21 May 2026
EMADOC-1700519818-2957373
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/0000334579

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[1]	**Description**	**Planned date**	**Actual Date**
☐	CHMP Rapporteur AR	28 April 2026	28 April 2026
☐	CHMP comments	11 May 2026	06 May 2026
☐	Updated CHMP Rapporteur AR	13 May 2026	N/A
☒	CHMP outcome	21 May 2026	21 May 2026

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1. Introduction

On 27 February 2026, 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

The MAH stated that study TAK-577-4001 "General drug use-results survey for Vonvendi intravenous" is a stand-alone study.

The MAH stated that study TAK-577-4001 "General drug use-results survey for Vonvendi intravenous" is not part of the PIP or the clinical development program of VEYVONDI.

No changes are proposed to the product information of VEYVONDI based on the results of the study.

2.2. Information on the pharmaceutical formulation used in the study

VEYVONDI (vonicog alfa) is a purified rVWF, in the drug class of blood coagulation factors, and the Anatomical Therapeutic Chemical System classification code is B02BD10.

Vonicog alfa is a purified recombinant human von Willebrand factor (rVWF). 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 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).

In the EEA, UK, and Switzerland, vonicog alfa is indicated for the prevention and treatment of haemorrhage or surgical bleeding in adults (aged 18 years and older) with VWD, when desmopressin treatment alone is ineffective or contraindicated. VEYVONDI should not be used in the treatment of haemophilia A. In the EEA, vonicog alfa was approved on 18 December 2025 for the treatment of haemorrhage in children (aged less than 18 years) with VWD, when desmopressin (DDAVP) treatment alone is ineffective or contraindicated.

As of 09 February 2026, Vonvendi is approved in Japan, for use in adults to control bleeding tendency in patients diagnosed with VWD aged 18 years and older. The indication includes on-demand treatment and control of BEs, perioperative management of bleeding, and prophylactic treatment for suppression of bleeding tendency.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

- TAK-577-4001: General drug use-results survey for Vonvendi intravenous (All-Case Survey)

2.3.2. Clinical study

TAK-577-4001: General drug use-results survey for Vonvendi intravenous (All-Case Survey)

Description

Study TAK-577-4001 was a non-interventional post-marketing all-case surveillance study designed to investigate the safety and efficacy of Vonvendi IV under the actual use status in daily medical practice in Japan.

The study was designed to capture data from all patients who received Vonvendi at Japanese medical institutions, including haematology and other relevant departments, with an observation period of 1 year from the initiation of Vonvendi treatment.

Survey period: 17 August 2020 to 31 March 2025

Date of survey completion (date of final analysis completion): 02 September 2025

Methods

Study participants

The study was an all-case survey including all patients who received Vonvendi at Japanese medical institutions.

Treatments

Participants came from medical institutions that administer Vonvendi. The dose, normally 40 to 80 IU/kg, was adjusted as needed based on the clinical condition and referring to the Japan Package Insert.

Objective

To investigate the safety and efficacy of Vonvendi under the actual use status in daily medical practice.

Outcomes/endpoints

Analysis items related to safety were:

- Occurrence status of Adverse Events
- Factors that may affect safety (gender, age, concomitant use of FVIII products, etc.).

Analysis items related to efficacy were:

- Haemostatic efficacy, including the number of infusions until achievement of haemostasis at the time of bleeding and in the perioperative period.

Sample size

It was planned to enrol 75 patients, based on the estimated market share of approximately 15% for Vonvendi 2 years after product launch and the number of patients with VWD in Japan.

Randomisation and blinding (masking)

Not applicable.

Statistical Methods

Statistical analyses were descriptive only; no inferential statistical hypothesis testing procedures were applied.

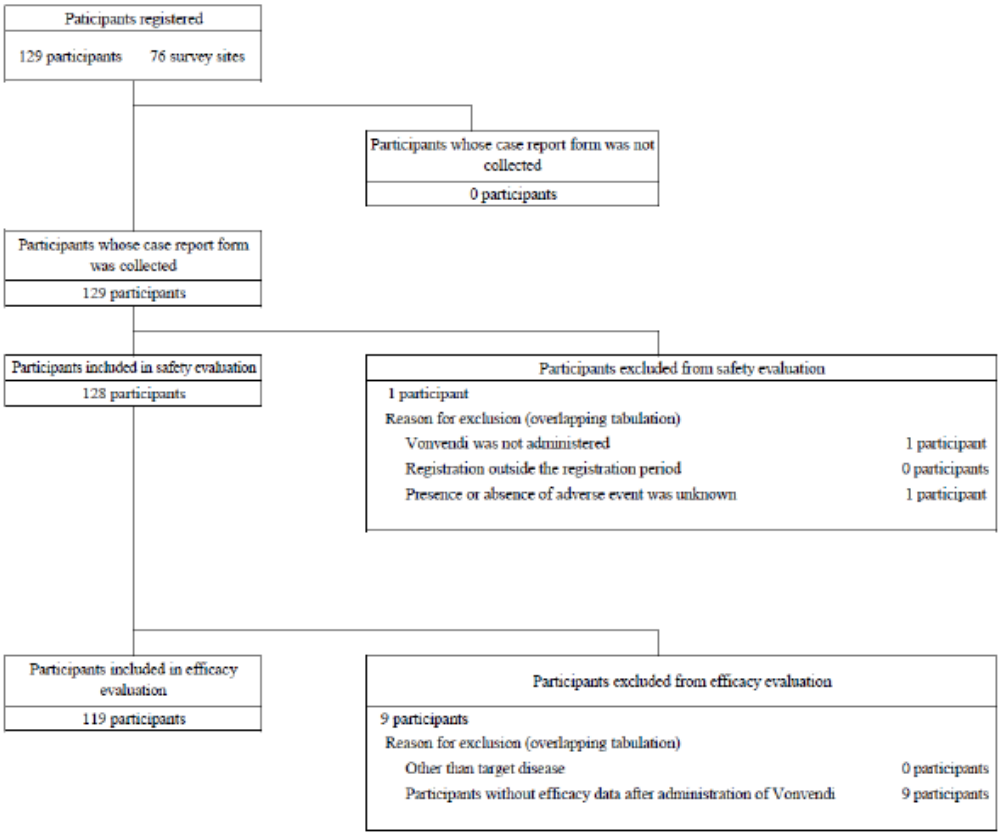
Results

Recruitment / Participant flow / Numbers analysed

Participant disposition is summarized in Figure 1 below. 129 participants were registered from 76 survey sites. The mean number of participants registered per survey site was 1.7, the minimum number of participants registered was 1, and the maximum number of participants registered was 13.

Of the participants whose case report form was collected, 128 participants were included in the safety evaluation, excluding 1 participant who did not receive Vonvendi and in whom the presence/absence of adverse events was unknown. Of the participants included in the safety evaluation, 119 participants were included in the efficacy evaluation, excluding 9 participants with no efficacy data available after administration of Vonvendi.

Figure 1: Disposition of Participants



Of the 128 participants who received at least 1 Vonvendi dose, 11 (8.6%) participants discontinued treatment. Excluding "Other", the reasons for discontinuing treatment administration were insufficient efficacy (3 participants, 27.3% of those who discontinued), occurrence of AEs (2 participants, 18.2%), and participant stopped visiting the hospital due to hospital transfer, etc (2 participants, 18.2%).

Baseline data

Overall, the mean (SD) age of participants for whom age was reported was 44.3 (19.79) years, and the median age was 42.0 years (range: 2, 86 years). A total of 79 (61.7%) participants were adults aged 18 to 64 years, 22 (17.2%) participants were adults aged ≥65 years, and 6 (4.7%) participants were children aged ≤17 years. Forty (31.3%) participants were male, and 88 (68.8%) participants were female. Among the 6 participants aged ≤17 years, 3 (50.0%) were male and 3 (50.0%) were female. In the population for whom race was reported, most participants were Japanese (127 participants, 99.2%).

Of the 113 participants with congenital VWD, the most common disease types were type 1 and type 2A, reported in 38 (33.6%) and 33 (29.2%) participants, respectively. Among the 6 participants aged ≤17 years reporting disease type, the most common type was type 2A, reported in 3 (50.0%) participants, followed by type 1 and type 2B, reported in 1 (16.7%) each.

Of the 79 participants out of 128 in the safety evaluation with available data, the mean (SD) number of BEs in the year prior to first Vonvendi dose was 3.8 (12.92), with a median of 0.0 (range: 0, 100).

Efficacy results

Overall, 50 of the 128 participants who received at least one dose of Vonvendi (39.1%) received Vonvendi for haemostatic treatment and management at the time of bleeding, 49 (38.3%) participants for perioperative haemostatic management, and 49 (38.3%) participants for regular administration to suppress bleeding tendency (other than at the time of bleeding or in the perioperative period). Paediatric study participants received Vonvendi either for haemostatic treatment and management at the time of bleeding or for the perioperative management of bleeding.

Haemostatic Treatment and Management at the Time of Bleeding

Vonvendi was used for the treatment and management at the time of bleeding of 163 bleeding events in 50 participants. Most bleeding events were mild or moderate in severity, and the cause of most events was spontaneous.

Treatment duration varied according to bleeding severity, with mean (SD) 4.3 (26.32) days for mild events, 6.2 (7.94) days for severe events, and 8.9 (17.27) days for moderate events. Overall, most BEs were resolved with 1 infusion (104 BEs, 63.8%), 2 infusions (18 BEs, 11.0%), or 3 infusions (20 BEs, 12.3%), while a smaller proportion required more infusions (4 infusions [6 BEs, 3.7%] and 5 infusions [15 BEs, 9.2%]). Concomitant use of coagulation FVIII products was limited and the majority of bleeding events were managed without FVIII supplementation ("Absent" in 140 [85.9%] events and "Present" in 23 [14.1%] events).

Haemostatic efficacy for treated BEs was mostly rated as "remarkably effective" or "effective", with ratings of "remarkably effective" in 50.3% of BEs and "effective" in 28.8% (Table 1 below).

Table 1: : Haemostatic efficacy ratings for treated BEs

Age Group (years)	N (%)	Number of Treated Nonsurgical BEs	Hemostatic Efficacy Rating n (%)			
			Remarkably effective	Effective	Slightly effective	Ineffective
Overall	50 (42.0)	163	82 (50.3)	47 (28.8)	31 (19.0)	3 (1.8)
≤17 [a]	4 (66.7)	17	14 (82.4)	3 (17.6)	0	0

Treated BEs for paediatric participants are summarized in Table 2 below. A total of 17 BEs were treated with Vonvendi in 4 paediatric participants aged 2 to 14 years with types 1, 2A, and 2B VWD. The treated BEs were traumatic and spontaneous in cause and predominantly moderate in severity.

Bleeding sites included muscle bleeds (gluteal and thigh), epistaxis, and endometrial bleeding. One participant experienced recurrent endometrial BEs. Across participants, Vonvendi was administered at maximum doses of approximately 41.94 to 59.26 IU/kg and average doses of approximately 38.72 to 53.70 IU/kg. The number of EDs per participant ranged from 2 to 30, reflecting variability in bleeding frequency and treatment requirements.

Most BEs were managed with 1 or 2 Vonvendi infusions per episode; however, additional infusions were administered when clinically indicated, such as in the participants with a BE in the muscles. Concomitant FVIII infusions were not required for any of the BEs. Haemostatic efficacy in paediatric

participants was consistently favourable, with treatment rated as either "remarkably effective" (82.4%) or "effective" (17.6%) (Table 1 above).

Table 2: Summary of paediatric participants with treated BEs

Participant	Participant [redacted]	Participant [redacted]	Participant [redacted]	Participant [redacted]
Age (years)	[redacted]	[redacted]	[redacted]	[redacted]
Sex	Female	Male	Female	Male
VWD type	2A	2B	2A	1
Site of bleeding	Left gluteal muscle bleeding	Left thigh muscle bleeding	1)-7) Endometrium (menorrhagia) 8) Endometrium (abnormal genital bleeding) 9)-13) Endometrium (menorrhagia)	1) Nose 2) Nose
Severity of bleeding	Moderate	Moderate	1)-7) Moderate 8) Mild 9)-13) Moderate	1) Moderate 2) Moderate
Cause of bleeding	Traumatic bleeding	Traumatic bleeding	1)-13) Spontaneous bleeding	1) Spontaneous bleeding 2) Traumatic bleeding
Maximum Vonvendi dose (IU/kg)	55.32	41.94	49.15	59.26
Average Vonvendi dose (IU/kg)	38.72	41.94	49.15	53.70
Total EDs per participant	5	30	17	2
Number of Vonvendi infusions per bleed	5	30	1) 3 2) 2 3) 1 4) 2 5)-13) 1	1) 1 2) 1
FVIII infusions	None	None	1)-13) None	1) and 2) None

Efficacy of Perioperative Management of Bleeding

In the overall efficacy evaluation, perioperative management with Vonvendi was assessed for 67 surgeries in 49 participants, including both minor (about 60%) and major (about 40%) surgical procedures.

Intraoperative bleeding was generally low, particularly for minor surgeries. The median amount of intraoperative bleeding for each surgery was 5.0 mL (range: 0, 1348 mL). By type of surgery, the median amount was 82.0 mL (range: 0, 1348 mL) for major surgery, and the median amount was 0.0 mL (range: 0, 88 mL) for minor surgery. Blood transfusions were done in 4 major surgeries (15.4%) and 0 minor surgeries.

Vonvendi was most commonly administered preoperatively, with limited intraoperative dosing and additional postoperative dosing administered when clinically indicated. The perioperative treatment duration was short, with a median duration of 2 days (range: 1, 16 days). Concomitant use of coagulation FVIII products was infrequent and primarily limited to the preoperative period, with minimal use postoperatively and no use during surgery. Overall haemostatic efficacy was favourable for all surgical procedures, with efficacy rated as either "remarkably effective" (65.7%) or "effective" (29.9%).

Perioperative management with Vonvendi was assessed in 3 paediatric participants undergoing 4 elective minor surgical procedures (summarized in Table 3 below). All surgical procedures were classified as minor and included gingivectomy with pulp treatment for dental caries, laparoscopic appendectomy following conservative management of appendicitis, and tooth extractions for dental abnormalities. All procedures were elective.

Vonvendi was administered preoperatively to all participants and postoperatively to 1 participant. No infusions were administered during surgery, and FVIII was not administered. Maximum and average Vonvendi doses were identical for each participant and ranged from 25.49 to 49.15 IU/kg, consistent with dosing recommendations for perioperative use. The total number of EDs per participant ranged from 1 to 4 days.

Haemostatic efficacy was favourable for all surgical procedures, with efficacy rated as either "remarkably effective" (50.0%) or "effective" (50.0%).

Table 3: Summary of perioperative management of bleeding in paediatric participant

Participant		Participant [redacted]	Participant [redacted]	Participant [redacted]
Age (years)		[redacted]	[redacted]	[redacted]
Sex		Male	Female	Female
VWD type		Unknown	2A	2A
Scheduled surgery or not		Elective surgery	Elective surgery	Elective surgery
Surgical procedures		Gingivectomy and pulp treatment: Caries of upper first molar	Laparoscopic appendectomy: Appendicitis (after conservative treatment)	Tooth extraction (2 surgeries: Dental abnormality)
Type of surgery		Minor surgery	Minor surgery	Minor surgery
Status of Vonvendi administration		Preoperative administration	Preoperative and postoperative administration	Preoperative administration
Maximum Vonvendi dose (IU/kg)		36.11	49.15	25.49
Average Vonvendi dose (IU/kg)		36.11	49.15	25.49
Total EDs per participant		1	4	2
Number of Vonvendi infusions per surgery	Before 12 to 24 h	1	1	1) 1 2) 1
	Before 1 h	None	1	1) and 2) None
	During Surgery	None	None	1) and 2) None
	After Surgery	None	3	1) and 2) None
FVIII infusions		None	None	1) and 2) None

Safety results

In the 128 participants included in the safety evaluation, the incidence of adverse events was 17.97% (23/128 participants), and no adverse events occurred in 2 or more participants. The incidence of serious adverse events was 7.81% (10/128 participants).

The incidence of adverse drug reactions was 3.13% (4/128 participants). These were events of plasma cell myeloma, palpitations, rash, chest discomfort, and blood pressure increased in 1 participant each. The only serious drug reaction reported was an event of worsening of multiple myeloma in a participant with pre-existing disease who died approximately 8 months after the day of the last dose of Vonvendi. This was a female with congenital type 1 VWD and multiple comorbidities. In 2023, the participant experienced a mild, spontaneous tongue BE. Initial treatment with vonicog alfa did not result in immediate haemostasis; however, bleeding was subsequently controlled following additional administrations. Prior to a scheduled tongue tumour resection in 2023, perioperative prophylaxis with vonicog alfa in combination with rurioctocog alfa pegol was administered. The surgical procedure was completed with minimal blood loss, and no blood transfusion was required. Postoperatively, the participant developed a local infection, which resolved following treatment with cefazolin sodium. The

participant died in 2024 due to progression of underlying plasma cell myeloma. The fatal outcome was considered related to treatment with vonicog alfa by the investigator. However, a company causality assessment determined that the fatal outcome was not related to treatment with vonicog alfa, as no evidence was identified to suggest an association between vonicog alfa and the development or progression of plasma cell myeloma in this case.

All other adverse drug reactions were nonserious and resolved. No specific participant characteristics or treatment-related factors were associated with an increased incidence of adverse drug reactions. Limited concomitant use of coagulation FVIII products did not appear to affect the safety profile of Vonvendi.

AEs corresponding to safety specifications in the Risk Management Plan

Rash occurred in 0.78% (1/128 participants) as an event corresponding to shock/anaphylaxis. This event was judged as "Related" and occurred approximately 4 months after the start of administration of Vonvendi for the purpose of regular replacement therapy. The event was non-serious, and the measure taken for Vonvendi was "No change" and Vonvendi was not discontinued. An antiallergic drug was administered, and the outcome of the event was "Recovered/Resolved".

Deep vein thrombosis occurred as an adverse event corresponding to the thromboembolic event in 0.78% (1/128 participants). This event was assessed by the survey doctor as non-serious, but was handled as serious because it is an event included in the Important Medical Events List. The participant received Vonvendi for 7 days from the day before major surgery (bilateral hip replacement for hip osteoarthritis) and developed deep vein thrombosis 1 week after the last day of postoperative administration. The outcome was "Recovering/Resolving", and the survey doctor judged the causal relationship with Vonvendi as "It is considered to be a complication of surgery and is therefore not related with Vonvendi".

No adverse events corresponding to inhibitor development occurred.

AEs in paediatric participants

Paediatric participants recorded a total of 54 EDs for OD treatment and 7 EDs for perioperative management. No AEs were reported.

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 TAK-577-4001 together with an updated Critical Expert Overview.

Study TAK-577-4001 was a non-interventional post-marketing all-case surveillance study designed to investigate the safety and efficacy of Vonvendi (trade name of vonicog alfa in Japan) under the actual use status in daily medical practice in Japan. The study was designed to capture data from all patients who received vonicog alfa at Japanese medical institutions, had an observation period of 1 year from the initiation of treatment and was completed on 02 September 2025.

The study included a total of 128 participants who received at least one dose of vonicog alfa for on-demand treatment of bleeding episodes (39.1%), perioperative haemostatic management (38.3%) or prophylactic treatment (38.3%).

Six (4.7%) of the participants were children <17 years of age (3 male and 3 female participants) with a minimum age of 2 years. Among these, the most common type of VWD was type 2A (n=3), followed by type 1 and type 2B, reported in one child (16.7%) each. Paediatric study participants received

vonicog alfa either for the on-demand treatment of bleeding episodes (n=17 mostly moderate BEs in 4 participants with a total of 54 EDs) or perioperative haemostatic management (n=4 elective minor surgical procedures in 3 participants with a total of 7 EDs).

In essence, results of the submitted surveillance study provide support for the effectiveness and safety of vonicog alfa under conditions of routine clinical use in daily medical practice. In the subgroup of children aged ≤17 years, vonicog alfa demonstrated effective on-demand treatment of bleeds (rated as "remarkably effective" in 82.4% of treated BEs) and perioperative management of haemorrhage without any reports of ineffective haemostatic efficacy. However, the paediatric subgroup of the study was small (n = 6) and did not include children with type 3 VWD. Furthermore, the paediatric dataset did not include any treatments for major bleeding events or surgical procedures.

The safety data obtained in study TAK-577-4001 are considered to be consistent with previous studies of vonicog alfa and do not raise concerns regarding potential age-related differences. Overall, the incidence of adverse drug reactions was low and there were no reports of severe hypersensitivity, anaphylaxis, or inhibitor development. The only reported thromboembolic event was an event of deep vein thrombosis, which was reasonably explained by the impact of major surgery for bilateral hip replacement, and was therefore not considered to be related to the administration of vonicog alfa.

In the paediatric subgroup of the study, no adverse events have been reported.

Therefore, overall, it is agreed with the MAH that the newly submitted data do not change the currently established favourable benefit-risk profile of vonicog alfa in the treatment of children with VWD and do not warrant any changes to the currently approved EU product information of VEYVONDI.

3. Rapporteur's overall conclusion and recommendation

In summary, results of the post-marketing all-case surveillance study TAK-577-4001 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