subjects in the full analysis set; SD=standard deviation; VWD=von Willebrand disease
% = Percentage of subjects relative to the number of subjects in the Safety Analysis Set

Numbers analysed

The presented interim efficacy analyses (data cut-off date of 30 Jun 2022) included 11 subjects (5 Prior OD and 6 Switch subjects) who completed Study 071301 and continued to receive prophylactic vonicog alfa in Study SHP677-304.

Outcomes and estimation

In Study SHP677-304, average compliance for the 2 cohorts was >95%, ranging from approximately 83% to 100%. As of the data cut-off date, the overall mean study duration was 918.8 days (range, 725 to 1094 days).

Endpoints Related to bleeding events:

sABR data is summarised by cohort for the first 12 months and the entire study (a total of 2 to 3 years of prophylactic treatment) in the table below.

Table 23. Study SHP677-304 sABR Based on Treated Bleeds During First 12 Months and Entire Study (Full Analysis Set)

Time Period sABR	Cohort 1 N=10	Cohort 2 N=1	Total N=11
First 12 Months			
Mean (SD)	1.328 (2.3822)	1.040 (-)	1.302 (2.2616)
Median (Min, Max)	0.000 (0.00, 7.47)	1.040 (1.04, 1.04)	0.000 (0.00, 7.47)
Entire Study			
Mean (SD)	1.094 (2.1408)	0.410 (-)	1.032 (2.0414)
Median (Min, Max)	0.000 (0.00, 6.57)	0.410 (0.41, 0.41)	0.000 (0.00, 6.57)

FAS=full analysis set; iCSR=interim clinical study report; Max=maximum; Min=minimum; N=number of subjects in the full analysis set; SD=standard deviation; sABR=spontaneous annualized bleeding rate

For the secondary efficacy analysis, the sABR for the entire Study SHP677-304 (through the data cut-off of 30 Jun 2022) is shown for each subject in Cohorts 1 and 2 in the table below.

Table 24. Study SHP677-304 Cohorts 1 and 2 sABR for Treated Bleeds by Subject (Full Analysis Set)

Subject ID Continuation Study/ Prophylaxis Study	Continuation Study SHP677-304						Prophylaxis Study 071301		
			First 12 Months		Entire Study		Through Data Cutoff Date		
	Cohort	Study Duration (Days)[a]	Number of Treated Spontaneous BEs & Locations	Treated sABR	Number of Treated Spontaneous BEs & Locations	Treated sABR	Cohort	Treated Spontaneous BEs & Locations	Treated sABR
	1	954	None	0	None	0	Prior OD	None	0
	1	841	None	0	None[b]	0	Switch	None	0
	1	812	None	0	None	0	Switch	None	0
	1	1094	None	0	None	0	Prior OD	None	0
	1	1057	8 BEs: Skin (1), Mucosal (1), Other (7)[c]	7.47	19 BEs: Skin (1), Mucosal (2), Other (17)[c]	6.57	Prior OD	6 BEs: Mucosal (2), Menorrhagia (2), Menstrual (1), Other (1)	5.78
	1	738	None	0	None	0	Switch	None	0
	1	1093	3 BEs[d]: Mucosal (2), Joint (1)	2.84	9 BEs[d]: Mucosal (7), Joint (2)	3.01	Prior OD	3 BEs: Mucosal (3)	2.84
	1	725	1 BE: Mucosal	1.02	1 BE: Mucosal	0.5	Switch	4 BEs: Mucosal (4)	3.85
	1	1043	None	0	None	0	Prior OD	None	0
	1	847	2 BEs: Mucosal (2)	1.95	2 BEs: Mucosal (2)	0.86	Switch	None	0
	2	903	1 BE: Mucosal	1.04	1 BE: Mucosal	0.41	Switch	None	0

ABR=annualized bleeding rate; BE=bleeding episode; iCSR=interim clinical study report; ID=identifier; OD=on demand; sABR=spontaneous ABR; SAE=serious adverse event
Spontaneous ABR is derived as [number of treated bleeds]/[duration in years].

[a] Study Duration (Days) derived as (Date of Data Cutoff) – (Date of Informed Consent) + 1. Data cutoff date is 30 Jun 2022.

[b] Subject did not report any bleeding in the eDiary or to the site; however, the subject had an SAE of anemia reported as associated with bleeds that occurred between December 2021 and March 2022 (approximately 2 years after the start of prophylactic treatment) in the SAE report. There were no source documents available for any bleeding and no principal investigator assessment was done.

[c] One BF was recorded at 2 locations.

[d] Subject had 1 bleed of unknown cause (mucosal, gum), which was counted as a spontaneous bleed only for the sABR calculation.

Endpoints Related to Vonicog Alfa Infusions and Weight-based Consumption

Throughout the entire study, the mean total number of prophylactic vonicog alfa infusions in Cohort 1 was 247.6 infusions, with a range of 104 to 310 infusions. The mean number of vonicog alfa infusions per week in Cohort 1 was 1.882, with a range of 1.00 to 2.50; the subject in Cohort 2 received a mean of 1.003 weekly infusions. The mean weekly vonicog alfa infusion dose for Cohort 1 was 94.80 IU/kg, with a range of 54.61 to 144.53 IU/kg. The 1 subject in Cohort 2 received 129 vonicog alfa infusions, with a mean weekly dose of 64.38 IU/kg. The mean total vonicog alfa dose per subject was 12403.025 IU/kg, with a range of 6334.32 to 16974.59 IU/kg, in Cohort 1; the subject in Cohort 2 received a total vonicog alfa dose of 8277.920 IU/kg.

Table 25. Study SHP677-304 Cohorts 1 and 2 Prophylactic Study Drug Administration (Full Analysis Set)

Characteristics	Cohort 1 (N=10)	Cohort 2 (N=1)	Total (N=11)
Total Number of Vonicog Alfa Infusions			
Mean (SD)	247.6 (57.83)	129.0 (--)	236.8 (65.49)
Median	259.5	129.0	259.0
Min, Max	104, 310	129, 129	104, 310
Average Number of Vonicog Alfa Infusions Per Week			
Mean (SD)	1.882 (0.3720)	1.003 (--)	1.802 (0.4413)
Median	1.945	1.003	1.923
Min, Max	1.00, 2.50	1.00, 1.00	1.00, 2.50
Total Vonicog Alfa Dose (IU/kg)			
Mean (SD)	12403.025 (3384.0275)	8277.920 (--)	12028.015 (3442.8813)
Median	13182.910	8277.920	12782.730
Min, Max	6334.32, 16974.59	8277.92, 8277.92	6334.32, 16974.59
Average Vonicog Alfa Dose (IU/kg) per Week			
Mean (SD)	94.803 (24.9505)	64.384 (--)	92.038 (25.3850)
Median	91.177	64.384	85.790
Min, Max	54.61, 144.53	64.38, 64.38	54.61, 144.53

iCSR=interim clinical study report; Max=maximum; Min=Minimum; N=number of subjects in the full analysis set; SD=standard deviation

As of the data cut-off date, a total of 68 BEs (55 spontaneous BEs) occurred in Cohorts 1 and 2. 36 BEs of all causes were treated in 5 subjects. A total of 35 all-cause BEs were treated with vonicog alfa and 19 were treated with ADVATE. The mean number of vonicog alfa infusions to treat a BE was 1.2 (1 subject had a vonicog alfa infusion to treat a bleed, which was not included in the listing due to a data entry error). The mean total vonicog alfa infused per bleed was 56.2 IU/kg per infusion. The majority of treated BEs (35 of 36) were assessed with an efficacy rating of "Excellent".

Of the 32 spontaneous BEs that required treatment, 17 (53.1%) were severe, 9 (28.1%) were moderate, and 6 (18.8%) were mild. The majority of the treated spontaneous BEs were in the locations of other (heavy menstrual bleeds) (17 BEs, 53.1%) and mucosal (13 BEs, 40.6%), with 2 BEs (6.3%) in the joint location and 1 BE (3.1%) in the skin location. The efficacy ratings for treated spontaneous BEs were "Excellent" (96.9%) and "Good" (3.1%)

Table 26. Study SHP677-304 Cohorts 1 and 2 Treated Spontaneous Bleeding Episodes by Location, Severity, and Treatment for the Entire Study up to Data Cutoff 30 Jun 2022 (Full Analysis Set)

Characteristic Statistic	Cohort 1 (N=10)	Cohort 2 (N=1)	Total (N=11)
Total number of subjects with bleeding episodes	4	1	5
Total number of bleeding episodes	31	1	32
Cause of bleeding episode (n [%])			
Spontaneous	30 (96.8)	1 (100)	31 (96.9)
Unknown	1 (3.2)	0	1 (3.1)
Location of bleeding episode (n [%])			
Skin	1 (3.2)	0	1 (3.1)
Mucosal	12 (38.7)	1 (100)	13 (40.6)
Joint	2 (6.5)	0	2 (6.3)
Other: menstrual bleeding/heavy menstrual bleeding	17 (54.8)	0	17 (53.1)
Severity [m (%)]			
Mild	6 (19.4)	0	6 (18.8)
Moderate	8 (25.8)	1 (100)	9 (28.1)
Severe/Major	17 (54.8)	0	17 (53.1)
Number of subjects with vonicog alfa-treated bleeds	4 (100)	1 (100)	5 (100)
Number of vonicog alfa infusions to treat bleeding episode[a]			
n	30	1	31
Mean (SD)	1.2 (0.43)	1.0 (-)	1.2 (0.43)
Median	1.0	1.0	1.0
Q1, Q3	1.0, 1.0	1.0, 1.0	1.0, 1.0
Min, Max	1, 2	1, 1	1, 2
Number of subjects with ADVATE-treated bleeds	2 (50.0)	0	2 (40.0)
Number of ADVATE infusions to treat bleeding episode[a]			
n	19	0	19
Mean (SD)	1.3 (0.48)	- (-)	1.3 (0.48)
Median	1.0	-	1.0
Q1, Q3	1.0, 2.0	-, -	1.0, 2.0
Min, Max	1, 2	-, -	1, 2
Efficacy rating[a] (n [%])			
Excellent	30 (96.8)	1 (100)	31 (96.9)
Good	1 (3.2)	0	1 (3.1)

Ancillary analyses

Exposure-response Analyses

Based on the final dataset from the prophylaxis Study 071301 and the interim data of Study SHP677-304 (Cohorts 1 and 2), the MAH conducted an ER analysis to investigate the effect of different VWF:RCo PK parameters on spontaneous BEs requiring treatment to investigate any causal links between PK/PD and BEs during prophylactic treatment with vonicog alfa.

For ER modelling, the exposure input was obtained from the population PK model simulations (see section 2.3.4 above). To test for an effect of VWF:RCo exposure, the simulated PK parameters included:

(1) the trough VWF:RCo level prior to the BE,

(2) the average levels of VWF:RCo in the dosing interval prior to the BE, and

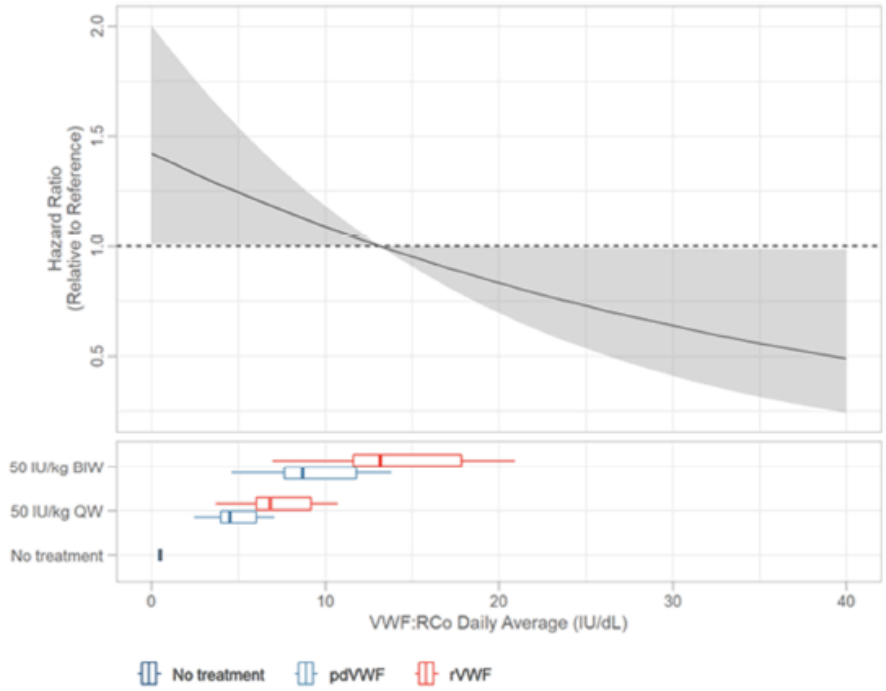
(3) the average VWF:RCo over the 24 hours prior to the BE.

In a first step, model discrimination was performed by comparing the goodness-of-fit of linear and nonlinear ER models using the PK input as described above. Of all models tested, a repeated time-to-event (RTTE) model with a linear ER function linking the average levels of VWF:RCo over 24 hours prior to the spontaneous BE was associated with the lowest AIC (Akaike information criterion).

A statistically significant ER was observed for VWF:RCo ($p<0.05$), whereby higher exposures were associated with a lower risk of spontaneous BEs.

The HRs for the probability of bleeding as a function of the daily average activity at steady state ($C_{ave,ss}$) of VWF:RCo for BIW or QW dosing of vonicog alfa as well as pdVWF are presented in the Figure below.

Figure 6. Hazard Ratio for the Probability of Bleeding for Twice Weekly and Once Weekly Dosing of Vonicog Alfa and Platelet-derived von Willebrand Factor Products in Type 3 Subjects



BIW=twice weekly; pdVWF=plasma-derived von Willebrand factor; rVWF=recombinant von Willebrand factor (vonicog alfa); QW=once weekly; VWF:RCo=von Willebrand factor ristocetin cofactor activity

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 27. Summary of Efficacy for Study 071301:

Title: A Prospective, Phase 3, Open-label, International Multicenter Study on Efficacy and Safety of Prophylaxis with rVWF in Severe von Willebrand Disease		
Study identifier	071301; EudraCT Number: 2016-001478-14	
Design	This was a prospective, open-label, uncontrolled, non-randomized, international, multicenter, Phase 3 study to evaluate efficacy and safety (including immunogenicity, thrombogenicity, and hypersensitivity reactions), as well as pharmacokinetics, pharmacodynamics, health-related quality of life, and pharmacoeconomics of prophylactic treatment regimen with vonicog alfa (recombinant von Willebrand factor; rVWF) in adult subjects with severe von Willebrand disease (VWD). Subjects received prophylactic treatment with vonicog alfa for a 12-month period; a longer duration was allowed if a study site did not have Continuation Study SHP677-304 initiated by the time a subject finished Month 12 in Study 071301. Any bleeding episodes requiring replacement therapy with VWF concentrate to control bleeding was to be treated with vonicog alfa with or without ADVATE (recombinant factor VIII). 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. After completing the study, subjects could continue into Continuation Study SHP677-304 during which they could continue receiving prophylactic vonicog alfa treatment or switch to on-demand vonicog alfa therapy.	
	Duration of main phase: Duration of run-in phase: Duration of extension phase:	12 to 15 months Not applicable Not applicable
Hypothesis	No formal hypothesis testing was performed. Intra-subject comparisons of on-study and historical data were performed for the Prior On-demand (OD) and Switch groups.	
Treatment groups	**Prior On-demand (OD)** This group included subjects who were receiving on-demand VWF prior to this study and had ≥3 documented spontaneous bleeds (not including menorrhagia) requiring VWF treatment during the 12 months prior to this study.	Prophylactic vonicog alfa for 12 to 15 months Treatment was initiated with twice-weekly infusions of 50±10 IU/kg per infusion. Dose adjustment to higher dose/frequency (up to 80 IU/kg per infusion, up to 3 infusions per week) was allowed due to individual variation in drug response. Number of subjects enrolled: 13
	Switch This group included subjects who had been receiving prophylactic plasma-derived von Willebrand factor (pdVWF) treatment for at least 12 months prior to this study.	Prophylactic vonicog alfa for 12 to 15 months Initial treatment was based on matching (±10%) the weekly pdVWF dose of each subject's prior pdVWF prophylaxis regimen. The initial prophylactic treatment regimen was twice weekly for most subjects but in some cases was 1 or 3 times a week, depending on the total weekly dose and the dosing regimen used in their previous pdVWF prophylaxis regimen. Dose adjustment to higher dose/frequency (up

			to 80 IU/kg per infusion, up to 3 infusions per week) was allowed due to individual variation in drug response. Number of subjects enrolled: 10
Endpoints and definitions	Primary endpoint	sABR	Annualized bleeding rate (ABR) for treated spontaneous (not related to trauma) bleeding episodes (BEs) during prophylactic treatment with vonicog alfa, calculated as the number of treated spontaneous bleeds divided by the observation period in years. Reduction in sABR was calculated by comparing on-study and historical sABR rates; the ratio (on-study:historical) was estimated within each subject group using a generalized linear mixed-effects model with 95% Wald confidence interval (CI).
	Secondary endpoint	ABR % reduction success	ABR percent reduction success for Prior OD subjects, defined as at least 25% reduction of ABR based on treated spontaneous BEs during vonicog alfa prophylaxis relative to the subject's own historical ABR during OD VWF treatment prior to this study
	Secondary endpoint	ABR preservation success	ABR preservation success for Switch subjects, defined as achieving an ABR based on treated spontaneous BEs during vonicog alfa prophylaxis that was no greater than the subject's own historical ABR based on spontaneous BEs during prophylactic treatment with pdVWF prior to this study
	Secondary endpoint	Categorized sABR	Categorized treated spontaneous ABR, defined as 0, >0 to 2, >2 to 5, or >5 treated spontaneous BEs during prophylactic treatment with vonicog alfa
	Secondary endpoint	Infusions	Total number of infusions and the average number of infusions per week during prophylactic treatment with vonicog alfa
	Secondary endpoint	Consumption	Total weight adjusted consumption of vonicog alfa during prophylactic treatment
	Secondary endpoint	sABR by location	ABR for treated spontaneous BEs by location of bleeding (gastrointestinal, epistaxis, joint bleeding, menorrhagia, oral and other mucosa, muscle, and soft tissue, etc) while on prophylactic treatment with vonicog alfa
Database lock	23 Oct 2020		
<u>Results and Analysis</u>			
Analysis description	**Primary Analysis**		
Analysis population and time point description	Full analysis set (FAS): all subjects who received vonicog alfa prophylaxis. The observation period for historical BEs was the 365 days prior to the first dose of vonicog alfa in Study 071301. The primary analyses of efficacy were based on data through Month 12 in Study 071301.		
Descriptive statistics and estimated variability	Treatment group	Prior OD	Switch
	Number of subjects	13	10

	Observation period	Historical	On-study	Historical	On-study
	Number of spontaneous treated BEs	201	9	50	18
	sABR, mean (SD)	15.462 (41.9536)	0.663 (1.7266)	5.000 (14.4222)	1.692 (3.8467)
	Model-based sABR, mean (95% CI)	6.541 (2.516, 17.004)	0.555 (0.150, 2.048)	0.514 (0.042, 6.307)	0.283 (0.021, 3.851)
	sABR category, n (%)				
	0	0	11 (84.6)	6 (60.0)	7 (70.0)
	>0 through 2	0	0	3 (30.0)	1 (10.0)
	>2 through 5	10 (76.9)	1 (7.7)	0	1 (10.0)
	>5	3 (23.1)	1 (7.7)	1 (10.0)	1 (10.0)
	sABR by anatomical location of bleeding while on vonicog alfa prophylactic treatment, mean (SD)				
	Hemarthrosis	NA	0.000 (0.0000)	NA	0.098 (0.3097)
	Menorrhagia	NA	0.222 (0.8018)	NA	0.000 (0.0000)
	Oral and other mucosa	NA	0.367 (0.9140)	NA	1.315 (3.0540)
	Other	NA	0.074 (0.2673)	NA	0.000 (0.0000)
	Unknown	NA	0.000 (0.0000)	NA	0.279 (0.8817)
	Prophylactic infusions per subject				
	Mean (SD)	NA	65.1 (38.4)	NA	87.8 (30.2)
	Min, max	NA	2, 116	NA	31, 116
	Weekly vonicog alfa prophylactic infusions per subject				
	Mean (SD)	NA	1.88 (0.7)	NA	1.85 (0.4)
	Min, max	NA	0.7, 3.5	NA	0.8, 2.1
	Monthly weight-adjusted prophylactic vonicog alfa dose per subject (IU/kg)				
	Mean (SD)	NA	427.2 (175.9)	NA	407.2 (131.8)
	Min, max	NA	151.2, 813.6	NA	207.9, 554.8
	Average dose administered per vonicog alfa prophylactic infusion (IU/kg)				
	Mean (SD)	NA	52.203 (3.7572)	NA	52.167 (16.1971)
	Min, max	NA	44.77, 58.84	NA	24.39, 79.41
Effect estimate per comparison	Primary endpoint	Comparison groups		Prior OD: On study vs historical	
		Reduction in sABR		91.5%	
		Model-based sABR ratio (95% CI)		0.085 (0.021, 0.346)	
		Comparison groups		Switch: On study vs historical	
		Reduction in sABR		45.0%	
		Model-based sABR ratio (95% CI)		0.550 (0.086, 3.523)	

	Secondary endpoint: ABR % reduction success	Comparison groups	Prior OD: On study vs historical
		Number (%) of subjects with ABR % reduction success	12 (92.3)
		95% CI	(64.0, 99.8)
	Secondary endpoint: ABR preservation success	Comparison groups	Switch: On study vs historical
		Number (%) of subjects with ABR preservation success	9 (90.0)
		95% CI	(55.5, 99.7)
Notes	Reasons for discontinuation in the Prior OD group were withdrawal of consent (2 subjects, 15.4%), and adverse event and other reason (extended hydrocortisone treatment) (each 1 subject, 7.7%). Reasons for discontinuation in the Switch group were withdrawal of consent and other reason (high-dose corticosteroid treatment) (each 1 subject, 10.0%). Analyses of the primary and secondary efficacy endpoints were repeated for the FAS using data through the end-of-study visit. Selected analyses were repeated for the mFAS and the PPAS; similar results were observed. The consistency of results for the FAS and the mFAS showed that data identified for removal for lack of ALCOA-C-compliant documentation did not change the overall efficacy conclusions of the study.		

ABR=annualized bleeding rate; ALCOAC=Attributable, Legible, Contemporaneous, Original, Accurate, and Complete; BE=bleeding episode; CI=confidence interval; CSR=clinical study report; max=maximum; min=minimum; mFAS=modified full analysis set; OD=on demand; NA=not applicable; pdVWF=plasma-derived von Willebrand factor; PPAS=per protocol analysis set; rVWF=recombinant von Willebrand factor; sABR=spontaneous annualized bleeding rate; SD=standard deviation; VWD=von Willebrand disease; VWF=von Willebrand factor

The mFAS included all subjects who received prophylaxis treatment with investigational product and did not have data (entire infusion or bleed record[s]) identified to be removed due to lack of proper ALCOAC-compliant source documentation.

The PPAS included FAS subjects who were ≥70% compliant regarding the number of scheduled prophylactic infusions and did not have any major protocol deviations that could affect the primary efficacy assessments.

Table 28. 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 Pediatric and Adult Subjects with Severe von Willebrand Disease	
Study identifier	SHP677-304; EudraCT Number: 2018-003453-16
Design	This is an ongoing, Phase 3b, prospective, open-label, uncontrolled, nonrandomized, multicenter study evaluating long-term safety and efficacy of vonicog alfa for prophylaxis and on-demand (OD) treatment of bleeding episodes (BEs) in pediatric and adult subjects with severe VWD. The study includes 6 cohorts in total: 4 prophylactic treatment cohorts and 2 OD treatment cohorts. However, only 2 of the cohorts (Cohorts 1 and 2) are relevant for the efficacy analyses of prophylactic vonicog alfa treatment included in this Type II Variation for the addition of a prophylaxis indication. These cohorts include only subjects who completed Prophylaxis Study 071301, in either the Prior OD or the Switch group. Subjects in Cohorts 1 and 2 continued prophylactic treatment with vonicog alfa. 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 substitution therapy with VWF concentrate to control bleeding was to be treated with vonicog alfa, with or without ADVATE (recombinant factor VIII; rFVIII). Dose and frequency were individualized based on the subject's

	weight, VWD type and severity of BE and monitoring of appropriate clinical and laboratory measures.		
	Duration of main phase: Duration of run-in phase: Duration of extension phase:		Minimum 12 months; maximum 3 years Not applicable Not applicable
Hypothesis	Descriptive statistics only		
Treatment groups	**Cohort 1** Adult subjects transitioning from the Phase 3 Parent Study 071301 who were to remain on the same prophylactic dose as in Parent Study 071301.		Prophylactic vonicog alfa for up to 3 years Treatment was continued with the same regimen as Parent Study 071301, which was expected to be twice-weekly infusions of 50±10 IU/kg per infusion for the majority of the subjects. At the time of data cutoff, the mean (SD) average number of infusions per week for Cohort 1 was 1.88 (0.37) and the mean (SD) average dose per week was 94.80 (24.95). Dose adjustment to higher dose/frequency (up to 80 IU/kg per infusion) was allowed due to individual variation in drug response. Number of subjects enrolled: 10
	Cohort 2 Adult subjects transitioning from Parent Study 071301 with no clinically significant BE for the past 6 months who were to start this Phase 3b continuation study at a lower dose/frequency compared to the dose received in Parent Study 071301.		Prophylactic vonicog alfa for up to 3 years Treatment dose was reduced compared with the regimen administered in Parent Study 071301. At the time of data cutoff, the average number of infusions per week for the only subject in Cohort 2 was 1.00 and the average rVWF dose per week was 64.38. Dose adjustment to higher dose/frequency (up to 80 IU/kg per infusion) was allowed due to individual variation in drug response. Number of subjects enrolled: 1
Endpoints and definitions	Primary endpoint	sABR over 12 months	Annualized bleeding rate (ABR) for treated spontaneous bleeding episodes (BEs) during the first 12 months of prophylactic vonicog alfa treatment, calculated as the number of treated spontaneous bleeds divided by the observation period in years.
	Secondary endpoint	sABR over entire study period	ABR for treated spontaneous BEs during the entire study period (through the cutoff date for interim analysis)
	Secondary endpoint	Categorized sABR	Categorized treated spontaneous ABR, defined as 0, >0 to ≤2, >2 to ≤5, or >5 spontaneous treated BEs per year

	Secondary endpoint	sABR by location	Treated sABR by bleeding location	
	Secondary endpoint	Infusions	Total number of infusions and the average number of infusions per week during prophylactic treatment with vonicog alfa	
	Secondary endpoint	Consumption	Total weight-adjusted consumption of vonicog alfa during prophylactic treatment	
Database lock	30 Jun 2022 (interim analysis cutoff date)			
Results and Analysis				
Analysis description	**Primary Analysis**			
Analysis population and time point description	Full analysis set (FAS): all subjects who satisfied all entry criteria and received any amount of investigational product. For the purposes of this data cut, the data presented are for the subjects from the FAS belonging to Cohorts 1 and 2 because these were the subjects who received prophylactic vonicog alfa treatment. The primary endpoint was analyzed based on the first 12 months of prophylactic vonicog alfa treatment. Secondary endpoints were analyzed based on the first 12 months and the entire study period.			
Descriptive statistics and estimated variability	Treatment group	Cohort 1	Cohort 2	Total
	Number of subjects	10	1	11
	sABR over 12 months, mean (SD)	1.33 (2.38)	1.04 (NC)	1.30 (2.26)
	sABR over entire study period, mean (SD)	1.09 (2.14)	0.41 (NC)	1.03 (2.04)
	Categorized sABR for first 12 months, n (%)			
	0	6 (60.0)	0	6 (54.5)
	>0 through ≤2	2 (20.0)	1 (100)	3 (27.3)
	>2 through ≤5	1 (10.0)	0	1 (9.1)
	>5	1 (10.0)	0	1 (9.1)
	Categorized sABR for entire study period, n (%)			
	0	6 (60.0)	0	6 (54.5)
	>0 through ≤2	2 (20.0)	1 (100)	3 (27.3)
	>2 through ≤5	1 (10.0)	0	1 (9.1)
	>5	1 (10.0)	0	1 (9.1)
	sABR by bleeding location for first 12 months, mean (SD)			
	Skin	0.093 (0.2941)	0.000 (NC)	0.085 (0.2804)
	Mucosal	0.579 (0.8115)	1.040 (NC)	0.621 (0.7823)
	Joint	0.095 (0.3004)	0.000 (NC)	0.086 (0.2864)
	Other: menstrual bleeding/heavy menstrual bleeding	0.654 (2.0681)	0.000 (NC)	0.595 (1.9719)
	sABR by bleeding location for entire study period, mean (SD)			
	Skin	0.035 (0.1107)	0.00 (NC)	0.032 (0.1055)

	Mucosal	0.439 (0.7464)	0.410 (NC)	0.436 (0.7082)
	Joint	0.067 (0.2119)	0.00 (NC)	0.061 (0.2020)
	Other: menstrual bleeding/heavy menstrual bleeding	0.587 (1.8563)	0.00 (NC)	0.534 (1.7699)
	Average number of vonicog alfa infusions per week for first 12 months			
	Mean (SD)	1.938 (0.4766)	1.017 (NC)	1.854 (0.5305)
	Min, max	1.01, 2.99	1.02, 1.02	1.01, 2.99
	Average number of vonicog alfa infusions per week for entire study period			
	Mean (SD)	1.882 (0.3720)	1.003 (NC)	1.802 (0.4413)
	Min, max	1.00, 2.50	1.00, 1.00	1.00, 2.50
	Average vonicog alfa dose per week (IU/kg) for first 12 months			
	Mean (SD)	100.268 (31.9190)	67.623 (NC)	97.301 (31.8406)
	Min, max	55.67, 173.88	67.62, 67.62	55.67, 173.88
	Average vonicog alfa dose per week (IU/kg) for entire study period			
	Mean (SD)	94.803 (24.9505)	64.384 (NC)	92.038 (25.3850)
	Min, max	54.61, 144.53	64.38, 64.38	54.61, 144.53
Effect estimate per comparison	Not applicable; efficacy analyses were descriptive only.			
Notes	As of the interim analysis cutoff date, no subjects had discontinued the study. The overall mean duration of study participation for the 11 subjects in Cohorts 1 and 2 through the interim analysis cutoff date of 30 Jun 2022 was 918.8 days (minimum 725 days, maximum 1094 days; ie, approximately 2 to 3 years). Together with the vonicog alfa prophylaxis these subjects received in Study 071301 (at least 1 year), this provides approximately 3 to 4 years of data to support the sustained efficacy of long-term prophylactic vonicog alfa treatment.			

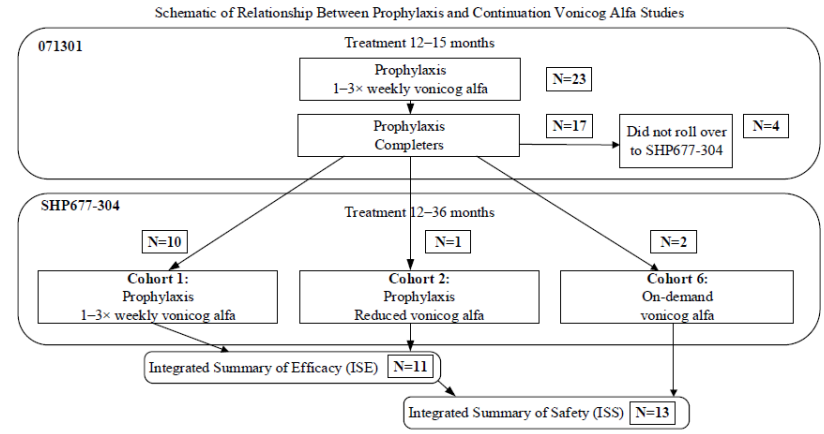
ABR=annualized bleeding rate; BE=bleeding episode; CSR=clinical study report; FAS=full analysis set; IU=International Unit; max=maximum; min=minimum; OD=on demand; NC=not calculated; rVIII=recombinant factor VIII; rVWF=recombinant von Willebrand factor; sABR=spontaneous annualized bleeding rate; SD=standard deviation; VWD=von Willebrand disease; VWF=von Willebrand factor

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

Integrated Efficacy Analysis: Studies 071301/SHP677-304

For subjects who completed Study 071301 and entered Study SHP677-304, the MAH performed an integrated analyses of data, i.e. from the day of the first dose of vonicog alfa prophylactic treatment in Study 071301 through the data cut-off date (30 Jun 2022) in the ongoing Continuation Study SHP677-304. Participant flow across the two studies is shown in the figure below.

Figure 7. Data Flow for Study 071301, Study SHP677-304, ISE (Studies 071301/SHP677-304), and ISS (Studies 071301/SHP677-304)



ISE=Integrated Summary of Efficacy; ISS=Integrated Summary of Safety; N=number of subjects

The integrated analyses of efficacy included the following endpoints:

- ABR for treated spontaneous BEs
- Number and percentage of subjects with ABR percent reduction or preservation success
- Categorized sABR, defined as 0, >0 to 2, >2 to 5, or >5 during prophylactic treatment with vonicog alfa
- Total and average monthly weight-adjusted consumption of vonicog alfa during prophylactic treatment
- Total number of infusions and average number of infusions per week during prophylactic treatment

Analysis Sets

Eleven subjects were included in the integrated efficacy analyses. Seventeen subjects completed Study 071301, and 13 subjects entered Study SHP677-304. However, 2 subjects entered Cohort 6 of Study SHP677-304 (i.e. switched back to OD treatment) and were excluded from the integrated efficacy analyses.

Efficacy analyses were performed for the following analysis sets:

- Rollover full analysis set (Rollover FAS): All subjects who received prophylactic treatment with vonicog alfa across Studies 071301/SHP677-304 (Cohorts 1 and 2) (N=11).
- Rollover subset full analysis set (Rollover sFAS): All subjects who received prophylactic treatment with vonicog alfa across Studies 071301/SHP677-304 (Cohorts 1 and 2) and had data identified to be removed due to lack of proper ALCOA-C-compliant source documentation in Prophylaxis Study 071301 (N=4). Note: No data were removed in Study SH677-304, so subjects in the Rollover sFAS had data removed in Prophylaxis Study 071301 but not in Study SH677-304.

Efficacy data were summarized in a descriptive manner.

Rollover Full Analysis Set

For the 11 subjects in the Rollover FAS, mean duration of vonicog alfa prophylaxis was approximately 44 months (ranging from 36.4 to 51.4 months). Treatment compliance was high (mean % compliance

approximately 92%) for the 11 subjects throughout the combined studies. For the Prior OD subjects, a reduction in the mean on-study sABR change from historical sABR was observed in the Rollover FAS. This was also the case when subjects in the Rollover FAS were analyzed by sex, race, and geographic region. For the Switch subjects, a slight reduction in mean on-study sABR change from historical sABR (when the subjects were treated prophylactically with pdVWF) was observed. Among the treated on-study spontaneous BEs, there was no body cavity bleed, no GI bleed, and no CNS bleed.

Table 29. Integrated Summary of Efficacy (Studies 071301/SHP677-304) Historical and On-study Treated sABR: Descriptive Statistics (Rollover Full Analysis Set)

	Study					
	Study 071301		Study SHP677-304		Overall	
Time Period Statistic	Prior OD (N=5)	Switch (N=6)	Prior OD (N=5)	Switch (N=6)	Prior OD (N=5)	Switch (N=6)
Historical Treated sABR						
n	5	6	5	6	5	6
Mean (SD)	3.800 (1.3038)	0.500 (0.8367)	3.800 (1.3038)	0.500 (0.8367)	3.800 (1.3038)	0.500 (0.8367)
Min, Max	3.00, 6.00	0.00, 2.00	3.00, 6.00	0.00, 2.00	3.00, 6.00	0.00, 2.00
On-Study Treated sABR						
n	5	6	5	6	5	6
Mean (SD)	1.348 (1.9936)	0.367 (0.8983)	1.915 (2.9078)	0.295 (0.3575)	1.737 (2.6185)	0.346 (0.4789)
Min, Max	0.00, 4.44	0.00, 2.20	0.00, 6.57	0.00, 0.86	0.00, 5.89	0.00, 1.20
Change from Historical ABR						
n	5	6	5	6	5	6
Mean (SD)	-2.452 (2.2174)	-0.133 (1.3953)	-1.885 (3.0779)	-0.205 (0.9260)	-2.063 (2.7997)	-0.154 (1.0560)
Min, Max	-4.00, 1.44	-2.00, 2.20	-4.00, 3.57	-1.59, 0.86	-4.00, 2.89	-1.71, 1.20
Percent Change from Historical ABR						
n	5	2	5	2	5	2
Mean (SD)	-62.8 (64.03)	-100.0 (0.00)	-46.2 (94.79)	-89.9 (14.35)	-51.4 (85.04)	-92.8 (10.16)
Min, Max	-100, 48	-100, -100	-100, 119	-100, -80	-100, 96	-100, -86

ABR=annualized bleeding rate; BE=bleeding episode; EOS=end of study; ISE=integrated summary of efficacy; Max=maximum; Min=minimum; n=number of subjects in each category; N=number of subjects in the rollover full analysis set; OD=on-demand; sABR=spontaneous annualized bleeding rate; SD=standard deviation; VWF=von Willebrand factor

Table 30. Integrated Summary of Efficacy (Studies 071301/SHP677-304) Individual Subject sABR Results (Rollover Full Analysis Set)

Subject	Historical sABR[a]	Study 071301 On-Study sABR[b]	Study SHP677-304 On-Study sABR[b]	ISE (Studies 071301/SHP677-304) On-Study sABR[c]
Prior OD				
	3.00	0.00	0.00	0.00
	4.00	0.00	0.00	0.00
	3.00	5.78	7.47	5.89
	6.00	2.84	2.84	2.80
	3.00	0.00	0.00	0.00
	2.00	0.00	1.04	0.29
	1.00	0.00	0.00	0.00
	0.00	0.00	0.00	0.00
	0.00	0.00	0.00	0.00
	0.00	3.85	1.02	1.20
	0.00	0.00	1.95	0.60

BE=bleeding episode; CSR=clinical study report; iCSR=interim clinical study report; ISE=integrated summary of efficacy; OD=on-demand; sABR=spontaneous annualized bleeding rate; VWF=von Willebrand factor

[a] Based on spontaneous, treated (with VWF) BEs within the 12 months before Day 1.

[b] Based on data from Day 1 through Month 12 for the indicated study.

[c] Based on data from Study 071301 Day 1 through the data cutoff date of 30 Jun 2022 for Study SHP677-304.

Nine of the 11 Rollover FAS subjects were on a 2× weekly infusion regimen throughout Study 071301. In Study SHP677-304, 8 of the 11 subjects started on the 2× weekly regimen, 2 subjects started on a 1× weekly regimen (1 additional subject had the dosing frequency reduced from 2× weekly in Study 071301 to 1× weekly based on meeting criteria for dose reduction and cohort assignments), and 1 subject started on a 3× weekly regimen. As of the data cut-off date (30 Jun 2022), 1 subject decreased prophylactic vonicog alfa dosing frequency from 3× weekly to 2× weekly (this reduction was due to no significant bleeding in the period rather than any dose-related safety considerations) and 1 subject increased dose (40 to 60 IU/kg) without increasing dose frequency during Study SHP677-304.

Table 31. Integrated Summary of Efficacy (Studies 071301/SHP677-304) Prophylactic Vonicog Alfa Infusions and Weight-Based Consumption (Rollover Full Analysis Set)

Parameter	Study Period		
	Study 071301 (N=11)	Study SHP677-304 (N=11)	Overall (N=11)
Total Number of Prophylactic Infusions[a]	1110	2605	3715
Prophylactic Infusions per Subject			
Mean (SD)	100.91 (30.231)	236.82 (65.487)	337.73 (81.434)
Min, Max	43.0, 142.0	104.0, 310.0	147.0, 426.0
Prophylactic Regimen (Infusions per Week) Used at Any Time, n (%) of subjects			
1× per week	1 (9.1)	2 (18.2)	2 (18.2)
2× per week	9 (81.8)	8 (72.7)	9 (81.8)
3× per week	1 (9.1)	1 (9.1)	1 (9.1)
Weekly Prophylactic Infusions per Subject			
Mean (SD)	1.724 (0.4547)	1.808 (0.4433)	1.774 (0.3743)
Min, Max	0.811, 2.015	0.997, 2.511	0.930, 2.303
Monthly Weight-Adjusted (IU/kg) Prophylactic Dose Per Subject			
Mean (SD)	389.190 (121.1182)	401.350 (110.7651)	395.363 (101.7059)
Min, Max	191.17, 520.50	238.32, 631.05	228.10, 585.13
Infusions Per Spontaneous BE			
Number of BEs	10	31	41
Mean (SD)	1.20 (0.422)	1.19 (0.402)	1.20 (0.401)
Median (Min, Max)	1.00 (1.0, 2.0)	1.00 (1.0, 2.0)	1.00 (1.0, 2.0)

BE=bleeding episode; ISE=integrated summary of efficacy; Max=maximum; Min=minimum; n=number of subjects in each category; N=number of subjects in the rollover full analysis set; OD=on-demand; PK=pharmacokinetic; SD=standard deviation

[a] Pharmacokinetic infusions (excluding first PK infusion for OD subjects) were counted as prophylactic infusions in this table.

Subject had 1 bleed with infusion number 97, 98, and no drug and dose information during Study 071301, as a result the bleed was not counted in this table. Subject had 1 bleed with infusion number 104 and no dose information during Study 071301, as a result the bleed was not counted in the table.

Rollover Subset Full Analysis Set

The Rollover sFAS of 4 subjects with some infusion data removed for lack of ALCOA-C-compliant source documentation was used to compare sABR and compliance results during Study 071301 (in which 10 subjects had some infusion records removed from the database because of lack of ALCOA-C-compliant source documentation) with results during Study SHP677-304 (in which subjects did not have data removed for lack of ALCOA-C-compliant source documentation) to demonstrate consistency of ABR results across studies within a subject despite differences in compliance rates.

Three Rollover sFAS subjects were in the Prior OD cohort and 1 subject was in the Switch cohort. They received prophylactic vonicog alfa infusions 2× or 3× weekly throughout both Studies 071301 and SHP677-304. For the 3 Prior OD subjects, the reduction in sABR from historical to on-study was >25% (meeting treatment success criteria based on sABR reduction) during both studies with the reduction occurring in Study 071301 and maintained in Study SHP677-304.

Historical and on-study treated sABRs for the Rollover sFAS subjects are summarized as follows:

Table 32. Study 071301 Descriptive Statistics for Historical and On-Study sABR Through Month 12 (Full Analysis Set and Modified Full Analysis Set VWD Type 3)

Table 37. Integrated Summary of Efficacy (Studies 071301/SHP677-304) Historical and On-Study Treated sABR (Rollover Subset Full Analysis Set)

	Study					
	Study 071301		Study SHP677-304		Overall	
Time Period Statistic	Prior OD (N=3)	Switch (N=1)	Prior OD (N=3)	Switch (N=1)	Prior OD (N=3)	Switch (N=1)
Historical Treated sABR						
n	3	1	3	1	3	1
Mean (SD)	4.333 (1.5275)	0.000 (--)	4.333 (1.5275)	0.000 (--)	4.333 (1.5275)	0.000 (--)
Min, Max	3.00, 6.00	0.00, 0.00	3.00, 6.00	0.00, 0.00	3.00, 6.00	0.00, 0.00
On-Study Treated sABR						
n	3	1	3	1	3	1
Mean (SD)	0.767 (1.3290)	2.200 (--)	1.002 (1.7364)	0.504 (--)	0.932 (1.6138)	1.196 (--)
Min, Max	0.00, 2.30	2.20, 2.20	0.00, 3.01	0.50, 0.50	0.00, 2.80	1.20, 1.20
Change from Historical sABR						
n	3	1	3	1	3	1
Mean (SD)	-3.566 (0.5129)	2.200 (--)	-3.331 (0.5795)	0.504 (--)	-3.402 (0.5283)	1.196 (--)
Min, Max	-4.00, -3.00	2.20, 2.20	-4.00, -2.99	0.50, 0.50	-4.00, -3.00	1.20, 1.20

2.4.2. Discussion on clinical efficacy

Design and conduct of clinical studies

Study 071301 was an exploratory study with a small sample size and no prespecified hypotheses. The design of Study 071301 has been subject to CHMP Protocol Assistance (EMEA/H/SA/1378/2/FU/1/2014/PA). Overall, the final design of the study, the number and type of enrolled subjects and the duration of follow-up comply with the guideline on clinical investigation of plasma-derived VWF (CPMP/BPWG/220/02). CHMP recommendations concerning the in-/exclusion criteria, endpoints, observation period and statistical plan have been taken into account. However, although considered in principle acceptable (particularly in view of the rarity of the targeted disease), the lack of randomization and the use of historical control data (i.e. external knowledge) instead of a run-in phase represent potential sources of bias.

Additional uncertainties arise from the introduction of a switch cohort (i.e. patients already receiving prophylactic treatment prior to study entry) with Global Protocol Amendment 6. In this context, it is noted that (i) the EMA clinical guideline (CPMP/BPWG/220/02) does not specify any requirements with regards to the prior treatment of study subjects, and (ii) CHMP considered the inclusion of patients already receiving prophylactic treatment to be acceptable in principle (EMEA/H/SA/1378/2/FU/1/2014/PA). However, as a potential selection bias due to an enrichment of favourable responders in the Switch group cannot be excluded, special attention should be paid to the pre-defined subgroup analyses of Prior OD subjects. In fact, with protocol amendment 6, patients with a poor response to prophylactic treatment (i.e. patients requiring more than 5 infusions or weekly doses exceeding 240 IU/kg at the time of screening) were formally excluded from the trial.

Most notably, the conduct of Study 071301 was compromised by a malfunctioning eDiary device, resulting in ALCOA-C non-compliant source documentation. This issue affected at least 10 of the 23 study subjects (to varying degrees) raising concerns about the reliability and quality of data, particularly in relation to the results reported for the FAS. However, further analyses of a modified FAS (excluding subjects affected by the non-compliant source documentation) and the availability of additional data from the continuation study SHP677-304 for 4 of the 10 subjects affected provide a certain degree of reassurance on a negligible impact of identified cases of inappropriate source documentation on the reported efficacy outcomes. The MAH also clarified that per study protocol, if a BE could not be captured

in the eDiary (e.g. due to device malfunction or user error), the subject still reported it to the study site (to receive instructions on treatment). Therefore, the study site was always able to record the BE in the EDC. In addition, the MAH pointed out that a subsequent review of EDC data (for confirming ALCOA-C compliant source documentation) did not result in any removal of BEs. Thus, the reporting of BEs can be considered complete.

Efficacy data and additional analyses

In Study 071301, all Prior OD subjects initiated vonicog alfa prophylactic treatment with 2× weekly infusions of 40 to 60 IU/kg per infusion. For Switch subjects, the initial vonicog alfa prophylactic treatment was based on matching (±10%) the weekly dose of their prior pdVWF prophylaxis regimen at 1 to 3 times per week. Consumption data reveal that the vast majority of the 23 subjects stayed on the same dose and dosing frequency. Dose escalations were limited to one subject in the Prior OD group and two subjects in the Switch group. Upon request, the MAH provided more detailed information on changes in dosing regimens during the study. Noteworthy, the highest increased dose was 65 IU/kg 3 times weekly. The only subject who received a dose of 80 IU/kg received this dose once weekly in accordance with previous prophylaxis regimen. Thus, it is noted that the data obtained in Study 071301 fall short in providing support for the per protocol permitted dose escalation up to 80 IU/kg per prophylactic infusion. However, 1) the importance of an individualised approach to the treatment of VWD is well recognised, 2) the notion of a potentially necessary deviation from the recommended "standard prophylaxis regimen" in SmPC sections 4.2 is consistent with alternative VWF products, and 3) the proposed maximum dose of 80 IU/kg corresponds to the currently approved maximum single dose of VEYVONDI. Hence, the proposed definition of a maximum prophylactic dose of 80 IU/kg in section 4.2 of the VEYVONDI SmPC is considered acceptable.

In the FAS, prophylaxis with rVWF reduced the mean on-study sABR compared to historical sABR in Prior OD subjects by 91.5%, from 6.541 to 0.555, and in Switch subjects by 45.0%, from 0.514 to 0.283, based on analysis using a negative binomial model. Most (78.3%) subjects had zero treated spontaneous BEs while on rVWF prophylactic treatment (84.6% of Prior OD and 70% of Switch subjects) providing further support for a clinically meaningful reduction of bleeding events under long-term prophylactic treatment.

However, high degree of interindividual heterogeneity and two remarkable cases with substantial numbers of untreated moderate and major bleeds (excluded from the primary analysis) were noted. The MAH clarified that for both subjects, high bleeding frequencies captured on-study support the validity of the reported high historical ABRs. In addition, Listing 16.2.4.14 confirms that historical BEs were indeed treated with VWF. The high frequency of "untreated" bleeding events on-study was explained by the per protocol option to receive non-VWF treatment (antifibrinolytics or topical hemostats). In fact, only if a bleeding had not stopped within 24 hours following administration of non-VWF treatment, infusions with vonicog alfa were to be started. Noteworthy, this permitted use of non-VWF treatments casts additional doubt on the value of comparisons to historical bleeding events. On the other hand, the frequent investigator's decision to omit additional VWF treatment can be seen as an indication of less severe bleeding during prophylactic treatment. Considering only the spontaneous bleeds treated with VWF, both patients showed substantially improved ABRs with zero reported BEs during Study 071301. For one patient, a substantially improved ABR despite consideration of all on-study BEs (i.e. treated and untreated) provides reassurance on the beneficial impact of vonicog alfa treatment. For another patient, despite an overall similar rate of historical and on-study bleeds, a certain improvement can be derived from the apparent lack of additional (on-demand) VWF treatment. However, assessment of the case of this patient is further complicated by the concomitant prophylactic use of oral tranexamic acid as well as an early discontinuation from the study after only 1 month of treatment. Thus, overall, the MAH's

response falls short in relieving concerns regarding a lack of clinical benefit for the subject. However, since additional questions are not considered likely to reduce the remaining uncertainties, it is decided to not pursue this issue further.

Additional sources of uncertainty relate to the actual severity of baseline bleeding phenotypes in the Prior OD cohort and a potential impact of concomitant haemostatic medication on the reported efficacy results. Moreover, results of Study 071301 revealed two cases of apparent worsening of disease phenotypes (i.e. substantially increased sABR despite initiation of or upon switching to vonicog alfa prophylaxis). The MAH clarified that for one patient, an sABR of only 0.5 in the continuation study (and sABR of 1.20 across both studies) provides reassurance on a beneficial impact of vonicog alfa prophylactic treatment. In this patient, reasons for the only incomplete bleeding protection remains hypothetical, particularly in view of the apparently unremarkable (i.e. satisfying) vonicog alfa-induced plasma levels of FVIII:C. On the other hand, the case of this patient may be explained by the generally heterogenous nature of VWD, natural fluctuations in disease severity and/or interindividual differences in treatment requirements, not questioning the value of prophylactic treatment per se. Since additional questions are not considered likely to shed any additional light on the apparently only incomplete bleeding protection of this patient, this issue was not pursued further.

Of note, data obtained in the mFAS, excluding all subjects who had data removed from the EDC due to ALCOA-C non-compliant source documentation, was largely comparable to the data reported for the FAS arguing against a significant impact of the identified cases of inappropriate source documentation on the reported study outcomes. In this context, it is considered particularly noteworthy that even the Prior OD cohort in the mFAS meets the EMA clinical guideline requirement of a minimum of 5 patients with type 3 VWD and showed results consistent with the overall reported outcomes.

For 11 of the 17 patients who completed Study 071301, the interim report of study SHP677-304 provides supportive evidence of consistency and sustained efficacy of prophylactic treatment with vonicog alfa beyond the 12-month duration of treatment in Study 071301.

However, four of the subjects who completed Study 071301 did not rollover into Study SHP677-304 and two subjects rolled over but switched back to OD treatment. Importantly, the cases of switch backs were based on personal preference and not attributed to a lack of efficacy as evidenced by an sABR of zero under prophylactic treatment in Study 071301. Nevertheless, given the generally higher likelihood of a rollover of favourable responders (in fact, both subjects with an historical sABR >10 and 2 of the 5 subjects with an sABR >0 under prophylactic treatment in study 071301 did not continue prophylactic treatment in Study SHP677-304), a potential impact of selection bias cannot be excluded and hence, the efficacy results obtained in Study SHP677-304 should be interpreted with caution.

As of the cut-off date of the presented interim analysis, subjects who continued prophylactic treatment in Study SHP677-304 received treatment for an additional mean duration of 918.8 days (minimum 725 days; maximum 1094 days). Eight of the 11 subjects started with a twice-a-week dosing regimen, 2 subjects started with once per week dosing, and these subjects stayed on this initial dosing interval throughout the study. The remaining subject initiated with a 3× per week dosing regimen but had a dosing interval change from 3× per week to 2× per week during the study.

Overall, the ABRs for treated spontaneous bleeds achieved with continued prophylactic vonicog alfa treatment were consistent with the ABRs observed in the parent study 071301. Six subjects out of 11 achieved zero on-study spontaneous BEs that required additional treatment. In the 5 subjects with an sABR >0, bleeding rates remained low and in view of the anticipated natural fluctuations, the slight increases compared to the sABRs obtained in study 071301 do not raise concerns regarding a potential long-term weakening of prophylactic efficacy. Of note, there were no CNS or GI bleeds under prophylaxis and spontaneous joint bleeds requiring treatment were limited to two events (one major, one moderate) affecting a single subject.

However, compared to a frequency of major bleeding events of only 1% of treated bleeds in the historical database (cf. Table 15 in the CSR of Study 071301), the reported frequency of 55% of treated spontaneous bleeds classified as severe/major in Study SHP677-304 was considered remarkable and requires further justification to address concerns regarding a significant worsening of bleeding protection under prophylactic treatment with vonicog alfa. As requested, the MAH provided additional information on annualized bleeding rates (historical vs. on-study) considering only the subset of severe spontaneous BEs requiring VWF treatment. Importantly, when excluding a subject who experienced several severe BEs upon switching back from prophylactic treatment in Study 071301 to on-demand treatment in Study SHP677-304, the increased rate of severe BEs noticed in Study SHP677-304 was attributed to a single patient who contributed a total of 16 severe spontaneous BEs, mostly heavy menstrual bleeding, to the dataset. Possible reasons for the apparent shift towards an increased frequency of severe bleeds in this subject are not further discussed/specified and thus remain hypothetical. However, the apparently only incomplete bleeding protection of this patient may be explained by the heterogenous nature of VWD, natural fluctuations in disease severity, and/or interindividual differences in treatment requirements. Furthermore, a potential impact of the ultimately subjective attribution of bleeding severities is acknowledged. Overall, the MAH clarified that the apparent increase in severe BEs in Study SHP677-304 (i.e. under continued vonicog alfa prophylactic treatment) was attributed to an isolated case, from which no general trend towards a higher frequency of more severe breakthrough bleeds can be deducted.

2.4.3. Conclusions on the clinical efficacy

The totality of clinical data submitted with this application supports the efficacy of VEYVONDI in prophylactic treatment of adults with severe VWD.

2.5. Clinical safety

Introduction

The present application includes safety data for a total of 23 unique subjects exposed to vonicog alfa across studies 071301 and SHP677-304. Study 071301 safety data are presented for 23 adult subjects who are included in the safety analysis set. Study SHP677-304 safety data (data cut-off date 30 Jun 2022) are presented for the 13 subjects who rolled over from Study 071301 into Study SHP677-304 Cohort 1 (same prophylaxis regimen as Study 071301), Cohort 2 (prophylaxis at a reduced dose and/or frequency than Study 071301), or Cohort 6 (OD treatment) and are included in the safety analysis set. Three of the subjects in the vonicog alfa prophylaxis study (071301) and continuation study (SHP677-304) also participated in the Phase 3 on-demand and surgery studies (1 in Study 071001 and 2 in Study 071101).

In addition, an Integrated Summary of Safety (ISS) analysis was performed. The ISS included the 13 subjects who completed Study 071301 after at least 12 months of vonicog alfa prophylactic treatment, rolled over into Study SHP677-304, and received at least 1 dose of vonicog alfa in Study SHP677-304 (rollover safety analysis set). Safety data for the ISS and Study SHP677-304 are based on interim analyses since SHP677-304 was ongoing as of the data cut-off date (and is still ongoing).

For detailed descriptions of Study 071301 and SHP677-304 and subject disposition across the two studies reference is made to section 2.4.1 and Figure 7 above.

In general, safety was assessed in terms of adverse events (AEs), hypersensitivity, immunogenicity, and thrombogenicity and included the following evaluations:

- Neutralising and binding antibodies to VWF
- Neutralising and binding antibodies to factor VIII (FVIII)
- Binding antibodies to CHO proteins, murine immunoglobulin G (IgG), and rFurin
- Signs of thrombosis or thromboembolic complications (clinical signs and measurement of thrombotic markers)
- Other IP-related AEs, including serious adverse events (SAEs), temporally associated AEs, AEs of special interest (AESIs; including thromboembolic events, hypersensitivity reactions (including allergic reactions or anaphylactic reactions), clinically significant changes in routine laboratory parameters (haematology, clinical chemistry, and coagulation), and vital signs
- Viral serology (hepatitis A virus, hepatitis B virus, hepatitis C virus, human immunodeficiency virus 1/2, and human parvovirus B19)

Patient exposure

In Study 071301, the 23 subjects in the safety analysis set received vonicog alfa as prophylactic treatment for a mean (standard deviation [SD]) of 10.7 (4.7) months. Overall, 23 subjects received 1813 prophylactic infusions (1887 total vonicog alfa infusions for any reason) during 1813 exposure days. The mean number of prophylactic vonicog alfa infusions received per subject over the course of the study was 78.8 and ranged from 2 to 142. The mean (SD) weight-adjusted prophylactic vonicog alfa dose per subject per month was 415.9 (154.4) IU/kg. Six subjects received a total of 42 vonicog alfa infusions as on-demand treatment for bleeds or to maintain hemostasis. Three subjects received at least 1 dose of ADVATE with vonicog alfa for on-demand treatment of bleeding episodes.

In Study SHP677-304, as of the data cut-off date of 30 Jun 2022, the overall number of days on study for the 11 subjects in Cohorts 1 and 2 ranged from 725 to 1094, and the number of prophylactic vonicog alfa infusions per subject ranged from 104 to 310. The 2 subjects in Cohort 6 spent 444 and 1094 days on study; these subjects did not receive prophylactic vonicog alfa infusions. Three subjects (2 from Cohort 1 and 1 from Cohort 6) received at least 1 dose of ADVATE with vonicog alfa for on-demand treatment of bleeding episodes.

In the ISS rollover safety analysis set, 13 subjects received vonicog alfa as prophylactic treatment for a mean (SD) of 39.03 (12.081) months across the 2 studies; 13 subjects received prophylactic treatment in Study 071301 for 13.49 (1.557) months and 11 out of the 13 subjects (Cohorts 1 and 2) received prophylactic treatment in Study SHP677-304 for 30.05 (4.554) months.

Adverse events

41 TEAEs were reported in 17/23 (73.9%) subjects during Study 071301; 76 TEAEs were reported in 9/11 (81.8%) subjects in Cohorts 1 and 2 and 11 TEAEs were reported in 2/2 (100%) subjects in Cohort 6 during ongoing Study SHP677-304. A total of 113 TEAEs were reported in 12/13 (92.3%) subjects in the ISS at the data cut-off date of 30 Jun 2022.

In Study 071301, most of the TEAEs were mild or moderate; 4 severe TEAEs (2 serious and 2 non-serious) were reported in 3 (13.0%) subjects. There were no fatal or life-threatening events and most TEAEs were non-serious. Three treatment-emergent SAEs, all unrelated to the IP, were experienced by 3 (13.0%) subjects. One (4.3%) subject discontinued vonicog alfa treatment due to a TEAE (non-serious headache) that was considered possibly related to vonicog alfa. No other TEAEs were considered to be

related to vonicog alfa. Two subjects experienced an AESI; both events (purpura [due to trauma] and rash pruritic) were nonserious, mild in severity, and not related to the IP.

In Study SHP677-304, most of the TEAEs were mild. Severe TEAEs were reported for 2 (18.2%) subjects in Cohorts 1 and 2 (bacteraemia and pneumonia in 1 subject and anaemia in 1 subject, both in Cohort 1) and for 2 (100%) subjects in Cohort 6 (ovarian cyst ruptured and anaemia in 1 subject each). No TEAEs were considered to be related to vonicog alfa. No AESIs were reported.

Table 33. Overall Summary of Vonicog Alfa Treatment-emergent Adverse Events in Study 071301, SHP677-304, and ISS (Studies 071301/SHP677-304) in Subjects Treated With Vonicog Alfa

	Clinical Studies					
	071301[a]	SHP677-304[b]				ISS (071301/ SHP677-304)[c]
		Prophylaxis			On-demand	
Parameter	Total (N=23) n (%) E	Cohort 1 (N=10) n (%) E	Cohort 2 (N=1) n (%) E	Total (N=11) n (%) E	Cohort 6 (N=2) n (%) E	Total (N=13) n (%) E
Duration of prophylactic treatment per subject in months, Mean (SD)	10.7 (4.7)	NC	NC	30.05 (4.554)[d]	NA	39.03 (12.081)
Any TEAE	17 (73.9) 41	8 (80.0) 66	1 (100.0) 10	9 (81.8) 76	2 (100.0) 11	12 (92.3) 113
IP-related nonserious TEAE	1 (4.3) 1	0	0	0	0	0
Severe TEAE	3 (13.0) 4	2 (20.0)	0	2 (18.2)	2 (100)	5 (38.5) 8
Temporally associated TEAE	7 (30.4) 9	6 (60.0) 29	1 (100) 2	7 (63.6) 31	1 (50.0) 1	9 (69.2) 37
Adverse event of special interest[e]	2 (8.7) 2	0	0	0	0	2 (15.4) 2
Serious adverse event	3 (13.0) 3	2 (20.0) 3	0	2 (18.2) 3	1 (50.0) 1	4 (30.8) 6
IP-related serious adverse event	0	0	0	0	0	0
Death	0	0	0	0	0	0
TEAE leading to discontinuation from study	1 (4.3) 1	0	0	0	0	0

AE=adverse event; CSR=clinical study report; E=number of events in each category; FVIII=factor VIII; iCSR=interim clinical study report; IP=investigational product (vonicog alfa alone or vonicog alfa with ADVATE); ISS=integrated summary of safety; MedDRA=Medical Dictionary for Regulatory Activities; n=number of subjects who had at least 1 event in the category; N=total number of subjects in the relevant analysis set and column; NA=not applicable; NC=not calculated; SD=standard deviation; SMQ=standardized MedDRA query; TEAE=treatment-emergent adverse event; VWF=von Willebrand factor

[a] Data for the safety analysis set for Study 071301; all subjects received prophylactic vonicog alfa treatment.

[b] Data for the safety analysis set for Study SHP677-304; subjects received prophylactic vonicog alfa treatment in Cohorts 1 and 2 (Prophylaxis) and on-demand vonicog alfa treatment in Cohort 6 (On-demand).

[c] Data for the rollover safety analysis set for the ISS; subjects received prophylactic vonicog alfa treatment in Study 071301 and prophylactic or on-demand vonicog alfa treatment in Study SHP677-304 (Cohorts 1, 2, and 6).

[d] Mean duration is for the 11 subjects in Cohorts 1 and 2 who received prophylactic vonicog alfa treatment in Study SHP677-304.

[e] Adverse events of special interest included thromboembolic events, hypersensitivity reactions (including allergic reactions or anaphylactic reaction), and development of neutralizing antibodies against VWF or FVIII.

In both studies (071301 and SHP677-304) and the ISS, most TEAEs were experienced as a single occurrence by 1 subject. In Study 071301, the following TEAEs were each experienced by more than 1 subject: headache (4 [17.4%] subjects), arthralgia (3 [13.0%] subjects), and ear infection, gastroenteritis, urinary tract infection (UTI), joint injury, and alanine aminotransferase (ALT) increased (2 [8.7%] subjects each).

In Study SHP677-304, the following TEAEs were each experienced by more than 1 subject in Cohorts 1 and 2: headache (4 [36.4%] subjects) and abdominal pain, abdominal pain upper, toothache, procedural pain, SARS-CoV-2 test positive, and anaemia (2 [18.2%] subjects each).

Adverse Events of Special Interest

In Study 071301, two (8.7%) subjects had 1 AESI each: a thromboembolic event of purpura (caused by trauma) and a hypersensitivity reaction of rash pruritic. Both events were mild, nonserious, and considered not related to the IP. Both events resolved with no action taken regarding study treatment. In Study SHP677-304, no AESIs were identified.

Immunogenicity

No subject developed binding antibodies to murine IgG, CHO protein, or rFurin. In Study 071301, no subject developed antibodies (binding or neutralising) to vonicog alfa or FVIII. In Study SHP677-304, no confirmed neutralising antibodies against human VWF or FVIII were reported. Two subjects each had 1 transient occurrence of a positive result for VWF inhibitor assays: 1 subjects had a borderline positive result for neutralising antibody to von Willebrand factor:collagen binding (VWF:CB) at a postoperative unscheduled visit, and the other subject had positive results for neutralizing antibody to VWF:CB and VWF:RCo at the Month 2 follow-up visit. However, none of the positive results were confirmed by a second test.

Serious adverse event/deaths/other significant events

A total of 7 treatment-emergent serious adverse events (SAEs: multiple injuries from a fall, rheumatoid arthritis, urinary tract infection, haemoglobin decreased, bacteraemia, anaemia, and ovarian cyst ruptured) were reported in 5 of the 23 unique subjects in the 2 studies (n=3 in Study 071301 and n=4 in Study SHP677-304). None of the SAEs were fatal, life threatening, or considered related to vonicog alfa by the investigator or sponsor.

Laboratory findings

In both studies, no clinically significant abnormalities in haematology, clinical chemistry, or coagulation values were attributed to vonicog alfa. No trends in vital signs were noted, and no clinically significant electrocardiogram (ECG) abnormalities were reported.

Safety in special populations

Sex: Overall, given the low number of TEAEs of each category and the low number of subjects of either sex experiencing each TEAE, there was no obvious difference in the AE profiles between male and female subjects.

Paediatric Population: Safety and effectiveness in paediatric subjects below the age of 18 years have not been established.

Geriatric Use: The number of subjects aged 65 years and older treated with vonicog alfa was too low (n=3 in the prophylaxis study) to determine whether this age group responds differently compared to younger subjects.

Discontinuation due to adverse events

In Study 071301, 1 (4.3%) subject discontinued vonicog alfa treatment due to a TEAE (non-serious headache) that was considered possibly related to vonicog alfa. No other TEAEs were considered to be related to vonicog alfa. No subjects have discontinued the ongoing Study SHP677-304 due to a TEAE as of the data cut-off date (30 Jun 2022).

Post marketing experience

As of 30 June 2022, the global cumulative post marketing subject exposure to vonicog alfa since launch is estimated to be approximately 19,347 patient-years.

Post marketing ADRs reported in association with vonicog alfa treatment include two cases of anaphylactic reactions and two cases of infusion-related reactions (IRR).

2.5.1. Discussion on clinical safety

The safety of VEYVONDI in routine prophylaxis (i.e. the requested EOI) was assessed in 23 unique subjects (≥18 years). In study 071301, subjects received a total of 1813 prophylactic infusions (1887 total vonicog alfa infusions for any reason) during 1813 exposure days. The number of prophylactic vonicog alfa infusions received per subject ranged from 2 to 142 with a mean of 78.8. As of the cut-off date of the presented interim report of Study SHP677-304, 11 of the 17 subjects who completed Study 071301 received additional prophylactic infusions ranging from 104-310 (mean: 236.82) over a mean (SD) duration of 30.05 (4.554) months. As such, the newly provided data provides an extensive and valuable addition to the existing safety database.

Notably, the population targeted by the requested EOI does not differ from the population for which the product is already approved (i.e. adults [age 18 and older] with von VWD, when DDAVP treatment alone is ineffective or not indicated). Given the known safety profile of VWF-containing products and the orphan nature of severe VWD, the small sample size of only 23 subjects is considered acceptable.

VEYVONDI represents a recombinant VWF. Safety aspects of particular importance to this class of drug include the risk of hypersensitivity reactions, thrombogenicity and the development of binding and/or neutralising alloantibodies. All of these potential and/or identified risks were tightly monitored during the studies and captured as adverse events of special interest.

Overall, safety data obtained in studies 071301 and SHP677-304 (up to the data cut-off date of the presented interim report) were consistent with previous clinical studies of VEYVONDI in VWD not indicating TEAEs specific to its long-term prophylactic use. TEAEs considered related to VEYVONDI were limited to a single case of moderate headache which occurred in Study 071301 and led to discontinuation from the study on day 37 of treatment. Noteworthy, this case has already been assessed in a previous variation procedure (EMEA/H/C/004454/II/0026, CHMP positive opinion on 12 January 2023) and led to the inclusion of headache as a very common ADR in section 4.8 of the VEYVONDI SmPC.

Besides this, no other TEAEs reported in Studies 071301 and SHP677-304 were considered to be related to vonicog alfa. As of the data cut-off of the interim report of Study SHP677-304 no other subject discontinued prophylactic treatment due to a TEAE.

In both studies, there were no fatal or life-threatening events and most TEAEs were non-serious. No thromboembolic event was assessed as related to vonicog alfa and no subject developed alloantibodies (binding or neutralising) to the drug.

With this application no updates of the safety sections of the VEYVONDI SmPC are proposed which is considered acceptable.

2.5.2. Conclusions on clinical safety

In conclusion, no new safety signals emerged from the newly presented data. Overall, the safety data presented with this application are consistent with previous clinical studies of VEYVONDI in VWD and support its safe and well tolerated use for long-term prophylactic treatment in adults.

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 an updated RMP version with this application.

The PRAC considered that the risk management plan version 4.1 is acceptable. The CHMP endorsed the Risk Management Plan version 4.1 with the following content:

Safety concerns

Summary of the 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

Pharmacovigilance plan was updated to include a category 3 study European Haemophilia Safety Surveillance System (EUHASS) registry.

The protocol relating to the additional category 3 study is expected within a separate post authorisation measure procedure.

On-going and planned additional pharmacovigilance activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
None				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
None				
Category 3 - Required additional pharmacovigilance activities				
VON (BAX0111) VWF-500 COL (ATHN-9) - A Real World Safety and Effectiveness Study of Factor Replacement for Clinically Severe von Willebrand Disease (VWD) Also referred to as ATHN9 study Ongoing	To collect and summarize safety and efficacy data of various VWF-containing products and to have targeted safety monitoring/follow-up information on the AESIs for this population while on treatment with VWF-containing products.	Hypersensitivity reactions Thromboembolic events Inhibitor formation	Final protocol	within 3 months after putative approval / CHMP opinion (Q3 2018)- completed September-2018
			Interim report	Q4 2020 - completed December-2020
			Final study report	Q3 2024 (planned)
TAK-577-4005 - Estimating Risk of Selected Adverse Events in Patients with Von Willebrand Disease Treated with VEYVONDI® (vonicog alfa; recombinant Von Willebrand Factor) Ongoing	• To estimate the risk of hypersensitivity reactions, thromboembolic events, and VWF inhibitor or FVIII inhibitor formation after treatment with VEYVONDI in the study population prescribed VEYVONDI for the treatment of haemorrhage and surgical bleeding and the prevention of surgical bleeding when DDAVP treatment alone is ineffective or not indicated. The risk of hypersensitivity reactions will be estimated during the 7 days after infusion; thromboembolic event risk will be estimated during the 30 days after infusion; and the risk of inhibitor formation will be estimated during the 6 months after infusion.	Hypersensitivity reactions Thromboembolic events Inhibitor formation	Final report	Q4 2023

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
	• To describe the association of thromboembolic events with use of FVIII concomitantly with VEYVONDI.			
Participation in registries (e.g., European Haemophilia Safety Surveillance (EUHASS) registry) and review of the data provided by the registries to further characterise the safety concerns for long term safety follow-up Planned	The EUHASS registry serve to collect further safety information in patients with vWD.	-Hypersensitivity reactions -Thromboembolic events (particularly in patients with low ADAMTS13 levels as well as other risk factors, and concomitant overuse of FVIII) -Inhibitor formation -Insufficient clinical data on use in pregnancy and lactation -Insufficient clinical data on use in geriatric patients	Regular updates	Data will be reviewed on an on-going basis as part of signal detection and reported within PSUR/ PBRERs when available.

Risk minimisation measures

No changes proposed; there are no additional risk minimisation measures for Veyvondi. The routine risk minimisation measures are sufficient to minimise the risks of the product in the proposed indication.

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 5.1, 5.2, 6.2 and 6.6 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

2.7.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the MAH show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Von Willebrand disease (VWD) represents 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. With this extension of indication the MAH is seeking to extend the indication to include "prophylactic treatment to prevent or reduce the frequency of bleeding episodes".

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 to control spontaneous bleeding or to prevent excessive bleeding during surgical procedures. However, a subset of patients with severe VWD (i.e. suffering from frequent and severe BEs) may benefit from long-term prophylactic treatment as also acknowledged by the wording of section 4.1 of the Core SmPC for human plasma derived VWF (CPMP/BPWG/278/02) *("Prevention and treatment of haemorrhage or surgical bleeding in von Willebrand disease (VWD), when desmopressin (DDAVP) treatment alone is ineffective or contra-indicated")* and the recently published ASH ISTH NHF WFH 2021 guideline on the management of VWD (Connell *et al.* 2021). Currently, several plasma-derived VWF/FVIII concentrates (containing different amounts and ratios of VWF and FVIII) are available for VWD prophylaxis treatment in the EU, including a centrally authorised product. Besides the problem of varying composition and overall plasma donor availability, drawbacks of plasma-derived VWF/FVIII products are given by a risk for excessive plasma FVIII levels (and an associated risk of thrombogenesis) upon repeated infusions and an at least theoretical risk of pathogen transmission as well as the presence of extraneous plasma proteins which may trigger allergic responses.

3.1.3. Main clinical studies

Study 071301: A Prospective, Phase 3, Open-label, International Multicenter Study on Efficacy and Safety of Prophylaxis with rVWF in 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 Pediatric and Adult Subjects with Severe von Willebrand Disease

3.2. Favourable effects

In the primary analysis of study 071301, prophylaxis with rVWF reduced the mean on-study sABR (annual bleeding rate for spontaneous bleeds treated with VWF infusions) compared to historical sABR in Prior OD subjects by 91.5%, from 6.541 to 0.555, and in Switch subjects by 45.0%, from 0.514 to 0.283, based on analysis using a negative binomial model.

The as-observed data showed a mean (SD) sABR reduction from historical to on-study treatment period through Month 12 of -14.798 (42.1849) for Prior OD subjects and -3.308 (10.8569) for Switch subjects.

At least 90% of Prior OD subjects (12 of 13; 92.3%) and Switch subjects (9 of 10; 90.0%) achieved treatment success as sABR reduction (defined as ≥25% reduction in on-study sABR compared with historical sABR) in the Prior OD group or sABR preservation (defined as on-study sABR no greater than historical sABR) in the Switch group, through Month 12.

Most (78.3%) subjects had zero treated spontaneous BEs while on rVWF prophylactic treatment (84.6% of Prior OD and 70% of Switch subjects) providing further support for a clinically meaningful reduction of bleeding events under long-term prophylactic treatment.

For 11 of the 17 patients who completed Study 071301, interim data of the continuation study SHP677-304 provide further support for consistency and maintained efficacy of prophylactic treatment beyond the 12-month duration of treatment in Study 071301 (with additional durations of treatment ranging from 725 to 1094 days). Six of the 11 rollover subjects had no spontaneous BEs requiring additional vonicog alfa treatment and in the remaining 5 subjects, bleeding rates remained low with no evidence of a potential long-term loss or weakening of prophylactic efficacy. Noteworthy, there were no CNS or GI bleeds under prophylaxis. Spontaneous joint bleeds requiring treatment were limited to two events (one major, one moderate) affecting a single subject, and the vast majority of treated spontaneous breakthrough bleeds (31 of 32) were assessed with an efficacy rating of 'Excellent', with only 1 additional infusion of vonicog alfa per bleed required.

In study 071301, all Prior OD subjects and 80% of Switch subjects started on a twice-a-week dosing regimen and the vast majority stayed on this regimen throughout the study with mean (SD) doses per infusion of 52.2 (3.8) IU/kg or 52.2 (16.2) IU/kg in Prior OD or Switch subjects, respectively. Across studies, dose escalations were limited to 1 Prior OD and 2 Switch subjects (both in study 071301). Furthermore, the proposed recommendation to initiate prophylactic treatment with a BIW 40-60 IU/kg regimen is supported by PK/PD model-based simulations predicting plasma FVIII:C levels in type 3 VWD to be above 40 IU/dL for an average of 5.29 days (i.e. 76% of weekly time).

In addition, steady-state PK/PD assessments performed during prophylactic treatment in study 071301 support the notion of a stable PK/PD behaviour of vonicog alfa over the duration of treatment, not only with regard to VWF:RCo PK but also with regard to the vonicog alfa-mediated upregulation of plasma FVIII activity with a statistically significant increase in trough (i.e. pre-dose) levels from 3.83 IU/dL at baseline to 18.7 IU/dL under prophylaxis in Prior OD subjects.

3.3. Uncertainties and limitations about favourable effects

Uncertainties about the favourable effects arise from the only small sample size, the lack of randomization and the use of historical control data (i.e. external knowledge) instead of a run-in phase. However, the design of study 071301 has to be seen in the context of the rarity of the targeted disease, has been subject to CHMP Protocol Assistance (EMEA/H/SA/1378/2/FU/1/2014/PA) and complies with the requirements set forth in the EMA guideline on clinical investigation of plasma-derived VWF (CPMP/BPWG/220/02).

Most notably, the conduct of Study 071301 was compromised by a malfunctioning eDiary device resulting in cases of ALCOA-C non-compliant source documentation. This issue affected at least 10 of the 23 study subjects (to varying degrees) raising concerns about the reliability and quality of data, particularly in relation to the results reported for the FAS. However, removal of data from the EDC was limited to infusion data and did not affect the primary analysis. Moreover, sensitivity analyses performed with a modified FAS (excluding subjects affected by the non-compliant source documentation) and the availability of additional data from study SHP677-304 for 4 of the 10 affected subjects provide some reassurance about the validity of the reported results. Moreover, it is considered noteworthy that even

the Prior OD cohort in the mFAS meets the EMA clinical guideline requirement of a minimum of 5 patients with type 3 VWD and shows results consistent with the overall reported outcomes.

In addition, the conduct of study 071301 was affected by several cases of early discontinuations which, even though not clearly attributable to a lack of efficacy, may have led to a certain enrichment of favourable responders and particularly questions the generalisability of steady-state PK data obtained at EOS, which are available for only 9 of the 13 Prior OD and 7 of the 10 Switch subjects who initiated treatment. Another source of bias may have resulted from the introduction of a switch cohort (i.e. patients already receiving prophylactic treatment prior to study entry) with Global Protocol Amendment 6. However, subgroup analysis of the Prior OD group provide reassurance on clinical efficacy in prophylaxis-naïve subjects and comparisons between Switch and Prior OD subjects indicate largely similar results.

Although a degree of heterogeneity seems inevitable given the targeted disease, two notable cases, both characterised by very high historical ABRs and a significant number of untreated moderate and major bleeds remain difficult to interpret and cast doubt on the appropriateness of excluding untreated bleeds from the primary analysis. For one of the two subjects, additional sensitivity analyses, considering not only treated but also untreated bleeds, provide reassurance on an improved bleeding protection under long-term prophylactic treatment. For the other subject, a certain benefit of prophylactic treatment may be inferred from a substantially lower number of BEs requiring VWF-based treatment. However, uncertainties remain due to a potential impact of concomitant haemostatic medication and an early discontinuation from the study after only 1 month of treatment.

Furthermore, it was noted that compared to the historical database, results of studies 071301 and SHP677-304 appear to indicate a substantial shift towards an increased incidence of major/severe bleeding complications (1% of treated spontaneous bleeds in the historical database vs. 11% in study 071301 and 55% in SHP677-304). However, upon a request for additional information, the MAH clarified that the apparent increase in severe BEs was attributed to a single patient, from which no general trend towards a higher frequency of more severe breakthrough bleeds can be deduced. Nevertheless, the reported case illustrates an apparently only incomplete bleeding protection under prophylactic treatment, which remains as an uncertainty.

Finally, remaining uncertainties relate to the actual severity of baseline bleeding phenotypes of study subjects. However, consensus criteria for the initiation of prophylactic treatment in VWD are lacking and the entry criteria for Study 071301 provide appropriate support for the assumption of severe disease phenotypes with a high probability of benefiting from prophylactic treatment.

3.4. Unfavourable effects

VEYVONDI represents a 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 neutralising alloantibodies. The Risk Management Plan of 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 remains an important potential risk.

As of the cut-off date of the interim report of study SHP677-304, no ADRs related to these key risks (identified or potential) were observed in the studies submitted with this application. Most TEAEs were mild to moderate in severity and were assessed by the investigator as not related to the study drug. Five subjects experienced 7 TESAEs; these were not fatal or life-threatening, and none of these was considered related to VEYVONDI by the investigator or the sponsor. The only TEAE which was considered possibly related to VEYVONDI was a single case of moderate headache which occurred in Study 071301 and led to discontinuation from the study on day 37 of treatment. Noteworthy, this case has already been

assessed in a previous variation procedure (EMEA/H/C/004454/II/0026, CHMP positive opinion on 12 January 2023) and led to the inclusion of headache as a very common ADR in section 4.8 of the VEYVONDI SmPC.

Overall, safety data obtained in the prophylaxis studies (up to 30 Jun 2022, i.e. the cut-off date of the interim report of study SHP677-304) are consistent with the known favourable safety profile of VEYVONDI in its already approved indications and do not raise concerns about risks specific to its long-term prophylactic use in adults with VWD.

3.5. Uncertainties and limitations about unfavourable effects

Uncertainties about the reported unfavourable effects arise from the non-controlled design of the prophylaxis studies and the relatively small sample size of only 23 unique subjects, which may have been too small to detect rare adverse events like e.g. thrombotic events in subjects with known risk factors for thrombosis. In addition, the safety database does not include pregnant or lactating women or patients with significant renal or liver disease, and the number of subjects aged 65 years and older was too low (n=3) to determine whether this age group responds differently compared to younger subjects. However, neither the population targeted by the requested EOI nor the maximum amount of vonicog alfa to be administered per infusion differs from its already approved indications. Furthermore, based on the currently available data, there is no evidence of risks specific to the use of VEYVONDI for long-term prophylactic treatment.

3.6. Effects Table

Table 34. Effects Table for Veyvondi for prophylactic treatment to prevent or reduce the frequency of bleeding episodes in adults with VWD (data cut-off: 30 Jun 2022).

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects						
Prevention /reduction in spontaneous BEs	1) Reduction in sABR was calculated by comparing on-study and historical sABR rates 2) the ratio (on study: historical) was estimated within each subject group using a generalized linear mixed-effects model with 95% Wald CI	1) % 2) ratio (95% CI)	1) Prior OD: 91.5%, Switch: 45% 2) Prior OD: 0.085 (0.021, 0.346), Switch: 0.550 (0.086, 3.523)	N/A	Supported by: Consistent results across subgroups (e.g. Type 3 Prior OD); IA of extension study; strong mechanistic rationale of prophylactic replacement of VWF in severe VWD. Uncertainties relate to: Small sample size; validity of historical control data; impact of few subjects with very high ABRs at baseline; defective eDiary device; increased frequency of severe bleeds under prophylaxis; clinical relevance of untreated bleeds	Section 5.4.1
Treatment success in prior OD subjects	≥25% reduction in on-study sABR compared	n (%) [95% CI]	12 (92.3) [64.0, 99.8]	N/A	See above	Section 5.4.1

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
	with historical sABR					
Treatment success in prior Switch subjects	on-study sABR no greater than historical sABR	n (%) [95% CI]	9 (90.0) [55.5, 99.7]	N/A	See above	Section 5.4.1
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. May not have been detected due to small sample size.	Section 5.5 and RMP part IV
Thromboembolic events	Clinical signs of thrombosis	n (%)	None	N/A	Important identified risk as per VEYVONDI RMP. May not have been detected due to small sample size.	Section 5.5 and RMP part IV
Inhibitor formation	Development of neutralizing antibodies to VWF	n (%)	None	N/A	Important potential risk as per VEYVONDI RMP. May not have been detected due to small sample size.	Section 5.5 and RMP part IV

Abbreviations: BE= Bleeding episode, CI= confidence interval, IA=interim analysis, n=number, N/A=not applicable, Prior OD= Subjects who were receiving on-demand treatment prior to study entry, RMP=Risk management plan, sABR= annualized bleeding rate for spontaneous (not related to trauma) bleeding episodes treated with VWF, Switch=Subjects who had been receiving prophylactic plasma-derived von Willebrand factor treatment prior to study entry, VWD=von Willebrand disease, VWF=von Willebrand factor

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Favourable effects indicate a clinically meaningful reduction in the rate of treated spontaneous BEs after initiation of prophylactic vonicog alfa therapy in adults with severe VWD which may reduce or prevent serious complications and sequelae (such as haemophilic-type arthropathy) associated with recurrent BEs.

Safety data submitted with this application were consistent with previous clinical studies of VEYVONDI in VWD and did not reveal unfavourable effects specific to the requested EOI. The only reported adverse event considered possibly related to the administration of VEYVONDI was a case of non-serious moderate headache which occurred in study 071301. Noteworthy this case has already been assessed in a previous variation procedure (EMEA/H/C/004454/II/0026), which led to the addition of headache into SmPC

section 4.8 (CHMP positive opinion on 12 January 2023). Although this event led to a discontinuation of treatment, it has not been considered to represent 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 long-term prophylactic treatment with vonicog alfa in adults with severe VWD are considered to outweigh the risks associated with such treatment.

3.7.3. Additional considerations on the benefit-risk balance

None.

3.8. Conclusions

The overall B/R of VEYVONDI in long-term prophylactic use in adults is positive.

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 change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include 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. As a consequence, sections 4.1, 4.2, 5.1 and 5.2of the SmPC are updated. In addition, changes to sections 4.4, 6.2 and 6.6 are made. The Package Leaflet is updated in accordance. Version 4.1 of the RMP has been accepted.

The variation leads to amendments to the Summary of Product Characteristics and Package Leaflet 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 and IIIB and to the Risk Management Plan are recommended.