13 November 2025
EMADOC-1700519818-2679383
Human Medicines Division

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Veyvondi

Vonicog alfa

Procedure no: EMA/PAM/0000291090

Note

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

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Status of this report and steps taken for the assessment			
Current step	**Description**	**Planned date**	**Actual Date**
☐	Submission	2 September 2025	29 July 2025
☐	Start date	15 September 2025	15 September 2025
☐	CHMP Rapporteur AR	20 October 2025	13 October 2025
☐	CHMP comments	3 November 2025	N/A
☐	Updated CHMP Rapporteur AR	6 November 2025	N/A
☒	CHMP outcome	13 November 2025	13 November 2025

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1. Introduction

On 29 July 2025 the MAH submitted a completed paediatric study for Veyvondi, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

As stated in the cover letter, study SHP677-304, "A phase 3b, prospective, open-label, uncontrolled, multicentre study on long-term safety and efficacy of rVWF in paediatric and adult subjects with severe von Willebrand disease (VWD)" is part of Veyvondi's clinical development program but not part of the PIP.

An interim analysis of SHP677-304 (with data cut-off date of 30 June 2022) was used to support an indication extension application for prophylactic treatment in adults with severe von Willebrand disease (procedure EMEA/H/C/004454/II/0030 with CHMP positive opinion on 12 October 2023).

An additional interim analysis (with data cut-off date of 26 January 2024) was used to support an indication extension application for the treatment of haemorrhage in children less than 18 years with von Willebrand disease. This application was submitted on 07 April 2025 (EMA/VR/0000264863).

Based on the final study data, no further changes are proposed to the product information of Veyvondi. Therefore, the current application is provided as a standalone post-authorization measure.

2.2. Information on the pharmaceutical formulation used in the study

Veyvondi (vonicog alfa) is a purified recombinant human von Willebrand factor (rVWF) in the drug class of blood coagulation factors, and the Anatomical Therapeutic Chemical System classification code is B02BD10. It is manufactured by recombinant DNA (rDNA) technology in the Chinese Hamster Ovary (CHO) cell line without the addition of any exogenous human-or animal-derived protein in the cell culture process, purification or final formulation. The only proteins present in the final container product, other than vonicog alfa, are trace quantities of murine IgG from the immunoaffinity purification process, host cell (CHO) protein, and rFurin.

Vonicog alfa is the first and the only rVWF authorized for marketing in the US, Canada, China, Japan (under the trade name VONVENDI), the EEA, the UK, Switzerland, and Australia (under the trade name Veyvondi). Currently, Veyvondi is approved in the EEA, UK, and Switzerland for the prevention and treatment of haemorrhage or surgical bleeding in adults (age 18 years and older) with VWD when DDAVP treatment alone is ineffective or contraindicated. Veyvondi should not be used in the treatment of haemophilia A.

Veyvondi is available in two strengths (650 IU and 1300 IU) and is provided as a powder and solvent for solution for intravenous injection

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for study:

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

2.3.2. Clinical study

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

Description

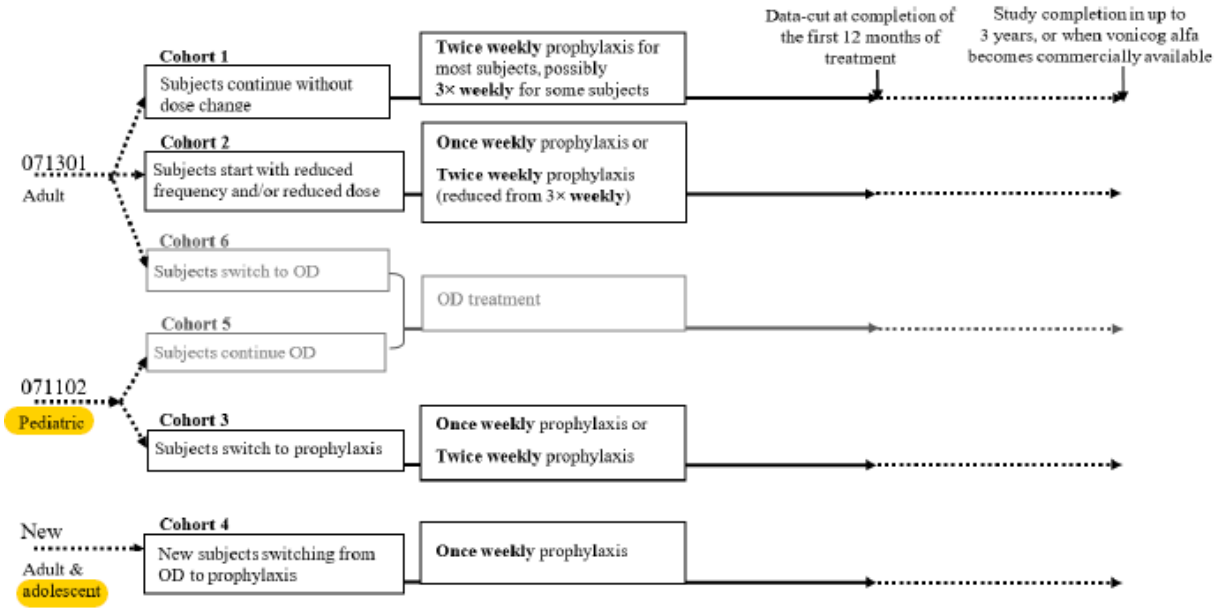
Study SHP677-304 was a phase 3b, prospective, open-label, uncontrolled, non-randomized, multicentre study that was designed i) to evaluate long-term safety and haemostatic efficacy of vonicog alfa prophylaxis in adult and adolescent (aged 12 to <18 years) subjects with severe VWD, and ii) to assess the safety and efficacy of vonicog alfa in on-demand (OD) treatment of bleeding episodes (BEs) and in perioperative management of surgical bleeding (if surgical treatment was required for a subject already participating in this study) in both adult and paediatric subjects with severe VWD.

Subjects who had completed the phase 3 parent studies, Study 071301 (adult prophylaxis study) or Study 071102 (paediatric OD and surgery study), and newly enrolled adult and adolescent subjects wishing to receive prophylaxis with vonicog alfa participated in this study.

The study included 4 prophylactic treatment cohorts and 2 OD treatment cohorts (Figure 1):

- Cohort 1: Adult subjects transitioning from Study 071301 who remained on the same prophylactic dose as in Study 071301.
- Cohort 2: Adult subjects transitioning from Study 071301 with no clinically significant BE for the past 6 months who started this continuation study at a lower dose/frequency compared to the dose received in Study 071301.
- Cohort 3: Adolescent subjects transitioning from Study 071102 who switched from receiving OD treatment to receiving once weekly or twice weekly prophylaxis in this continuation study.
- Cohort 4: Newly enrolled adult and adolescent subjects switching from OD treatment with VWF products who started once weekly prophylaxis with vonicog alfa in this continuation study.
- Cohort 5: Paediatric subjects of all ages from Study 071102 who continued receiving OD treatment in this continuation study.
- Cohort 6: Adult subjects from Study 071301 who switched back from prophylactic treatment in Study 071301 to OD treatment in this continuation study.

Figure 1: Study schematic diagram



In 2024, decisions were made to close the study before the planned sample size of the non-rollover Cohort 4 had been reached. Closure of non-US sites began in the week of 10 June 2024, and closure of the US sites began in the week of 09 September 2024. The sponsor closed the study because study objectives had been achieved, and all ongoing subjects had completed the required minimum 12-month treatment period (although not reaching the maximum 3 years of treatment).

Methods

Study participants

Inclusion criteria:

Subjects who have completed Study 071301 or Study 071102 (or subjects who have completed the surgery in Study 071102 and want to continue to receive OD treatment) and are willing to immediately transition into this study, must meet the following 2 criteria to be eligible for this study:

1. If female of childbearing potential, has a negative blood/urine pregnancy test at screening and agrees to employ highly effective birth control measures (including sterilization, implant, intra-uterine device (IUD), correct and consistent use of hormonal contraception, and abstinence) for the duration of the study.
2. Subject and/or legally authorized representative is willing and able to comply with the requirements of the protocol.

New subjects (Cohort 4) who meet the above 2 and ALL the following additional criteria are eligible for this study:

3. Subject has a documented diagnosis of severe VWD (baseline VWF:RCo <20 IU/dL) with a history of substitution therapy with VWF concentrate required to control bleeding:
    a. Type 1 (VWF:RCo <20 IU/dL) or,

b. Type 2A (as verified by multimer pattern), Type 2B (as diagnosed by genotype), Type 2M or,

c. Type 3 (VWF:Ag ≤3 IU/dL).

Diagnosis is confirmed by genetic testing and multimer analysis, documented in patient history or at screening.

4. Subject has been receiving OD therapy with VWF products for at least 12 months, and prophylactic treatment is recommended by the investigator.
5. Subject has ≥3 documented spontaneous bleeds (not including menorrhagia) requiring VWF treatment during the past 12 months.
6. Subject has available records that reliably evaluate type, frequency, and treatment of bleeding episodes for at least 12 months preceding enrolment; up to 24 months of retrospective data should be collected if available.
7. Subject is ≥12 years old at the time of screening and has a body mass index ≥15 but <40 kg/m^2.

Exclusion criteria

1. The subject has been diagnosed with Type 2N VWD, pseudo VWD, or another hereditary or acquired coagulation disorder other than VWD (e.g., qualitative and quantitative platelet disorders or elevated prothrombin time (PT)/international normalized ratio [INR] >1.4).
2. The subject has a history or presence of a VWF inhibitor at screening.
3. The subject has a history or presence of a FVIII inhibitor with a titre ≥0.4 Bethesda units (BU) (by Nijmegen modified Bethesda assay) or ≥0.6 BU (by Bethesda assay).
4. The subject has a known hypersensitivity to any of the components of the study drugs, such as mouse or hamster proteins.
5. The subject has a medical history of immunological disorders, excluding seasonal allergic rhinitis/conjunctivitis, mild asthma, food allergies, or animal allergies.
6. The subject has a medical history of a thromboembolic event.
7. The subject is human immunodeficiency virus (HIV) positive with an absolute Helper T cell (CD4) count <200/mm^3.
8. The subject has been diagnosed with significant liver disease per investigator's medical assessment of the subject's current condition or medical history or as evidenced by, but not limited to any of the following: serum alanine aminotransferase (ALT) greater than 5 times the upper limit of normal; hypoalbuminemia; portal vein hypertension (e.g., presence of otherwise unexplained splenomegaly, history of oesophageal varices) or liver cirrhosis classified as Child-Pugh class B or C.
9. The subject has been diagnosed with renal disease, with a serum creatinine (CR) level ≥2.5 mg/dL.
10. The subject has a platelet count <100,000/mL at screening (for subjects with type 2B VWD, platelet count(s) at screening will be evaluated taking into consideration historical trends in platelet counts and the Investigator's medical assessment of the patient's condition).

11. The subject has been treated with an immunomodulatory drug, excluding topical treatment (e.g., ointments, nasal sprays), within 30 days prior to signing the informed consent (or assent, if appropriate).
12. The subject is pregnant or lactating at the time of enrolment.
13. The subject has cervical or uterine conditions causing menorrhagia or metrorrhagia (including infection, dysplasia).
14. The subject has participated in another clinical study involving another investigational product (IP) or investigational device within 30 days prior to enrolment or is scheduled to participate in another clinical study involving an IP or investigational device during the course of this study.
15. The subject has a progressive fatal disease and/or life expectancy of less than 15 months.
16. For new OD subjects, the subject is scheduled for a surgical intervention.
17. The subject is identified by the investigator as being unable or unwilling to cooperate with study procedures.
18. The subject has a mental condition rendering him/her unable to understand the nature, scope and possible consequences of the study and/or evidence of an uncooperative attitude.
19. The subject is member of the study team or in a dependent relationship with one of the study team members which includes close relatives (i.e., children, partner/spouse, siblings and parents) as well as employees.

Treatments

Prophylactic Treatment

Adult subjects who transitioned from Study 071301 and agreed to continue prophylactic treatment were re-evaluated with respect to their prophylactic dose at the beginning of this study; if a subject had not experienced any BE over the last 6 months of their prophylactic treatment in Study 071301, the subject could be considered for a reduced dosage in this study (Cohort 2). Otherwise, subjects continued with the prophylactic treatment regimen from Study 071301 (Cohort 1), which was expected to be 50±10 IU/kg vonicog alfa twice weekly for most subjects.

Adolescent subjects (aged 12 to <18 years) who transitioned from the Study 071102 with at least 3 BEs (excluding menorrhagia) that required treatment with a VWF product over the past 12 months and were considered eligible by the investigator for switching to prophylaxis could go on prophylactic treatment with vonicog alfa (Cohort 3) at a dose of either 50±10 IU/kg once weekly or twice weekly, based on the investigator's assessment and recommendation.

Newly enrolled adult and adolescent (aged 12 to <18 years) subjects (Cohort 4), who (a) had available records that reliably evaluated the type, frequency, and treatment of BEs for at least 12 months before enrolment, (b) had at least 3 documented spontaneous BEs (excluding menorrhagia) that required VWF treatment over the past 12 months, and (c) had been receiving OD treatment with VWF products for at least 12 months, were initially assigned to a prophylactic regimen of 50±10 IU/kg vonicog alfa once weekly.

The starting dose for subjects in Cohorts 3 and 4 could be individualized within the range of 50±10 IU/kg and, in consultation with the sponsor, increased up to 80 IU/kg if considered necessary to assure effective prophylaxis, based on: (a) available historical PK data; (b) type and severity of BEs; and (c)

monitoring of appropriate clinical and laboratory measures. For all subjects on prophylactic treatment (Cohorts 1–4), dose and/or dose frequency could be increased based on BE dose escalation criteria.

For all cohorts, during the entire study observation period, any BEs requiring replacement therapy with VWF concentrate were to be treated with vonicog alfa with or without Advate. If surgery or dental procedures were needed, subjects were to receive vonicog alfa, with or without Advate, for the management of perioperative bleeding.

OD treatment of BEs:

Dosage and frequency were to be individualized based on the subject's weight, VWD type, severity of the BE, and monitoring of appropriate clinical and laboratory measures. In general, an initial dose of 40 to 60 IU/kg vonicog alfa was recommended. Depending on the subject's baseline FVIII level, vonicog alfa was to be given with or without 30 to 45 IU/kg Advate (vonicog alfa:Advate ratio of 1.3± 0.2:1). In cases of major BEs, a dose of up to 80 IU/kg vonicog alfa could be infused. If necessary, subsequent doses of 40 to 60 IU/kg could be administered every 8 to 24 hours with or without Advate (Advate use only if plasma FVIII levels fell below 30 IU/dL during the treatment period) to maintain VWF:RCo and FVIII levels for as long as deemed necessary by the investigator.

Management of Perioperative Bleeding

The dose and frequency of vonicog alfa administration were to be individualized based on the type of surgery, PK results, and VWF and FVIII levels. In general, the dose was to be 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. Advate could be administered following vonicog alfa infusion to raise FVIII:C levels to recommended levels.

Objectives and endpoints

Primary Objective and associated endpoint

Primary Objective	**Primary Endpoint**
To evaluate the efficacy of vonicog alfa prophylaxis based on the ABR of spontaneous (not related to trauma) BEs in adult and adolescent (aged 12 to <18 years) subjects during the first 12 months on study treatment.	**Efficacy of Prophylaxis:** • sABR during prophylaxis treatment with vonicog alfa based on the data collected during the first 12 months on study treatment.

Secondary Objectives and associated endpoints

Secondary Objectives	Secondary Endpoints
To evaluate the long-term safety of vonicog alfa in adult and pediatric subjects as assessed by AEs including thrombogenicity, hypersensitivity, and immunogenicity, as well as by vital signs and clinical laboratory parameters	**Safety:** • AEs/SAEs: incidence, severity, causality. • Occurrence of thromboembolic events. • Occurrence of hypersensitivity reactions. • Immunogenicity – Development of neutralizing antibodies (inhibitors) to VWF and FVIII. – Development of total binding antibodies to VWF and FVIII. – Development of binding antibodies to CHO proteins, mouse IgG and rFurin. • Clinically significant changes in vital signs and clinical laboratory parameters relative to baseline.
To evaluate the efficacy of vonicog alfa prophylaxis in adult and adolescent (aged 12 to <18 years) subjects while enrolled in the study To evaluate the efficacy of different dose regimens for prophylactic treatment in adult and adolescent (aged 12 to <18 years) subjects	**Efficacy of Prophylaxis:** • sABR under prophylactic treatment with vonicog alfa while enrolled in the study. • Categorized weekly number of infusions defined as 1, 2, or ≥3 during prophylactic treatment with vonicog alfa. • Categorized sABR defined as 0, 1 to 2, 3 to 5, or >5 BEs during vonicog alfa prophylaxis. • Time to first bleeding event under each prophylaxis regimen. • sABR by location of bleeding (for example, GI, epistaxis, joint bleeding, menorrhagia, oral, muscle and soft tissue) while on 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. • Transfusion free maintenance of hemoglobin and ferritin levels over time.
To assess the efficacy of vonicog alfa for OD treatment of BEs (spontaneous and traumatic) in adult and pediatric subjects	**Efficacy of the Treatment of BEs:** • Overall hemostatic efficacy rating at the resolution of bleed with respect to the treatment of BEs for the initial 12 months on study treatment. • Number of infusions of vonicog alfa and Advate utilized to treat BEs while enrolled in the study. • Weight-adjusted consumption of vonicog alfa and Advate per BE while enrolled in the study.

Exploratory objectives were to obtain additional data on the efficacy of perioperative bleeding management with vonicog alfa if surgery is required; to assess PK and PD of vonicog alfa and to monitor IR of vonicog alfa over time in adult and paediatric subjects; and to assess health related quality of life data, treatment satisfaction, and health resource utilization over time for subjects receiving vonicog alfa prophylaxis.

Sample size

The study planned to enrol up to 71 paediatric and adult subjects with severe VWD. Sample size was not based on a power calculation for a significance test. No formal statistical tests were planned. According to the clinical study report, the number of subjects was driven by practical considerations and the EMA Guideline on the Clinical Investigation of Human Plasma Derived von Willebrand Factor Products (CPMP/BPWG/220/02).

Statistical Methods

No formal statistical tests were performed. Efficacy analyses were based on the FAS unless stated otherwise. Safety analyses were performed using the SAF.

Analysis sets were defined as follows:

- ENR: The ENR consisted of all subjects who signed the informed consent (either from subject or from subject's legally acceptable representative) as obtained from the screening eCRF.
- SAF: The SAF consisted of all subjects who received any amount of vonicog alfa as obtained from the study drug administration eDiary, study drug administration details eCRF, or PK infusion eCRF.
- FAS: The FAS consisted of all subjects who satisfied all entry criteria and received any amount of study drug.
- PPAS: The PPAS consisted of all subjects included in the FAS who had no major or critical protocol violations that might have had an impact on the efficacy assessment of the study drug.
- PKAS: The PKAS consisted of all subjects in prophylaxis cohorts (1 to 4) who completed the required washout period, received at least one study drug infusion, and provided at least one quantifiable PK or PD post-dose measurement for PK and/or PD analysis. The subjects should not have been actively bleeding at the time of PK assessment.

Results

Recruitment / Participant flow / Numbers analysed

Study SHP677-304 enrolled a total of 40 subjects (19 subjects in the prophylactic treatment arm cohorts [Cohorts 1 to 4] and 21 subjects in the OD cohorts [Cohorts 5 to 6]).

In the prophylactic treatment arm, 2 subjects screened for Cohort 4 did not meet all eligibility criteria (hence, screen failure); the other 17 subjects (3 paediatric and 14 adult) received at least 1 dose of vonicog alfa and were included in the SAF, FAS, PPAS, and PKAS. Note that 1 of the 2 subjects who failed screening was subsequently rescreened and entered the study with a different subject ID, therefore, the subject was counted as 2 individuals in Cohort 4 in the ENR. Of the 17 subjects in the SAF, 15 (88.2%) completed the study, and 2 (11.8%) (both were adolescents in Cohort 4) discontinued the study. One subject discontinued on Study Day 460 due to physician's decision (new diagnosis of juvenile idiopathic arthritis), and 1 subject discontinued on Study Day 585 due to study termination by sponsor (early study closure).

In the OD cohorts (Cohorts 5 and 6), 3 subjects in Cohort 5 did not receive vonicog alfa because they did not need treatment for BEs or management of surgical bleeding. The other 18 subjects (14 paediatric and 4 adult) received at least 1 dose of vonicog alfa and were included in the SAF, FAS, and PPAS. Of the 18 subjects in the SAF, 16 (88.9%) completed the study, and 2 (11.1%) discontinued the study. One paediatric subject in Cohort 5 discontinued the study due to study termination by sponsor (early study closure), and 1 adult subject in Cohort 6 withdrew consent for personal reasons.

Baseline data

Most subjects were White and not Hispanic or Latino. The prophylactic cohorts included 3 adolescent subjects (a male with type 3 VWD in cohort 3 and a male with type 1 VWD and a female with type 3

VWD in cohort 4) and 14 adult subjects. The mean (SD) age overall was 37.0 (20.35) years. 10 subjects (58.8%) were male and 7 subjects (41.2%) were female.

The OD cohorts included 14 paediatric subjects (3 aged <6 years, 5 aged 6 to <12 years, and 6 aged 12 to <18 years) and 4 adult subjects. The mean (SD) age overall was 11.9 (6.76) years. Eight subjects (44.4%) were male and 10 subjects (55.6%) were female.

Most subjects had VWD type 3, including 12 subjects (70.6%) in the prophylactic cohorts and 10 subjects (55.6%) in the OD cohorts. No subjects had a presence of VWF inhibitor or FVIII inhibitor at screening

Pharmacokinetics and Pharmacodynamics

Subjects in Cohort 4 (i.e. newly enrolled adult and adolescent subjects switching from OD to prophylactic treatment) underwent a PK and PD assessment at the baseline visit using a dose of 50 (±5) IU/kg vonicog alfa. In addition, subjects in Cohorts 1 to 4 underwent a PK and PD assessment at the EOS visit using a scheduled prophylaxis dose. VWF activity was determined using VWF:RCo, VWF:CB, and the VWF:Ag assays. FVIII activity (FVIII:C) was measured using the 1-stage clotting assay to assess the PD of vonicog alfa. IR of vonicog alfa (Cohorts 1–4) was determined at each follow-up visit (until the 12-month visit) based on VWF:RCo activity assessed before and after study drug infusion.

In Cohort 4 subjects (N=5 with VWD types 1 [N=1], 2A [N=3], and 3 [N=1], aged 12 to 59 years) received a PK dose between 43.7 and 50.2 IU/kg. Using a NCA approach, initial PK assessments showed a VWF:RCo mean (SD) of 1446 (682.1) h*IU/dL for $AUC_{0\text{-}96h}$, 2049 (741.7) h*IU/dL for $AUC_{0\text{-}\infty}$, 90.16 (28.86) IU/dL for C_{max}, 1.886 (0.5949) (IU/dL)/(IU/kg) for IR at C_{max}, 0.02560 (0.009709) dL/h/kg for CL, 0.8125 (0.4191) dL/kg for V_{ss}, 33.25 (14.48) h for MRT, and 19.70 (9.466) h for $t_{1/2}$. No obvious differences in these PK parameters between adolescents and adults were observed (see table 1 below); similar trends were observed for VWF:Ag and VWF:CB.

Table 1: PK/PD parameters (Cohort 4 - initial PK/PD assessment)

Assessment Parameter	Subject 1	Subject 2	Subject 3	Subject 4	Subject 5	n	Mean (SD), (Min, Max)
Age group	Adult	Adult	Adult	Adolescent (12 to 18 years)	Adolescent (12 to 18 years)	-	-
VWD type	Type 2A	Type 2A	Type 2A	Type 1	Type 3	-	-
VWF:RCo							
Actual dose (IU/kg)	50.21	43.7	47	49.12	49.64	-	-
C_{max} (IU/dL)	136	101	75.8	71.4	66.6	5	90.16 (28.86), (66.6, 136)
IR at C_{max} ((IU/dL)/(IU/kg))	2.709	2.311	1.613	1.454	1.342	5	1.886 (0.5949), (1.34, 2.71)
t_{max} (h)	0.47	0.48	0.33	0.43	1.07	5	NA (NA), (0.33, 1.1)
AUC_{0-96h} (h*IU/dL)	1802	2432	965.1	1300	731.6	5	1446 (682.1), (732, 2430)
C_{max}/D ((IU/dL)/(IU/kg))	2.709	2.311	1.613	1.454	1.342	5	1.886 (0.5949), (1.34, 2.71)
AUC_{0-96h}/D ((h*IU/dL)/(IU/kg))	35.89	55.64	20.53	26.46	14.74	5	30.65 (16.01), (14.7, 55.6)
$AUC_{0-\infty}$ (h*IU/dL)	1853	2869	1189 [a]	1425	896.8 [a]	3	2049 (741.7), (1420, 2870)
$AUC_{0-\infty}$/D ((h*IU/dL)/(IU/kg))	36.91	65.65	25.29 [a]	29.00	18.07 [a]	3	43.86 (19.28), (29.0, 65.6)
CL (dL/h/kg)	0.02709	0.01523	0.03953 [a]	0.03448	0.05535 [a]	3	0.02560 (0.009709), (0.0152, 0.0345)
Vss (dL/kg)	0.4670	0.6918	0.9506 [a]	1.279	0.8601 [a]	3	0.8125 (0.4191), (0.467,1.28)
MRT (h)	17.24	45.42	24.05 [a]	37.08	15.54 [a]	3	33.25 (14.48), (17.2, 45.4)
$t_{1/2}$ (h)	12.26	30.92	15.31	28.88	11.11	5	19.70 (9.466), (11.1, 30.9)
FVIII:C							
Actual dose (IU/kg)	50.21	43.7	47	49.12	49.64	-	-
C_{max} (IU/dL)	41.0	58.0	39.0	56.0	65.0	5	51.80 (11.30), (39.0, 65.0)
t_{max} (h)	23.72	28.32	23.92	9.18	23.82	5	NA (NA), (9.18, 28.32)
AUC_{0-96h} (h*IU/dL)	2220	2987	2590	3538	2694	5	2806 (492.7), (2220, 3540)
C_{max}/D ((IU/dL)/(IU/kg))	0.8166	1.327	0.8298	1.140	1.309	5	1.085 (0.2496), (0.817, 1.33)
AUC_{0-96h}/D ((h*IU/dL)/(IU/kg))	44.22	68.35	55.11	72.03	54.27	5	58.79 (11.32), (44.2, 72.0)

Initial PD assessments (Cohort 4) revealed FVIII:C mean (SD) of 2806 (492.7) h*IU/dL for AUC_{0-96h} and 51.80 (11.30) IU/dL for C_{max}, with no notable differences between the age groups. Similar PK/PD parameters were observed at the EOS, although conducted in different subjects.

The IR values remained relatively constant over time across VWF measures of VWF:RCo (Cohorts 1 to 4) with mean values of 1.32 to 1.64, VWF:Ag with mean values of 1.43 to 1.72, VWF:CB with mean values of 2.15 to 2.73.

Median values for FVIII:C over 12 months of treatment (Cohorts 1 to 4) range between 15 to 34 IU/dL, with mixed minimum and maximum values across VWD types.

Assessor's comment:

Initial PK/PD assessments were only carried out in cohort 4 (newly enrolled subjects). Data are available for a total of 5 subjects (3 adults and 2 adolescents) with different types of VWD. Only one of the subjects had type 3 disease. Overall, the reported mean values are largely consistent with the known PK behaviour of Veyvondi (as e.g. reflected in SmPC section 5.2). However, results indicate a high degree of interindividual heterogeneity. The small sample size, which included only two adolescent subjects, generally hinders interpretation and precludes meaningful comparisons regarding potential age-related differences.

EOS data are only available for 2 subjects (1 subject from Cohort 1 and 1 subject from Cohort 4), which precludes a meaningful assessment of potential longitudinal changes in PK/PD behaviour.

IR and pre-dose FVIII activity levels over time were only analysed for the entire study population, without separate analyses of adolescents. However, given the small sample size of just 3 adolescent subjects, this issue will not be pursued further.

Noteworthy, the PK/PD data of one subject in cohort 4, i.e. the subject who experienced a notably high number of severe breakthrough bleeds during prophylaxis (see below), do not indicate conspicuous abnormalities.

Efficacy results

Efficacy of Prophylaxis

Bleeding data

ABR data, based on treated spontaneous BEs, by study period (first 12 months and the entire study period) are summarized in Table 2 below. The study treatment duration for the 17 subjects ranged from 422 to 1120 days. Across prophylactic cohorts, the mean (SD) sABR over the entire study was 2.060 (3.0469) (median: 0.620) for adolescent subjects and 1.137 (1.7865) (median: 0.505) for adult subjects.

Table 2: sABR by Age Group and Study Period (FAS)

Study period	Cohort 1	Cohort 2	Cohort 3	Cohort 4			Total	
Statistic	Adult ≥18 years (N=10)	Adult ≥18 years (N=1)	Pediatric 12 to <18 years (N=1)	Pediatric 12 to <18 years (N=2)	Adult ≥18 years (N=3)	Total (N=5)	Pediatric 12 to <18 years (N=3)	Adult ≥18 years (N=14)	Total (N=17)
First 12 months									
n	10	1	1	2	3	5	3	14	17
Mean (SD)	1.430 (2.3894)	1.040 (-)	0.000 (-)	4.020 (4.2709)	2.357 (1.2113)	3.022 (2.4746)	2.680 (3.8088)	1.601 (2.0873)	1.791 (2.3522)
95% CI	0,3.139	-, -	-, -	0, 42.393	0, 5.366	0, 6.095	0, 12.142	0.396, 2.806	0.582, 3.001
Median	0.000	1.040	0.000	4.020	2.990	2.990	1.000	1.000	1.000
Q1, Q3	0.000, 2.040	1.040, 1.040	0.000, 0.000	1.000, 7.040	0.960, 3.120	1.000, 3.120	0.000, 7.040	0.000, 2.840	0.000, 2.840
Min, Max	0.00, 7.47	1.04, 1.04	0.00, 0.00	1.00, 7.04	0.96, 3.12	0.96, 7.04	0.00, 7.04	0.00, 7.47	0.00, 7.47
Entire study									
n	10	1	1	2	3	5	3	14	17
Mean (SD)	1.122 (2.1084)	0.330 (-)	0.000 (-)	3.090 (3.4931)	1.457 (0.5119)	2.110 (1.9954)	2.060 (3.0469)	1.137 (1.7865)	1.300 (1.9711)
95% CI	0,2.630	-, -	-, -	0, 34.474	0.185, 2.728	0,4.588	0, 9.629	0.106, 2.169	0.287, 2.313
Median	0.170	0.330	0.000	3.090	1.360	1.360	0.620	0.505	0.620
Q1, Q3	0.000, 0.680	0.330, 0.330	0.000, 0.000	0.620, 5.560	1.000, 2.010	1.000, 2.010	0.000, 5.560	0.000, 1.360	0.000, 1.360
Min, Max	0.00, 6.52	0.33, 0.33	0.00, 0.00	0.62, 5.56	1.00, 2.01	0.62, 5.56	0.00, 5.56	0.00, 6.52	0.00, 6.52

Assessor's comment

Of note, the higher mean sABR in adolescents compared to adults is driven by the high sABR of one subject in Cohort 4, who suffered from an unusual high number of severe joint bleeds during prophylaxis (see also under OD treatment below). Listing 16.2.6.2.1 summarizes the bleeding data of the two adolescent subjects from Cohort 4:

				During Study			
		Historic		First 12 Months		Entire Study	
Cohort	Cause	Number of Treated Bleeds	Treated ABR	Number of Treated Bleeds	Treated ABR	Number of Treated Bleeds	Treated ABR
Cohort 4	Overall	3	3	11	11.07	11	8.73
	Spontaneous	3	3	7	7.04	7	5.56
	Injury/Trauma	0	0	4	4.02	4	3.18
	Surgery	0	0	0	0	0	0
	Menstrual Bleeding	0	0	0	0	0	0
	Other	0	0	0	0	0	0
Cohort 4	Overall	6	6	1	1	1	0.62
	Spontaneous	5	5	1	1	1	0.62
	Injury/Trauma	0	0	0	0	0	0
	Surgery	1	1	0	0	0	0
	Menstrual Bleeding	0	0	0	0	0	0
	Other	0	0	0	0	0	0

One Subject (male with type 1 VWD) showed an increase in sABR during the first 12 months of prophylactic treatment (historic sABR of 3 vs. on-treatment sABR of 7.04) and had an on-treatment sABR for the entire study period of 5.56. According to the CSR, the subject's prophylactic dosing frequency was escalated from the initial once weekly to twice weekly on Study Day 142 and to 3 times weekly on Study Day 301, then reduced to twice weekly on Study Day 363, and returned to once weekly on Study Day 407. The subject had a medical history of arthralgia (described as right knee pain). All BEs reported during the study (11 BEs, including 7 spontaneous BEs) were joint bleeds and were treated with vonicog alfa. The subject had 2 joint surgeries (arthroscopy with partial

meniscectomy medial [Study Day 259] and left knee arthroscopic partial lateral meniscectomy [Study Day 348]).

Importantly, on Study Day 363, this subject was newly diagnosed of juvenile idiopathic arthritis (Listing 16.2.7.1), which led to a premature discontinuation of study treatment on Study Day 422 based on physician decision. Thus, given this significant rheumatoid comorbidity, the apparently poor bleeding protection in this subject remains difficult to interpret, especially since arthritis-induced pain may have been mistaken for a symptom of bleeding.

Consumption data

Overall, 1 subject in Cohort 1 and all of the 7 subjects in Cohorts 2–4 started prophylactic treatment in this study with a once weekly dosing regimen. Eight subjects in Cohort 1 started with a twice weekly regimen, and 1 subject in Cohort 1 started with a 3 times weekly regimen.

During the entire study period, the mean (SD) total number of vonicog alfa infusions was 235.8 (78.52) infusions (range: 99-359 infusions), with a mean (SD) of 1.63 (0.447) infusions per week. Most subjects (76.5%) had an average of 1 to <2 vonicog alfa infusions per week. The mean (SD) average weight-adjusted dose of vonicog alfa per week was 83.77 (23.989) IU/kg per week. The mean (SD) average vonicog alfa dose per prophylactic infusion was 52.52 (10.794) IU/kg per infusion. Drug consumption in adolescent and adult subjects was generally similar. 6 subjects (35.3%) had at least 1 increase in dosing frequency, including all 3 adolescent subjects (100% in Cohort 3 and Cohort 4) and 3 adult subjects (21.4%, all in Cohort 4).

Assessor's comment

Notably, all of the three adolescent study subjects required dose escalations (compared to 21.4% of adults). However, this group includes an adolescent whose disease (and treatment) course was very likely affected by a concomitant, newly diagnosed juvenile idiopathic arthritis (see Assessor's comment above). For the remaining two subjects, details of dose escalations are summarized as follows:

The adolescent subject who transitioned from Study 071102 and switched from receiving OD treatment in Study 071102 to prophylactic treatment (Cohort 3) started an initial planned prophylactic regimen of 50 IU/kg vonicog alfa once weekly. Subject increased their dosing frequency to twice weekly on Study Day 874 due to increased BEs (BEs resulting from injuries) and maintained the twice weekly dosing frequency for the rest of the study (last prophylactic infusion: Study Day 1087).

Subject 5 in Cohort 4 started an initial planned prophylactic regimen of 50 IU/kg vonicog alfa once weekly and increased their dosing frequency to twice weekly on Study Day 29 (within 12 months) due to several left elbow bleedings. The dosing frequency maintained at twice weekly for the rest of the study (last prophylactic infusion: Study Day 582).

Efficacy of OD treatment:

Prophylactic Cohorts:

For the entire study period, 75 BEs in 13 subjects were treated with vonicog alfa (Table 3). Overall, most treated BEs were spontaneous BEs (53 BEs [70.7%]), followed by BEs resulting from injury (19 BEs [25.3%]). The most common bleeding locations (≥15% of BEs) were joint (21 BEs [28.0%]), menstrual/heavy menstrual (20 BEs [26.7%]), and mucosal (oral) (18 BEs [24.0%]). Most treated BEs were minor/mild or moderate in severity; 31 BEs (41.3%) were of severe/major severity.

In the 3 adolescent subjects, 21 BEs occurred during the study. The most common bleeding locations (≥15% of BEs) were joint (14 BEs [66.7%]), followed by other (4 BEs [19.0%]). 11 BEs (52.4%) were

severe/major in severity, all experienced by 1 single subject in Cohort 4; severity was missing for 5 BEs (23.8%). 16 of the 21 BEs (76.2%) were treated with vonicog alfa. The median time to first spontaneous bleed in adolescent subjects was 49.5 (95% CI: 11, NE) days for the once weekly regimen (n=2 subjects with event). 1 adolescent subject did not have a spontaneous bleed during the study and was censored.

For the entire study period, the overall haemostatic efficacy rating was "Excellent" for 68 BEs (90.7%), "Good" for 6 BEs (8.0%), and "Fair" for 1 BE (1.3%).

Most BEs used 1 to 2 vonicog alfa infusions for OD treatment during the entire study period; the mean (SD) number of vonicog alfa infusions to treat a BE was 1.6 (1.25) infusions (median: 1.0 infusion). The mean (SD) total vonicog alfa infused per bleed was 78.348 (65.2734) IU/kg, and the mean (SD) average vonicog alfa dose infused per infusion per bleed was 48.824 (8.8653) IU/kg. 29 of the 75 treated BEs in 6 subjects were also treated with Advate, with a mean (SD) number of Advate infusions of 1.3 (0.45) infusions (median: 1.0 infusion). The mean (SD) total Advate infused per bleed was 32.261 (14.4959) IU/kg, and the mean (SD) average Advate dose infused per infusion per bleed was 26.048 (8.4124) IU/kg.

Table 3: Treated BEs by Prophylactic Cohorts and Age Group (FAS)

Study period	Cohort 1	Cohort 2	Cohort 3	Cohort 4			Total		
Characteristic	Adult ≥18 years (N=10)	Adult ≥18 years (N=1)	Pediatric 12 to <18 years (N=1)	Pediatric 12 to <18 years (N=2)	Adult ≥18 years (N=3)	Total (N=5)	Pediatric 12 to <18 years (N=3)	Adult ≥18 years (N=14)	Total (N=17)
Entire study									
Total number of subjects with BEs	6	1	1	2	3	5	3	10	13
Total number of BEs	38	1	4	12	20	32	16	59	75
Severity [n (%)]									
Minor/mild	8 (21.1)	0	4 (100)	0	6 (30.0)	6 (18.8)	4 (25.0)	14 (23.7)	18 (24.0)
Moderate	13 (34.2)	1 (100)	0	1 (8.3)	11 (55.0)	12 (37.5)	1 (6.3)	25 (42.4)	26 (34.7)
Severe/major	17 (44.7)	0	0	11 (91.7)	3 (15.0)	14 (43.8)	11 (68.8)	20 (33.9)	31 (41.3)
Number of vonicog alfa infusions to treat BE [a]									
n	38	1	4	12	20	32	16	59	75
Mean (SD)	1.2 (0.41)	1.0 (-)	1.8 (0.96)	2.3 (1.61)	1.9 (1.83)	2.1 (1.74)	2.2 (1.47)	1.4 (1.15)	1.6 (1.25)
95% CI	1.1, 1.3	-, -	0.2, 3.3	1.3, 3.4	1.0, 2.8	1.4, 2.7	1.4, 3.0	1.1, 1.7	1.3, 1.9
Median	1.0	1.0	1.5	2.0	1.0	1.0	2.0	1.0	1.0
Q1, Q3	1.0, 1.0	1.0, 1.0	1.0, 2.5	1.0, 3.5	1.0, 2.0	1.0, 2.0	1.0, 3.0	1.0, 2.0	1.0, 2.0
Min, Max	1, 2	1, 1	1, 3	1, 6	1, 8	1, 8	1, 6	1, 8	1, 8
Min, Max	18.18, 107.14	48.92, 48.92	46.37, 96.03	57.54, 293.94	37.47, 402.43	37.47 402.43	46.37, 293.94	18.18, 402.43	18.18, 402.43
Efficacy rating [n (%)]									
Excellent	36 (94.7)	1 (100)	3 (75.0)	10 (83.3)	18 (90.0)	28 (87.5)	13 (81.3)	55 (93.2)	68 (90.7)
Good	2 (5.3)	0	1 (25.0)	1 (8.3)	2 (10.0)	3 (9.4)	2 (12.5)	4 (6.8)	6 (8.0)
Fair	0	0	0	1 (8.3)	0	1 (3.1)	1 (6.3)	0	1 (1.3)
None	0	0	0	0	0	0	0	0	0

Assessor's comment

On average, consumption data indicate higher consumption in adolescents compared to adults. However, the group of adolescents was small (N=3 adolescents vs N=14 adults). In addition, the group of adolescents was characterized by a much higher rate of treated severe/major BEs (68.8% of all BEs in adolescents vs. 33.9% of all BEs in adults) and joint bleeds (81.3% in adolescents vs. 13.6% in adults). Consequently, the reported consumption data do not allow for meaningful comparisons of the two age groups. Of note, all of the severe/major BEs in adolescents (N=11, all joint bleeds affecting multiple joints) occurred in a subject in cohort 4, whose disease course was complicated by a newly diagnosed, concurrent juvenile idiopathic arthritis and for whom interpretation of efficacy outcomes remains difficult. In the group of adolescents, BEs requiring >3 infusions of vonicog alfa were limited to 2 severe BEs affecting the aforementioned subject with concurrent juvenile idiopathic arthritis and 1 moderate BE in a female with an efficacy rating of "Excellent".

OD Cohorts:

For the entire study period, 202 BEs in 18 subjects were treated with vonicog alfa (Table 4). Overall, most treated BEs were spontaneous BEs and BEs resulting from injury (93 BEs [46.0%], each). The most common bleeding locations (≥15% of BEs) were joint (52 BEs [25.7%]), other (49 BEs [24.3%]), and mucosal (nasal) (43 BEs [21.3%]). Most treated BEs were minor/mild or moderate in severity (105 BEs [52.0%] and 82 BEs [40.6%], respectively).

For the entire study period, the overall haemostatic efficacy rating was "Excellent" for 194 BEs (96.0%) and "Good" for 4 BEs (2.0%); the efficacy rating was missing for 4 BEs (2.0%). Most BEs used 1 vonicog alfa infusion for OD treatment; the mean (SD) number of vonicog alfa infusions to treat a BE was 1.1 (0.62) infusions (median: 1.0 infusion). The mean (SD) total vonicog alfa infused per bleed was 57.090 (32.1079) IU/kg, and the mean (SD) average vonicog alfa dose infused per infusion per bleed was 50.990 (7.9198) IU/kg. 48 of the 202 treated BEs in 8 subjects were also treated with Advate, with a mean (SD) number of Advate infusions being 1.1 (0.24) infusions (median: 1.0 infusion). The mean (SD) total Advate infused per bleed was 39.049 (10.8726) IU/kg, and the mean (SD) average Advate dose infused per infusion per bleed was 36.641 (3.9677) IU/kg.

Across both cohorts, there were no major differences between age groups.

Table 4: Treated BEs by OD Cohorts and Age Group (FAS)

Study period	Cohort 5					Cohort 6	Total	
Characteristic	Pediatric <6 years (N=3)	Pediatric 6 to <12 years (N=5)	Pediatric 12 to <18 years (N=6)	Adult ≥18 years (N=2)	Total (N=16)	Adult ≥18 years (N=2)	Adult ≥18 years (N=4)	Total (N=18)
Entire study								
Total number of subjects with BEs	3	5	6	2	16	2	4	18
Total number of BEs	35	48	55	29	167	35	64	202
Severity [n (%)]								
Minor/mild	25 (71.4)	24 (50.0)	37 (67.3)	5 (17.2)	91 (54.5)	14 (40.0)	19 (29.7)	105 (52.0)
Moderate	10 (28.6)	22 (45.8)	17 (30.9)	19 (65.5)	68 (40.7)	14 (40.0)	33 (51.6)	82 (40.6)
Severe/major	0	2 (4.2)	0	4 (13.8)	6 (3.6)	7 (20.0)	11 (17.2)	13 (6.4)
Missing	0	0	1 (1.8)	1 (3.4)	2 (1.2)	0	1 (1.6)	2 (1.0)
Number of vonicog alfa infusions to treat BE								
n	35	48	55	29	167	35	64	202
Mean (SD)	1.0 (0.17)	1.2 (1.02)	1.0 (0.19)	1.2 (0.77)	1.1 (0.65)	1.2 (0.45)	1.2 (0.61)	1.1 (0.62)
95% CI [b]	1.0, 1.1	0.9, 1.5	1.0, 1.1	0.9, 1.5	1.0, 1.2	1.0, 1.3	1.0, 1.3	1.0, 1.2
Median	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Q1, Q3	1.0, 1.0	1.0, 1.0	1.0, 1.0	1.0, 1.0	1.0, 1.0	1.0, 1.0	1.0, 1.0	1.0, 1.0
Min, Max	1, 2	1, 8	1, 2	1, 5	1, 8	1, 3	1, 5	1, 8
Efficacy rating [n (%)]								
Excellent	34 (97.1)	46 (95.8)	55 (100)	28 (96.6)	163 (97.6)	31 (88.6)	59 (92.2)	194 (96.0)
Good	1 (2.9)	2 (4.2)	0	0	3 (1.8)	1 (2.9)	1 (1.6)	4 (2.0)
Fair	0	0	0	0	0	0	0	0
None	0	0	0	0	0	0	0	0
Missing	0	0	0	1 (3.4)	1 (0.6)	3 (8.6)	4 (6.3)	4 (2.0)

Assessor's comment

Of note, the OD dataset includes only 2 treated major/severe BEs in paediatric subjects. One of these, a muscle bleed affecting a female, was the only BE in paediatrics which required >3 vonicog alfa infusions (8 infusions with a total dose of 391.67 IU/kg plus 2 infusions of Advate with a total dose of 70.2 IU/kg). Efficacy ratings for both of the major/severe BEs in paediatrics were "Excellent" (Listing 16.2.6.1).

Safety results

Extent of exposure

Prophylactic cohorts: A total of 4211 doses (14636229 IU) of vonicog alfa were administered to 17 subjects in the prophylactic cohorts. The mean (SD) cumulative weight-adjusted vonicog alfa dose per subject was 12626.869 (3889.5846) IU/kg. A total of 42 Advate infusions (94863 IU) were administered to 6 subjects (2 subjects in Cohort 1, 1 subject in Cohort 3, and 3 subjects in Cohort 4), primarily to treat breakthrough BEs (36 infusions). The mean (SD) cumulative weight-adjusted Advate dose per subject was 181.482 (239.4663) IU/kg.

OD cohorts: A total of 202 BEs were treated with vonicog alfa in the OD cohorts; 48 BEs were also treated with Advate. The mean (SD) total dose of vonicog alfa administered per bleed was 57.090 (32.1079) IU/kg and the mean (SD) total dose of Advate administered per bleed was 39.049 (10.8726) IU/kg.

Subjects who had surgery: For perioperative management of bleeding, vonicog alfa was used for 14 surgeries (6 in paediatric subjects); Advate was used for 2 surgeries (1 in paediatric subject) in addition to vonicog alfa. For surgeries in paediatric subjects, the mean (SD) total perioperative dose of vonicog alfa administered was 166.930 (59.2875) IU/kg, and the mean (SD) total perioperative dose of Advate administered was 37.040 (-) IU/kg (n=1 surgery).

Adverse events

No deaths were reported in the study. No TEAEs in the prophylactic or OD cohorts led to withdrawal of vonicog alfa or Advate, or to discontinuation from the study. No confirmed neutralizing antibodies against VWF or FVIII were reported, and no thromboembolic events or severe hypersensitivity reactions were reported during the study.

Prophylactic cohorts: Overall, 14 subjects (82.4%) who received vonicog alfa experienced 155 TEAEs, and 5 subjects (83.3%) who received Advate experienced 33 Advate TEAEs. Most TEAEs were mild in severity (120 of 155 TEAEs). Four subjects (23.5%) experienced 7 severe TEAEs; 3 adult subjects experienced 5 severe TEAEs and 1 adolescent subject experienced 2 severe TEAEs. Four subjects (23.5%) experienced 7 SAEs; all were adults.

None of the TEAEs were considered related to vonicog alfa or to Advate by the investigator. One adult and 1 adolescent subject experienced 1 and 2 TEAEs, respectively, that were considered related to the study procedure by the investigator.

OD cohorts: Overall, 17 subjects (94.4%) who received vonicog alfa experienced 129 TEAEs, and 7 subjects (77.8%) who received Advate experienced 44 Advate TEAEs. Most TEAEs were mild in severity (92 of 129 TEAEs). By age group, in subjects aged <6 years, 3 subjects (100%) experienced 4 TEAEs; 2 subjects (66.7%) experienced 4 SAEs (fall, medical device site extravasation, Coronavirus infection, hypotension). There were no severe TEAEs. 1 subject (33.3%) experienced 2 temporally associated TEAEs. In subject aged 6 to <12 years, 5 subjects (100.0%) experienced 26 TEAEs; 1 subject (20.0%) experienced 1 SAE (spinal compression fracture). There were no severe TEAEs. 1 subject (20.0%) experienced 3 temporally associated TEAEs. In subjects aged 12 to <18 years, 6 subjects (100.0%) experienced 33 TEAEs. There were no SAEs. 1 subject (16.7%) experienced 1 severe TEAE. 1 subject (16.7%) experienced 1 temporally associated TEAE. In adult subjects, 3 subjects (75.0%) experienced 28 TEAEs; 1 subject (25.0%) experienced 1 SAE. 2 subjects (50.0%) experienced 2 severe TEAEs. 2 subjects (50.0%) experienced 2 temporally associated TEAEs.

None of the TEAEs were considered related to vonicog alfa, to Advate, or to the study procedure by the investigator.

Immunogenicity

Subjects were tested for the development of binding and neutralizing antibodies to VWF and FVIII as well as the presence of binding antibodies against the trace amount of proteins that could be found in the vonicog alfa drug product, including CHO protein, murine IgG, and rFurin.

No confirmed neutralizing antibodies against VWF or FVIII were reported during the study and no subject was tested positive for binding antibodies to VWF or to murine IgG, CHO protein, and/or rFurin. However, 1 paediatric subject in Cohort 5 tested positive for binding IgG antibody to FVIII prior to the first study drug treatment in this study at Month 18, then after treatment at Month 24, Month 33, and EOS visits. The binding IgG antibody to FVIII did not have a notable impact on the efficacy and safety responses in this subject. A haemostatic efficacy rating of "Excellent" was achieved in both of the BEs (moderate severity) that the subject experienced, each treated with a single infusion of vonicog alfa without Advate.

Assessor's comment

One paediatric roll-over subject was repeatedly tested positive for binding IgG to FVIII. Of note, the subject was already tested positive prior to the first study treatment. Thus, the aetiology of these FVIII-binding antibodies remains unclear. Antibody titres of these positive tests were in the low range (2x 1:80, 1x 1:160) and additional tests for neutralising FVIII antibodies remained negative (Listing 16.2.8.5). In addition, the positive test results at months 18, 24, 33 and EOS alternate with negative tests up to month 18 as well as at months 21, 27 and 30. As pointed out by the MAH, the FVIII binding antibody did not have any notable impact on efficacy and safety responses. The subject did not experience any severe AE, serious AE, AE leading to discontinuation of treatment with vonicog alfa, thromboembolic event, allergic reaction, or severe hypersensitivity reaction during the study.

Thus, in summary, the sporadic positive tests for binding IgG to FVIII reported in SHP677-304 do not raise concerns regarding the immunogenicity of vonicog alfa.

2.3.3. Discussion on clinical aspects

In accordance with Article 46 of regulation (EC) No 1901/2006, the MAH submitted the final report of study SHP677-304 together with an updated Critical Expert Overview.

Study SHP677-304 was a phase 3b, prospective, open-label, uncontrolled, non-randomized, multicentre study that was designed i) to evaluate long-term safety and haemostatic efficacy of vonicog alfa prophylaxis in adult and adolescent (aged 12 to <18 years) subjects with severe VWD, and ii) to assess the safety and efficacy of vonicog alfa in on-demand (OD) treatment of bleeding episodes (BEs) in both adult and paediatric subjects with severe VWD.

The study included a total of 4 prophylaxis and 2 OD cohorts and was open to subjects who had completed either Study 071301 (adult prophylaxis study) or Study 071102 (paediatric OD and surgery study). In addition, new adult and adolescent subjects wishing to receive prophylaxis with vonicog alfa could be enrolled.

An interim analysis of study SHP677-304 (with data cut-off date of 30 June 2022) was used to support an indication extension application for prophylactic treatment in adults with severe von Willebrand disease (procedure EMEA/H/C/004454/II/0030 with CHMP positive opinion on 12 October 2023). More recently, an additional interim analysis (with data cut-off date of 26 January 2024) was submitted to EMA to support an indication extension application for the treatment of haemorrhage in children less than 18 years. The latter submission is under review in procedure EMA/VR/0000264863.

The prophylaxis cohorts included 3 adolescent subjects (a male with type 3 VWD, a male with type 1 VWD and a female with type 3 VWD) and 14 adults. The OD cohorts included a total of 14 paediatric subjects (3 aged <6 years, 5 aged 6 to <12 years, and 6 aged 12 to <18 years) and 4 adults.

In essence, final results of this long-term extension study provide additional support for the efficacy and safety of Veyvondi in its currently approved indication (i.e. prevention and treatment of haemorrhage in adults). Results obtained in paediatric subjects in the OD cohorts are considered consistent with the interim report submitted in procedure EMA/VR/0000264863 (currently under review). Paediatric data in the prophylaxis cohorts are limited to three adolescents (a male with type 3 VWD, a male with type 1 VWD and a female with type 3 VWD) and are therefore not considered sufficient to draw any final/meaningful conclusions regarding the efficacy and safety of Veyvondi in patients under 18 years of age. Furthermore, interpretation of the data obtained in adolescents is complicated by a case of newly diagnosed, concurrent idiopathic juvenile arthritis, which not only led to premature discontinuation of study treatment, but is also likely to have significantly impacted the efficacy outcomes reported for this subject.

Safety data obtained in study SHP677-304 are considered consistent with previous clinical studies of vonicog alfa and do not raise concerns regarding potential age-related differences. Neither types nor frequencies of reported TEAEs are considered remarkable. No TEAEs led to withdrawal of study treatment or to discontinuation from the study. No deaths, no confirmed neutralizing antibodies against VWF or FVIII, and no thromboembolic events or severe hypersensitivity reactions were reported. None of the reported TEAEs were considered related to vonicog alfa or to Advate by the investigator. The newly reported data do not indicate any clinically relevant differences with regard to the safety profile of Veyvondi in children, adolescents and adults. However, the small sample size of the different age groups does not allow for drawing definitive conclusions. In summary, the safety data submitted as part of this article 46 procedure are considered consistent with previous clinical studies of vonicog alfa and do not indicate adverse events specific to the paediatric population.

3. Rapporteur's overall conclusion and recommendation

In summary, the final data of study SHP677-304 do not change the favourable benefit risk profile of Veyvondi in its approved indication. The submitted data do not warrant any update of its Product information and no regulatory actions are required.

☒ **Fulfilled:**

No regulatory action required.

4. Request for supplementary information

None

MAH responses to Request for supplementary information

Not applicable