19 September 2024
EMA/534073/2024
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: EMEA/H/C/004454/P46/004

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**
☐	Start of procedure	01.04.2024	01.04.2024
☐	CHMP Rapporteur Assessment Report	06.05.2024	30.04.2024
☐	CHMP members comments	21.05.2024	n/a
☐	Updated CHMP Rapporteur Assessment Report	23.05.2024	n/a
☐	CHMP adoption of conclusions:	30.05.2024	30.05.2024
☐	Submission	20.08.2024	12.08.2024
☐	Re-start	21.08.2024	21.08.2024
☐	CHMP Rapporteur Assessment Report	04.09.2024	04.09.2024
☐	CHMP members comments	09.09.2024	n/a
☐	Updated CHMP Rapporteur Assessment Report	12.09.2024	n/a
☒	CHMP adoption of conclusions:	19.09.2024	19.09.2024

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1. Introduction

On 11 March 2024, 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-577-4007 is a stand-alone study. The study is not part of the agreed Paediatric Investigation Plan (EMEA-001164-PIP01-l l-M07).

2.2. Information on the pharmaceutical formulation used in the study

Veyvondi (vonicog alfa) is currently authorised in EU for the prevention and treatment of haemorrhage or surgical bleeding in adults (age 18 years and older) with von Willebrand disease (VWD), when desmopressin (DDA VP) treatment alone is ineffective or contraindicated. Veyvondi should not be used in the treatment of haemophilia A. The registered tradename in the US is Vonvendi.

Assessor's comment

The provided expert overview does not include the requested information on the pharmaceutical formulation used in the study.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

- Study TAK-577-4007, "Evaluation of Real-World Treatment Patterns and Outcomes in Patients with Von Willebrand Disease Treated Prophylactically with Vonvendi across Treatment Centers in the US".

The purpose of this study was to describe the real-world clinical characteristics, treatment pattems, outcomes, and health resource use (HRU) of VWD patients treated prophylactically with Vonvendi in the United States using a center-based chart review.

The MAH did not propose an amendment of the Product Information of Veyvondi.

2.3.2. Clinical study

Clinical study number and title

TAK-577-4007: Evaluation of Real-World Treatment Patterns and Outcomes in Patients with Von Willebrand Disease Treated Prophylactically with Vonvendi across Treatment Centers in the US

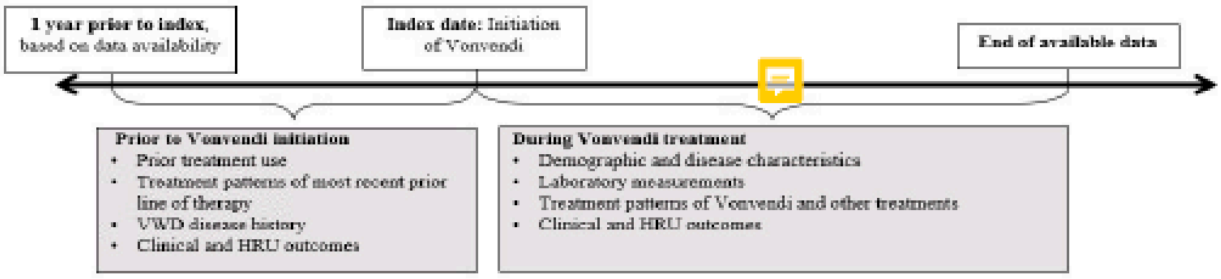
Description

This study used a retrospective chart review study design to characterize the real-world characteristics of VWD patients treated prophylactically with Vonvendi in the US, describe prophylactic use of Vonvendi, and when available, treatment patterns prior to Vonvendi prophylaxis initiation in this patient population.

US healthcare centers that manage patients with VWD receiving prophylactic treatment with Vonvendi were identified for inclusion in the study. Participating centers selected all adolescent and adult patients with VWD receiving prophylactic Vonvendi treatment. Following patient selection, an electronic case report fonn (eCRF) was used to abstract data from eligible patients participating in the study. Patient data were collected both prior to (up to 1 year prior) and following the initiation of Vonvendi for prophylactic treatment for up to 18 months. Prior to Vonvendi initiation (up to I year prior), the use of relevant treatments, detailed infonnation on the most recent prior Iine of therapy for VWD, clinical outcomes, and HRU were captured. During Vonvendi treatment, demographic and disease characteristics, treatment pattems of Vonvendi and other treatments, laboratory measurements, clinical outcomes, and HRU were captured (Figure 1).

Extracted data were pooled across centers. Data were summarized both pre- and post-Vonvendi initiation.

Figure 1. Study Design Scheme



Methods

Study participants

A total of 11 sites contributed data to this study. Among these were general hospitals and clinics, in addition to specialized institutions. The number of patients per site was dependent on the number of available patients with VWD treated prophylactically at each site.

Inclusion criteria

- Age ≥ 12 years at Vonvendi initiation with a confirmed diagnosis of congenital VWD

- Patients age < 12 years at Vonvendi initiation were included if they received Vonvendi prophylaxis for at least 6 months after the age of 12

- Received Vonvendi for the prophylactic trcatment of VWD for at least 6 months, either as:
  - Continuous prophylactic treatment (prima,y population o.f interest)
  - Intennittent prophylactic treatment for heavy menstrual bleeding (secondmy population)
- Had medical records available prior to Vonvendi initiation (index date)
  - Only patients who had ≥6 months of medical records prior to Vonvendi initiation were included in analyses of outcomes of interest
- Had medical records available for ≥6 months after index date except in the case of death, and up to 18 months

Exclusion criteria

- On-study clinical trial participants, data from patients while in any VWD clinical trial
- Acquired VWD/S

Treatments

Receiving Vonvendi for the prophylactic treated of VWD (either continuously or intermittently) for ≥6 months.

Objective(s)

To describe the real-world clinical characteristics, treatment patterns, and outcomes of VWD patients treated prophylactically with Vonvendi in the United States using a center-based chart review.

Outcomes/endpoints

Patient demographic, clinical, and disease characteristics were assessed during the baseline period. Rates of bleeds, healthcare resource utilization (HRU), laboratory values, and treatment patterns were the main outcomes of interest, and were assessed during the baseline and Vonvendi periods. All variables were summarized separately during the baseline and Vonvendi periods, and stratified by continuous versus intermittent Vonvendi prophylaxis treatment.

Sample size

A total of 30 patients were included in the study.

Randomisation and blinding (masking)

N/A

Statistical Methods

The study was descriptive in nature and thus the sample size was determined based on expected feasible patient counts and was not based on statistical considerations.

Extracted data were pooled across the centers. All baseline characteristics and outcomes were summarized descriptively in the baseline and Vonvendi periods separately for each treatment cohort.

Means, standard deviations (SDs), medians, interquartile ranges (IQRs), and ranges were calculated for continuous variables; counts and percentages were calculated for categorical variables. Differences in outcomes at the patient level were compared during the baseline and Vonvendi periods separately for each treatment cohort. Continuous variables were compared using Wilcoxon signed-rank tests; categorical variables were compared using McNemar's test.

Results

Number analysed

A total of 30 patients with VWD were treated with Vonvendi prophylaxis and included in the study. Among these, 23 (76.7%} patients received continuous prophylactic treatment with Vonvendi (i.e., 'continuous' group). The remaining 7 (23.3%) patients received intermittent treatment with Vonvendi due to heavy menstrual bleeding. (i.e., 'intermittent' group)

Baseline data

Mean ± SD age at Vonvendi prophylaxis initiation was 42.0 ± 21.4 years and 27.7 ± 11.6 years among the patients in the continuous and intermittent prophylaxis treatment groups, respectively. Fifty-two percent of the continuous prophylaxis group and 100.0% of the intermittent prophylaxis group was female. The majority of patients where white (continuous: 56.5%; intermittent: 85. 7%).

Among the 23 patients treated with continuous Vonvendi prophylaxis, age at first VWD diagnosis was 0-5 years (17.4%), 6-10 years (21.7%), l l-18 years (8.7%), and >18 years old (26.1 %); 6 (26.1 %) had an unknown age at VWD diagnosis. The most common type of VWD was Type 2 (43.5%), followed by Type 3 (39.1%) and Type 1 (17.4%). Among those with Type 2 VWD, patients had Type 2A (60.0%) and Type 2B (40.0%). Eight (34.8%) patients in the continuous treatment group were diagnosed via genetic testing. The most common multimer profiles among patients treated with continuous Vonvendi prophylaxis were loss of HMW multimers (30.4%), absence of multimers (26.1 %), and unknown (26. l %).

Among the 7 patients treated with intermittent Vonvendi prophylaxis, age at first VWD diagnosis was 0-5 years (42.9%), 6-10 years (14.3%), 11-18 years (14.3%), and >18 years old (28.6%). An equal amount patients had VWD Type 1 (42.9%) and VWD Type 2 (42.9%), while 14.3% had VWD Type 3. Among the 3 patients with Type 2, 2 (66.7%) had Type 2B. Three (42.9%) were diagnosed with VWD via genetic testing. Four (57.1 %) patients had a normal distribution of multimers. The remaining 3 patients had absence of multimers, loss of HMW multimers, and unknown, respectively. All 7 patients had a history of heavy menstrual bleeding, and none had a history of fibroids, endometriosis, or endometrial hyperplasia or any neoplasia.

Assessor`s comment

There were 5 subjects < 18 years of age among the 23 patients with continuous Vonvendi prophylaxis and 2 subjects < 18 years of age among the 7 patients treated with intermittent Vonvendi prophylaxis. These findings do not comply with the indication of Vonvendi in the US which refers to "age 18 and older" for the use. In addition, the group of continuous Vonvendi prophylaxis also includes two patients who were 10 years old at the time of initiation of Vonvendi prophylaxis. These baseline data do also not comply with the inclusion criteria of the study.

A separate analysis of the subjects < 18 years of age has not been provided.

Efficacy results

Among patients treated with continuous Vonvendi prophylaxis, the majority of patients were female, White, and had Type 2 VWD. Most patients received a prophylaxis treatment with plasma derived VWF (pdVWF) prior to switching to Vonvendi and had ongoing treatment with Vonvendi at the time data abstraction.

The mean initial weekly dose of Vonvendi prophylaxis was 132.2 IU/kg. Over the course of treatment with Vonvendi prophylaxis, there was an average numerical decrease of 14.2 IU/kg in the total weekly dose.

Among patients with available data, the mean overall annualized bleed rate was 3.2 bleeds per year during baseline and 1.5 bleeds per year during the Vonvendi pcriod. In addition, there was a trend towards lower annualized bleed rates and HRU in the Vonvendi period relative to the baseline period, though results had varying degrees of statistical significance. Statistically significant reductions in the mean annualized overall and major bleed rates of 1 .6 and 0.9 bleeds, respectively, were observed. In general, HRU dccreased in the Vonvendi period relative to the baseline period. Notably, there were significantly fewer overall and bleed related inpatient visits (0.7 and 0.6 fewer visits) in the Vonvendi period compared to baseline.

Additionally, there were on average 0.5 fewer surgeries in the Vonvendi period relative to the baseline period ($p<0.05$). Reductions in outpatient and ER visits were observed, though these reductions were not statistically significant. Relative to the period immediately prior to Vonvendi initiation, patients experienced an average decrease in select laboratory values following Vonvendi initiation.

Safety results

N/A

2.3.3. Discussion on clinical aspects

This retrospective chart review study descriptively assessed the real-world clinical characteristics, treatment and outcome pattern among patients with VWD in the US who were treated with Vonvendi prophylaxis on a continuous regimen or intermittent regimen (only for patients with heavy menstrual bleeding). The evaluated number of patients was quite low. But, the findings could support future studies to fully understand the impact of Vonvendi prophylaxis on patients with VWD. Seven subjects < 18 years of age have been included in this study but have not been analysed separately.

3. CHMP Rapporteur's overall conclusion and recommendation

☒ Not fulfilled:

Based on the data submitted, the MAH should provide responses to the identified questions as part of this procedure. (see section "Request for supplementary information")

4. Request for supplementary information

Based on the data submitted, the MAH should address the following questions as part of this procedure:

1. The provided expert overview does not include the requested information on the pharmaceutical formulation used in the study. The MAH should address.
2. There were 5 subjects < 18 years of age among the 23 patients with continuous Vonvendi prophylaxis and 2 subjects < 18 years of age among the 7 patients treated with intermittent Vonvendi prophylaxis. These findings do not comply with the indication of Vonvendi in the US which refers to "age 18 and older" for the use. In addition, the group of continuous Vonvendi prophylaxis also includes two patients who were 10 years old at the time of initiation of Vonvendi prophylaxis. These baseline data do also not comply with the inclusion criteria of the study. The applicant should comment.
3. The presentation of retrospective outcome data regarding prophylactic treatment in VWD obtained in study TAK-577-4007 covers the entire study population. To enable an assessment of prophylactic treatment in the paediatric subset, the MAH should provide a separate analysis of clinical characteristics, health resource use and study outcomes collected in participants <18 years of age.

The timetable is a 30 day response timetable without clock stop.

5. MAH responses to Request for supplementary information

Question 1

The provided expert overview does not include the requested information on the pharmaceutical formulation used in the study. The MAH should address.

MAH's responses

The pharmaceutical formulation used in Study TAK-577-4007 is powder for solution for injection 650 and 1300 IU, which corresponds to the approved formulation in both the United States (US) and European Union. The short Critical Expert Overview has been updated with the information on the pharmaceutical formulation.

Assessment of the MAH's responses

The MAH provided the requested information on the pharmaceutical formulation and updated the short Critical Expert Overview accordingly.

Conclusion: *Point resolved.*

Question 2

There were 5 subjects < 18 years of age among the 23 patients with continuous Vonvendi prophylaxis and 2 subjects < 18 years of age among the 7 patients treated with intermittent Vonvendi prophylaxis. These findings do not comply with the indication of Vonvendi in the US which refers to "age 18 and older" for the use. In addition, the group of continuous Vonvendi prophylaxis also includes two patients who were 10 years old at the time of initiation of Vonvendi prophylaxis. These baseline data do also not comply with the inclusion criteria of the study. The applicant should comment.

MAH's responses

TAK-577-4007 was a real-world study that included both on-label and off-label von Willebrand disease (VWD) patients. The primary objectives of this study were:

1. To describe demographic and clinical characteristics of patients with VWD treated prophylactically with Vonvendi

2. To describe Vonvendi use in VWD patients treated prophylactically and describe treatment patterns prior to initiation of Vonvendi prophylaxis

3. To assess clinical outcomes and health resource use (HRU) of patients with VWD treated prophylactically with Vonvendi before, during, and after (when available) Vonvendi treatment.

As stated in both the protocol and the clinical study report (CSR): "Patients aged <12 years at Vonvendi initiation were included if they received Vonvendi prophylaxis for at least 6 months after the age of 12. The sponsor decided to include those 2 patients considering the duration of treatment for these 2 patients.

Assessment of the MAH's responses

Since the study intended to collect real-world data, subjects < 18 years of age were also included. The MAH explained that the inclusion of the patients aged <12 years was covered by the study protocol due to fulfilment of the precondition "prophylaxis for at least 6 months after the age of 12"

Conclusion: *Point resolved.*

Question 3

The presentation of retrospective outcome data regarding prophylactic treatment in VWD obtained in study TAK-577-4007 covers the entire study population. To enable an assessment of prophylactic treatment in the paediatric subset, the MAH should provide a separate analysis of clinical characteristics, health resource use and study outcomes collected in participants <18 years of age.

MAH's responses

As requested, the Applicant provided a separate analysis of clinical characteristics, HRU, and study outcomes collected in patients <18 years of age.

Baseline Demographics and Clinical Characteristics of Patients <18 Years of Age

Overall, baseline characteristics were similar across the continuous (n=5) and intermittent (n=2) Vonvendi prophylaxis groups in patients <18 years of age.

Mean (standard deviation [SD]) age at Vonvendi prophylaxis initiation was 12.6 (3.0) years and 15.0 (1.4) years among the patients in the continuous and intermittent prophylaxis treatment groups, respectively. Female patients represented 40.0% and 100.0% of patients in the continuous prophylaxis group and the intermittent prophylaxis group, respectively. White patients represented 40.0% and 100.0% of patients in the continuous prophylaxis group and intermittent prophylaxis group, respectively.

Among the 5 patients treated with continuous Vonvendi prophylaxis, age at first VWD diagnosis was 6-10 years (80.0% of patients) and 11-18 years (20.0%). The reported types of VWD were type 2 and type 3 (both 40.0%), followed by type 1 (20.0%). Among patients with type 2 VWD, 50.0% patients had type 2A and 50.0% had type 2B VWD.

Two patients were treated with intermittent Vonvendi prophylaxis. At first VWD diagnosis, 1 patient was 0-5 years and the other patient was 6-10 years. One patient had type 1 VWD and the other patient had type 2B VWD.

Data on laboratory values at the time of initial diagnosis proved difficult to collect and was therefore not reported for all patients in either the continuous or intermittent Vonvendi prophylaxis group.

Relevant comorbid conditions were only reported in the 2 patients with intermittent Vonvendi prophylaxis group: both patients reported heavy menstrual bleeding diagnosed prior to Vonvendi initiation.

Treatment Characteristics of Patients <18 Years of Age Receiving Continuous Vonvendi Prophylaxis

The total weekly initial dose (IU/kg) was 148.2 ± 26.1 (mean±SD) and the total weekly most recent dose (IU/kg) was 145.0 ± 39.8.

Mean (SD) duration of continuous prophylaxis treatment with Vonvendi was 3.8 (1.8) years. None of the 5 patients experienced treatment gaps between infusions of Vonvendi. The most common reasons for initiating continuous Vonvendi treatment were to improve bleed control (60.0%), caregiver's preference (20.0%), and access to treatment (20.0%). Three (60.0%) patients were receiving ongoing continuous Vonvendi treatment at electronic case report form (eCRF) completion. Improvement in signs/symptoms was the reason provided by the only patient who discontinued continuous Vonvendi treatment; this patient then initiated subsequent prophylaxis.

Treatment Characteristics of Patients <18 Years of Age Receiving Intermittent Vonvendi Prophylaxis

The initial mean dose (IU/kg) was 39.4 ± 9.3 and the recent mean dose (IU/kg) was 60.0 received during menses.

Mean (SD) duration of intermittent prophylaxis treatment with Vonvendi was 4.3 (1.2) years. None of the 2 patients experienced treatment gaps between planned infusions of Vonvendi. The reason provided for initiating intermittent Vonvendi treatment by both patients was to improve bleed control. Both patients were receiving ongoing intermittent Vonvendi treatment at eCRF completion.

Bleeds of Patients <18 Years of Age Treated with Continuous Vonvendi Prophylaxis

Of the 5 patients who received continuous Vonvendi prophylaxis treatment, no patients had no bleeds during the baseline period and 1 (20.0%) patient had no bleeds during the Vonvendi period. Mean (SD) annualized bleed rate during baseline was 4.6 (6.4) bleeds per year. Mean (SD) time to bleed resolution per bleed was 3.0 (1.9) hours and most (91.3%) bleeds were spontaneous. The most common bleed location was epistaxis (82.6%). Four (80.0%) patients treated with continuous Vonvendi prophylaxis had a bleed during the Vonvendi period; they experienced a mean (SD) annualized bleed rate of 2.0 (3.0) bleeds per year and the time to bleed resolution of 2.4 (1.7) hours per bleed. Of the bleeds experienced by patients in the Vonvendi period, the most common bleed location was epistaxis (73.3%); Most bleeds (80.0%) were spontaneous (see Table 1).

Table 1. Bleed Patterns in the Baseline and Vonvendi Prophylaxis Treatment Periods Among Patients with Von Willebrand Disease (VWD), Diagnosed with VWD at Age < 18 years

	Continuous prophylaxis treatment[1] N = 5		Intermittent prophylaxis treatment[2] N = 2	
	Baseline period[3]	Vonvendi period[3]	Baseline period[3]	Vonvendi period[3]
Patients with no bleed, n (%)	0 (0.0)	1 (20.0)	0 (0.0)	1 (50.0)
Annualized bleed rate				
Mean ± SD	4.6 ± 6.4	2.0 ± 3.0	1.0 ± 0.0	0.3 ± 0.5
Median (IQR)	2.0 (1.0, 3.0)	0.7 (0.7, 1.3)	1.0 (1.0, 1.0)	0.3 (0.0, 0.7)
Annualized bleed rate (major bleeds)				
Mean ± SD	0.4 ± 0.9	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
Median (IQR)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)
Annualized bleed rate (minor bleeds)				
Mean ± SD	1.0 ± 1.2	0.5 ± 0.6	0.5 ± 0.7	0.3 ± 0.5
Median (IQR)	1.0 (0.0, 1.0)	0.7 (0.0, 0.7)	0.5 (0.0, 1.0)	0.3 (0.0, 0.7)
Time to bleed resolution per bleed (hours)[3]				
Mean ± SD	3.0 ± 1.9	2.4 ± 1.7	-	-
Median (IQR)	2.0 (2.0, 4.0)	2.0 (1.0, 3.0)	-	-
Location of bleeds, n (%)[4,5]				
Epistaxis	19 (82.6)	11 (73.3)	0 (0.0)	0 (0.0)
Gastrointestinal bleed	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Joint bleed[4,6]	2 (8.7)	0 (0.0)	1 (50.0)	0 (0.0)
Knee	0 (0.0)	0 (0.0)	1 (100.0)	0 (0.0)
Elbow	2 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)
Ankle	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Shoulder	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Wrist	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hand	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hip	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Foot	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other joint[7]	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Unspecified joint	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Mucosal: Mouth and oral cavity	2 (8.7)	2 (13.3)	0 (0.0)	0 (0.0)
Mucosal: Nasopharyngeal	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other location[8]	0 (0.0)	2 (13.3)	0 (0.0)	1 (100.0)
Type of bleed, n(%)[5]				
Spontaneous	21 (91.3)	12 (80.0)	1 (50.0)	1 (100.0)
Traumatic	2 (8.7)	3 (20.0)	1 (50.0)	0 (0.0)
Bleed subtype, n(%)[5]				
Hemorrhage	17 (73.9)	13 (86.7)	1 (50.0)	0 (0.0)
Hemarthrosis	2 (8.7)	0 (0.0)	0 (0.0)	0 (0.0)
Contusion	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hematoma	0 (0.0)	1 (6.7)	1 (50.0)	0 (0.0)
Effusion	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other[9]	4 (17.4)	1 (6.7)	0 (0.0)	1 (100.0)
Treatment given on-demand in addition to Vonvendi prophylaxis, n (%)[4]	0 (0.0)	8 (53.3)	1 (50.0)	0 (0.0)
Antifibrinolytics				
Aminocaproic acid	2 (8.7)	2 (13.3)	1 (50.0)	0 (0.0)
Tranexamic acid	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other antifibrinolytics	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other medications				
Desmopressin acetate nasal spray	1 (4.3)	0 (0.0)	0 (0.0)	0 (0.0)
Desmopressin acetate injection	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Emicizumab	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hormonal therapy				
Oral contraceptive	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hormonal IUD	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hormonal implant	0 (0.0)	0 (0.0)	0 (0.0)	1 (100.0)
Hormonal injection	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
pdVWF: Antihemophilic factor/Von Willebrand factor complex				
Humate-P	4 (17.4)	2 (13.3)	1 (50.0)	0 (0.0)
Alphanate	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Koate-DVI	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Wilate	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other[10]	6 (26.1)	2 (13.3)	0 (0.0)	0 (0.0)
Vonvendi	0 (0.0)	5 (33.3)	1 (50.0)	0 (0.0)
Iron deficiency replacement	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
FVIII treatment	1 (4.3)	0 (0.0)	0 (0.0)	0 (0.0)
Painkillers	0 (0.0)	0 (0.0)	1 (50.0)	0 (0.0)
Other on-demand treatment[11]	9 (39.1)	4 (26.7)	0 (0.0)	0 (0.0)

	Continuous prophylaxis treatment[1] N = 5		Intermittent prophylaxis treatment[1] N = 2	
	Baseline period[2]	Vonvendi period[2]	Baseline period[2]	Vonvendi period[2]
Bleed patterns[12, 13]				
Number of bleeds that resulted in any healthcare visit (per patient)				
Mean ± SD	3.6 ± 4.8	3.5 ± 6.4	0.5 ± 0.7	1.0 ± .
Median (IQR)	2.0 (1.0, 3.0)	0.5 (0.0, 7.0)	0.5 (0.0, 1.0)	1.0 (1.0, 1.0)
Number of bleeds that resulted in an outpatient visit (per patient)				
Mean ± SD	0.6 ± 0.9	1.3 ± 2.5	0.5 ± 0.7	1.0 ± .
Median (IQR)	0.0 (0.0, 1.0)	0.0 (0.0, 2.5)	0.5 (0.0, 1.0)	1.0 (1.0, 1.0)
Number of bleeds that resulted in an inpatient visit (per patient)				
Mean ± SD	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± .
Median (IQR)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)
Number of bleeds that resulted in an ER visit (per patient)				
Mean ± SD	3.0 ± 4.6	2.3 ± 3.9	0.0 ± 0.0	0.0 ± .
Median (IQR)	1.0 (0.0, 3.0)	0.5 (0.0, 4.5)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)

Abbreviations: ER: emergency room; IQR: interquartile range; SD: standard deviation.

Notes:

[1] Bleed pattern analyses were conducted among patients with at least 6 months of data during the baseline period.

[2] The baseline period was defined as the 1-year period prior to Vonvendi initiation (index date) and the Vonvendi period was defined as the 1.5 year period after Vonvendi initiation.

[3] Time to bleed resolution was calculated among bleeds with available data.

[4] Values may not add up to 100% as patients may have fallen under more than one category.

[5] Percentages were calculated out of the total number of bleeds across all patients.

[6] Types of joint bleeds were calculated out of the total number of joint bleeds in each period by prophylaxis type.

[7] Other joint bleeds included toe bleeds.

[8] Other bleed locations included urinary tract, soft tissue post operation, hematuria, hematoma s/p vasectomy, muscle, left eye, rectum, heel of foot, and forearm.

[9] Other bleed subtypes included hematuria, melena, menstrual bleeding, nosebleed, hematochezia, mucosal bleeding, muscle bleeds and unknown subtypes.

[10] Those who reported other pdVWF: Antihemophilic factor/Von Willebrand factor complex treatments had unknown complex types.

[11] Other on-demand treatments include platelets, afrin and silver nitrate, RBC and platelets, blood transfusion, and Danazol.

[12] Number of bleeds that resulted in any healthcare visits were calculated among patients with any bleed in each period for each prophylaxis type.

[13] Standard deviations are not reported when only one patient has data available.

Bleeds of Patients <18 Years of Age Treated with Intermittent Vonvendi Prophylaxis

Of the 2 patients who received intermittent Vonvendi prophylaxis treatment, no patients had no bleeds during the baseline period and 1 patient had no bleeds during the Vonvendi period. Mean (SD) annualized bleed rate was 1.0 (0.0) bleed per year. The annualized bleed rate for the 1 (50.0%) patient with a bleed during the Vonvendi period was 0.3 (0.5) bleeds per year. Time to bleed resolution per bleed was not calculated for patients receiving intermittent prophylaxis in either the baseline or Vonvendi periods due to insufficient data. The most common bleed location was joint bleed (50.0%) and other location (100.0%) in the baseline and Vonvendi periods, respectively. Most bleeds were spontaneous; 50.0% and 100.0% in the baseline and Vonvendi periods, respectively (see Table 1).

Healthcare Resource Utilization of Patients <18 Years of Age Treated with Continuous Vonvendi Prophylaxis

Among the 5 patients who received continuous Vonvendi prophylaxis treatment, 4 (80.0%) and 5 (100.0%) had an outpatient visit during the baseline and Vonvendi periods, respectively. The mean (SD) (median) number of outpatient visits per patient per year (PPPY) was 3.8 (3.1) (3.0) visits PPPY in the baseline period and 6.4 (8.2) (4.0) visits PPPY in the Vonvendi period. In the baseline and Vonvendi periods, patients on continuous Vonvendi treatment experienced 0.8 (1.0) outpatient visits PPPY and 0.8 (1.8) outpatient visits PPPY related to bleeds, respectively. One (20.0%) patient had an inpatient visit during the baseline period and 1 (20.0%) patient had an inpatient visit during the Vonvendi period. Four (80.0%) and 3 (60.0%) patients had an emergency room (ER) visit during the baseline and Vonvendi periods, respectively. The mean (SD) (median) number of ER visits was 4.3 (4.6) (2.5) visits during the baseline period and 2.4 (3.1) (0.7) visits during the Vonvendi period. A total of 2 (40.0%) patients had any surgery in the baseline period, and 2 (40.0%) patients had any surgery in the Vonvendi period. There were 1.5 (0.7) (1.5) surgeries in the baseline period and 0.8 (0.2) (0.8) surgeries in the Vonvendi period, PPPY. The on-demand treatments used during surgeries in the baseline period were Humate-P (33.3%), Vonvendi (33.3%), and Other on-demand treatment (33.3%). In the Vonvendi period, the only on-demand treatment was Vonvendi (100.0%); 50.0% did not use a treatment.

Healthcare Resource Utilization of Patients <18 Years of Age Treated with Intermittent Vonvendi Prophylaxis

Of the 2 patients treated with intermittent Vonvendi prophylaxis, both (100.0%) patients had an outpatient visit during both the baseline and Vonvendi periods. The mean (SD) (median) number of outpatient visits PPPY was 1.5 (0.7) (1.5) visits PPPY in the baseline period and 2.7 (0.9) (2.7) visits PPPY in the Vonvendi period. Neither patient had an inpatient visit or an ER visit during either the baseline or Vonvendi periods. One (50.0%) patient had a surgery during the baseline period, with a mean number of surgeries of 1.0 PPPY. The on-demand treatment used during the surgery was Vonvendi (100.0%). Neither patient had a surgery during the Vonvendi period.

Assessment of the MAH's responses

The separate analysis of patients < 18 years of age reviewed the data from 5 patients who received continuous Vonvendi prophylaxis and 2 patients who received intermittent Vonvendi prophylaxis.

Overall, patients treated with continuous Vonvendi prophylaxis had a mean (SD) age of 12.6 (3.0) years, were mostly male (60%), and had type 2 VWD (n=2), type 3 VWD (n=2), type 1 VWD (n=1). The mean (SD) total weekly dose was 148.2 (26.1) IU/kg and mean (SD) number of annualized infusions given for continuous prophylaxis treatment was 95.4 (55.5). In general, there were a trend to fewer bleeding rates and also fewer surgeries in the Vonvendi treatment period compared to the baseline period. However, the analysed number of subjects < 18 years of age was very low.

Two female patients (one type 2 VWD and one type 1 VWD) received intermittent Vonvendi prophylaxis treatment, but data collection on outcome of bleeds was insufficient. Of note, both patients reported heavy menstrual bleeding and received doses during menses.

The Applicant also provided additional separate analysis for patients at age ≥12 years and <18 years (n=5), and patients at age <12 years (n=2) in the Appendix of the CSR tak-577-4007. No further conclusions can be made from this analysis due to very low number of subjects in each group. Both patients at age < 12 years were treated with continuous infusion.

Conclusion: ***Point resolved.***

6. CHMP Rapporteur’s overall conclusion on the MAH’s responses and recommendation

☒ Fulfilled, no further action required