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BLA Clinical and Clinical Pharmacology Review Memorandum

Application Type	s-BLA
STN	125577/691
CBER Received Date	March 12, 2025
PDUFA Goal Date	September 11, 2025
Division / Office	CBER/OTP
Priority Review (Yes/No)	Yes
Reviewer Name(s)	Clinical: Christine Knoll, MD Clinical Pharmacology: Xiaofei Wang, PhD
Review Completion Date / Stamped Date	September 5, 2025
Supervisory Concurrence	Megha Kaushal, MD, MSc; Branch Chief Asha Das, MD, Acting Director Office of Clinical Evaluation
Applicant	Takeda Pharmaceuticals USA, Inc.
Established Name	von Willebrand Factor (Recombinant) (rVWF), Vonvendi
(Proposed) Trade Name	Vonvendi
Pharmacologic Class	Recombinant Coagulation Factor
Formulation(s), including Adjuvants, etc.	Sterile Water for injection, diluent; polysorbate 80, additive; mannitol, additive; glycine, stabilizer; trehalose dehydrate, stabilizer
Dosage Form(s) and Route(s) of Administration	Lyophilized powder in single-use vials containing nominally 650 or 1300 international units for intravenous use
Dosing Regimen	<u>On-Demand Treatment and Control of BEs</u>: • For each BE, administer the first dose with an approved recombinant (non-von Willebrand factor containing) factor VIII, if factor VIII baseline levels are below 40% or are unknown. **Minor BE:** Initial Dose: 40 to 50 IU/kg Subsequent Doses: 40 to 50 IU/kg every 8 to 24 hours **Major BE:** Initial Dose: 50 to 80 IU/kg Subsequent Doses: 40 to 60 IU/kg every 8 to 24 hours for approximately 2 to 3 days <u>Perioperative Management of Bleeding:</u> <u>For Elective Surgical Procedure:</u> • A dose may be given 12 to 24 hours prior to surgery to allow the endogenous factor VIII levels to increase to at least 30 IU/dL (minor surgery) or 60 IU/dL (major surgery)

<table>
<tr><td></td><td>• Assess FVIII:C levels within 3 hours prior to surgery. If the FVIII:C levels are at or above the recommended minimum target levels, administer a dose of Vonvendi alone within 1 hour prior to the procedure. If the FVIII:C levels are below the recommended minimum target levels, administer recombinant factor VIII in addition to Vonvendi to raise VWF:RCo and FVIII:C.
<u>For Emergency Surgery:</u>
• Assess baseline VWF:RCo and FVIII:C levels within 3 hours prior to surgery. If not available, use weight-based dosing calculation.
• Administer Vonvendi 1 hour before surgery with or without recombinant factor VIII and adjust the dose to raise VWF:RCo and FVIII:C to adequate level
<table><tr><th rowspan="2">Type of Surgery</th><th colspan="2">Target Peak Plasma Level</th><th rowspan="2">Calculation of rVWF Dose (IU VWF:RCo required)</th></tr><tr><th>VWF:RCo</th><th>FVIII:C</th></tr><tr><td>Minor</td><td>50 to 60 IU/dL</td><td>40 to 50 IU/dL</td><td>Δ VWF:RCo x BW (kg)/IR</td></tr><tr><td>Major</td><td>100 IU/dL</td><td>80 to 100 IU/dL</td><td>Δ VWF:RCo x BW (kg)/IR</td></tr></table>• Continue to monitor the VWF:RCo and FVIII:C plasma levels after surgical procedure.
<u>Routine Prophylaxis to Reduce the Frequency of BEs in Adults:</u>
Initial dosage of Vonvendi is 40 to 60 IU/kg body weight to be administered twice weekly. The dose may be adjusted up to 60 IU/kg twice weekly based on frequency of BEs.</td></tr>
<tr><td>Indication(s) and Intended Population(s)</td><td>VONVENDI [von Willebrand factor (recombinant)] is a recombinant von Willebrand factor (rVWF) indicated in adult and pediatric patients with von Willebrand disease (VWD) for:
• On-demand treatment and control of bleeding episodes.
• Perioperative management of bleeding.
For adult patients only:
Routine prophylaxis to reduce the frequency of bleeding episodes</td></tr>
<tr><td>Orphan Designated (Yes/No)</td><td>Yes</td></tr>
</table>

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Glossary

AE	Adverse Event
AESI	Adverse Event of Special Interest
ABR	Annualized Bleeding Rate
BE	Bleeding Events
BLA	Biologics License Application
BU	Bethesda Unit
CBER	Center for Biologics Evaluation and Research
eCRF	Electronic Case Report Form
FAS	Full Analysis Set
FVIII	Factor VIII
FVIII:C	Factor VIII clotting activity
IP	Investigational Product
IR	Information Response
ISE	Integrated Summary of Efficacy
ISS	Integrated Summary of Safety
MedDRA	Medical Dictionary for Regulatory Activities
OD	On demand
PD	Pharmacodynamic
pdVWF	Plasma derived vWF product
PeRC	Pediatric Review Committee
PK	Pharmacokinetic
PMC	Post-marketing commitment
PMR	Post-marketing requirement
PP	Per-protocol
PT	Preferred Term
PTP	Previously Treated Patient
PUP	Previously Untreated Patient
RWE	Real World Evidence
rFVIII	Recombinant Factor VIII
rVWF	Recombinant von Willebrand Factor
sABR	Spontaneous Annualized Bleeding Rate
SAE	Serious Adverse Event
SAF	Safety Analysis Set
sBLA	Biologics License Application supplement
SD	Standard deviation
SOC	System Organ Class
TEAE	Treatment-emergent adverse event
USPI	United States Prescribing Information
VWD	von Willebrand Disease
VWF	von Willebrand Factor
VWF:Ag	von Willebrand Factor Antigen
VWF: CB	von Willebrand Factor Collagen Binding
VWF:RCo	von Willebrand Factor: Ristocetin cofactor activity

1. EXECUTIVE SUMMARY

Vonvendi is a recombinant VWF product. It was approved for:

- On-demand treatment (OD) and control of BEs in adults with VWD in December 2015.
- Perioperative management of bleeding in adults with VWD in April 2018.
- Prophylaxis in adults with type 3 VWD receiving on-demand therapy in January 2022.

This efficacy supplement for Vonvendi includes the efficacy and safety data from three Phase 3 clinical studies (parent studies 071301 and 071102 and continuation study SHP 677-304) and three RWE studies (ATHN 9, CCR-2024-200475, and TAK-577-4007).

The RWE studies reviewed and evaluated included patients meeting the pre-specified criteria (age and severity and type of VWD) in the clinical trials supporting the submission.

Studies 071301 and SHP 677-304 support the proposed indication expansion of routine prophylaxis to include adults with type 1 and type 2 VWD with RWE study ATHN 9 providing additional data for support.

Studies 071102 and SHP 677-304 support the proposed indication of OD treatment and control of BEs and perioperative management of bleeding in children (0 to <18 years of age) with VWD with RWE study CCR-2024-200475 providing additional data for support.

Prophylaxis indication expansion to include types 1 and 2 VWD:

Study 071301 was a prospective, open-label, uncontrolled, non-randomized, international, multicenter, phase 3 study to evaluate the efficacy and safety of routine prophylaxis with Vonvendi in adult patients with severe VWD. 12 months was planned for each patient. It included 22 patients who received either:

-VWF product on-demand (OD) for the treatment of BEs (BEs) (Prior OD group).
-Prior plasma-derived Von Willebrand factor (pdVWF) product as routine prophylaxis (Switch group).

The primary endpoint was annualized spontaneous bleeding rate (sABR) during prophylaxis with Vonvendi. Five patients with Types 1 and 2 VWD received prophylaxis. Study 071301 demonstrated that Vonvendi is safe and effective in patients with Type 1 and Type 2 VWD with 100% decrease in sABR in prior OD patients and Switch patients on prior prophylaxis with pd-VWF maintaining 0 sABR without significant safety concerns.

After completion of study 071301, patients could enroll on continuation study SHP677-304. The results were similar showing that Vonvendi prophylaxis is safe and effective in patients with Type 1 and Type 2 VWD with prior OD patients having at least a 25% decrease in sABR and Switch patients on prior prophylaxis with pd-VWF maintaining 0 sABR. No significant safety concerns.

ATHN 9 is a Natural History Cohort Study of the Safety, Effectiveness, and Practice of Treatment for People with Severe Von Willebrand Disease (VWD) and supported the results within the clinical trials.

TAK-577-4007 was not included in this review as there were no datasets provided and we were unable to verify severity of VWD in the patients included in the study.

In conclusion, Vonvendi is safe and effective for prophylaxis for adults with all types of VWD.

Pediatric indication expansion:

Study 071102 was a phase 3, prospective, multicenter, uncontrolled, open-label clinical study to determine the efficacy, safety, and tolerability of Vonvendi with or without Advate in the treatment and control of BEs, the efficacy and safety of Vonvendi in elective and emergency surgeries, and the pharmacokinetics (PK) of Vonvendi in children diagnosed with severe VWD. It included 29 patients enrolled for a 12-month duration.

There were 3 treatment arms including OD, elective surgery, and emergency surgery. The 3 age cohorts with 8 evaluable patients originally targeted in each cohort included Cohort 1: ages ≥12 to <18, Cohort 2: ages ≥6 to <12, and Cohort 3: ages <6 (at least 3 patients with type 3 VWD).

The primary endpoint was hemostatic efficacy, defined as the number of pediatric patients with treatment success for Vonvendi-treated nonsurgical BEs using a 4-point scale. BE treatment success was defined as a mean efficacy rating score of <2.5 for treated BE's with excellent = 1, good = 2, moderate = 3, and none = 4. The surgery endpoint was overall hemostatic efficacy 24 hours after the last perioperative infusion of Vonvendi or on post-op day 14, whichever came earlier.

Treatment success of hemostatic efficacy was achieved for all nonsurgical BE's in the OD arm. Minor elective and emergency surgeries had excellent overall hemostatic efficacy without post-operative bleeding.

After completion of study 071301, patients could enroll on continuation study SHP677-304. The results were similar with all nonsurgical BE's treated with Vonvendi having treatment success of hemostatic efficacy in the OD arm. All surgeries had excellent outcomes. There were no significant safety concerns.

RWE study CCR-2024-200475 was a retrospective analysis of the safety, effectiveness of surgery management with Vonvendi in children with VWD in the ATHN dataset with 2 patients included in this review and supported the results within the clinical trials.

In conclusion, Vonvendi is safe and effective for the treatment of OD bleeding episodes and perioperative management in pediatric patients with VWD.

1.1 Demographic Information: Subgroup Demographics and Analysis Summary

Table 1 Demographics of clinical trials (071301 and SHP 677-304) and RWE study (ATHN 9) supporting adult prophylaxis indication expansion (FAS)

	Study 071301 N = 4	**Study SHP 677-304 N = 4**	**Total clinical trials N = 7**	**ATHN 9 N = 10**	**Total Including RWE data N = 17**
Age (years)					
Mean	60	50	52	58	55
Min, Max	20, 77	30, 76	20, 77	19, 89	19, 89
Sex, n (%)					
Male	4 (100)	3 (75)	6 (86)	3 (30)	9 (53)
Female	0	1 (25)	1 (14)	7 (70)	8 (47)
Race, n (%)					
White	4 (100)	4 (100)	7 (100)	8 (80)	15 (88)
Asian	0	0	0	1 (10)	1 (6)
Black	0	0	0	1 (10)	1 (6)
Hispanic/Latino	2 (50)	1 (25)	2 (29)	0	2 (12)
Not Hispanic/Latino	2 (50)	3 (75)	5 (71)	10 (100)	15 (88)
BMI (kg/m2)					
Mean	26	31	28	31	30
Min, Max	24, 29	21, 39	21, 39	19, 49	19, 49
VWD Type (%)					
Type 1	2 (50)	0	2 (29)	1 (10)	3 (18)
Type 2A	1 (25)	4 (100)	4 (57)	8 (80)	12 (70)
Type 2 B	1 (25)	0	1 (14)	1 (10)	2 (12)
Prior Treatment (%)					
OD	2 (50)	3 (75)	5 (71)	2 (20)	7 (41)
Prophylaxis	2 (50)	1 (25)	2 (28)	8 (80)	10 (59)
Geographic Region (%)					
Europe	4 (100)	3 (75)	6 (86)	0	6 (35)
US and Canada	0	1 (25)	1 (14)	10 (100)	11 (65)

* Source: Integrated CSR and ADSL datasets for 071301 and SHP 677-304; CSR and ADSL and ADVS dataset for ATHN 9

Reviewer's Comment:
1 patient participated in both studies 071301 and SHP 677-304.

Table 2 Demographics of clinical trials (071102 and SHP 677-304) supporting pediatric on-demand (OD) indication expansion (FAS)

	Study 071102 N = 18	Study SHP 677-304 N = 16	Total N = 21
Age (years)			
Mean	10	10.4	10
Min, Max	1, 17	2, 18	1, 17
Age category, n (%)			
≥12 to <18 years	6 (33)	8 (50)	7 (33)
≥6 to <12 years	9 (50)	5 (31)	9 (43)
<6 years	3 (17)	3 (19)	5 (24)
Sex, n (%)			
Male	7 (39)	7 (44)	10 (48)
Female	11 (61)	9 (56)	11 (52)
Race, n (%)			
White	15 (94)	14 (93)	18 (95)
Multiple	1 (6)	1 (7)	1 (5)
Not reported	2	1	2
Hispanic/Latino	1 (6)	1 (7)	1 (5)
Not Hispanic/Latino	16 (94)	14 (93)	19 (95)
Not reported	1	1	1
BMI (kg/m2)			
Mean	21	22	20
Min, Max	13, 41	13, 41	13, 41
VWD Type (%)			
Type 1	2 (11)	4 (25)	4 (19)
Type 2A	3 (17)	1 (6)	3 (14)
Type 2 B	2 (11)	3 (19)	3 (14)
Type 3	11 (61)	8 (50)	11 (52)
Geographic Region (%)			
Europe	13 (72)	7 (44)	8 (38)
US	5 (28)	9 (56)	13 (62)

*Source: CSR and ADSL datasets (integrated and 90-day update) for 071102 and SHP 677-304

Reviewer's Comment:

- *16 patients participated in both studies 077102 and SHP 677-304.*
- *3 patients were included in the FAS for SHP 677-304 but not 071102 (071102-(b) (6), 071102-(b) (6), and 071102-(b) (6)).*
- *5 patients were included in the FAS for 071102 but not SHP 677-304 (071102-(b) (6), 071102-(b) (6), 071102-(b) (6), 071102-(b) (6), and 071102-(b) (6)).*

Table 3 Demographics of clinical trials (071102 and SHP 677-304) and RWE study (CCR-2024-200475) supporting pediatric surgery indication expansion (FAS) and (SAF)

	Study 071102 N = 4	Study SHP 677-304 N = 4	Total in clinical trials N = 8	CCR-2024-200475 N = 2	Total including RWE data N = 10
Age (years)					
Mean	9	13	10	15	11
Min, Max	6, 12	12, 15	6, 13	12, 17	6, 17
Age category, n (%)					
≥12 to <18 years	2 (50)	4 (100)	4 (50)	2 (100)	6 (60)
≥6 to <12 years	2 (50)	0	4 (50)	0	4 (40)
<6 years	0	0	0	0	
Sex, n (%)					
Male	3 (75)	4 (100)	7 (88)	1 (50)	8 (80)
Female	1 (25)	0	1 (12)	1 (50)	2 (20)
Race, n (%)					
White	4 (100)	4 (100)	8 (100)	2 (100)	10 (100)
Not Hispanic/Latino	4 (100)	4 (100)	8 (100)	2 (100)	10 (100)
BMI (kg/m2)					
Mean	17	22	20		20
Min, Max	14, 22	16, 34	14, 33		14, 33
Not reported	0	0	0	2	2
VWD Type, n (%)					
Type 1	1 (25)	2 (50)	3 (38)	1 (50)	4 (40)
Type 2A	0	0	0	1 (50)	1 (10)
Type 2 B	0	1 (25)	1 (12)	0	1 (10)
Type 3	3 (75)	1 (25)	4 (50)	0	4 (40)
Geographic Region, n (%)					
Europe	2 (50)	3 (75)	5 (62)	0	5 (50)
US	2 (50)	1 (25)	3 (38)	2 (100)	5 (50)
Surgery Category, n (%)					
Major	0	0	0	1 (50)	1 (10)
Minor	4 (100)	4 (90)	7 (88)	1 (50)	8 (80)
Oral	0	1 (10)	1 (12)	0	1 (10)

* Source: CSR and ADSL datasets (integrated and 90-day update) for 071102 and SHP 677-304, CSR and ADSL dataset for CCR 2024-200475.

Reviewer's Comment:

- *1 emergency surgery patient in 071102 also included in OD population.*
- *1 patient had two minor procedures.*
- *1 patient who had a minor surgery also had a major surgery with commercial Vonvendi. The major surgery was not included in the analysis.*

1.2 Patient Experience Data

Data Submitted in the Application

Check if Submitted	Type of Data	Section Where Discussed, if Applicable
☒	Patient-reported outcome	6.1.11.5 and 6.2.11.5
☐	Observer-reported outcome	
☒	Clinician-reported outcome	
☐	Performance outcome	
☐	Patient-focused drug development meeting summary	
☐	FDA Patient Listening Session	
☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel)	
☐	Observational survey studies	
☐	Natural history studies	
☐	Patient preference studies	
☐	Other: (please specify)	
☐	**If no patient experience data were submitted by Applicant, indicate here.**	

Check if Considered	Type of Data	Section Where Discussed, if Applicable
☐	Perspectives shared at patient stakeholder meeting	
☐	Patient-focused drug development meeting	
☐	FDA Patient Listening Session	
☐	Other stakeholder meeting summary report	
☐	Observational survey studies	
☐	Other: (please specify)	

2. CLINICAL AND REGULATORY BACKGROUND

2.1 Disease or Health-Related Condition(s) Studied

VWD is the most common inherited bleeding disorder affecting 1% of the general population. The prevalence of symptomatic disease is estimated to be 1 in 10,000. There are 3 types of VWD including quantitative (types 1 and 3) and qualitative (type 2) abnormalities in VWF; Type 1 VWD constitutes 70-80% of cases, 20% of cases are Type 2, and type 3 is the rarest form of disease and constitutes approximately 1-5% of cases.

VWF plays an important role in primary hemostasis by binding to both platelets and endothelial components at sites of endothelial injury and between adjacent platelets in areas with high shear. It also contributes to secondary hemostasis by acting as a carrier protein for factor VIII. Deficiency of VWF can be associated with low levels of FVIII, and concurrent treatment with exogenous FVIII is sometimes required for hemostasis.

It is an autosomal disorder presenting equally in men and women. A brief description of subtypes:

Type 1 (most common):

Partial quantitative deficiency of normally functioning VWF with normal distribution of multimers.

Type 2 (4 subtypes):

• Type 2A (most common Type 2): Loss of largest VWF multimers and platelet dependent VWF functions.

• Type 2B: Gain-of-function in the platelet-binding domain, with increased affinity of VWF for platelets resulting in binding of VWF to platelets. This can result in thrombocytopenia and inadequate high multimers.

• Type 2M: Decreased platelet binding due to mutations that inactivate specific ligand binding sites.

• Type 2N: Mutations in the FVIII binding domain of VWF resulting in a mild hemophilia A-like disorder.

Type 3 (least common):

An almost complete absence of VWF resulting in severe bleeding symptoms. The absence of VWF results in a secondary deficiency of FVIII. There can be spontaneous joint and soft tissue bleeding, and it is possible that some of these patients will develop alloantibodies to VWF with replacement therapy (incidence of 7.5-9.5%). Anaphylactic reactions to exogenous VWF can occur in patients with complete deficiency of VWF antigen.

Type 3 VWD, severe Type 1 and Types 2 disease may require replacement therapy with a VWF-containing product for BEs and surgery. Some may require prophylaxis with VWF-containing products to prevent BEs.

2.2 Currently Available, Pharmacologically Unrelated Treatment(s)/Intervention(s) for the Proposed Indication(s)

FDA-approved products for VWD include:

- Wilate is indicated in children and adults with VWD for:
  - On-demand treatment and control of BEs (all ages) approved December 8, 2009.
  - Perioperative management of bleeding (all ages) approved August 13, 2015.
  - Routine prophylaxis to reduce the frequency of BEs (≥ 6 years of age) December 7, 2023.
- Humate-P was approved in April 2007 in VWD for indications (1) treatment of spontaneous and trauma-induced BEs, and (2) prevention of excessive bleeding during and after surgery.
- Alphanate was approved in February 2007 for surgical and/or invasive procedures in patients with VWD. It is not indicated for patients with severe VWD (Type 3) undergoing major surgery.
- DDAVP was approved in 1978 for patients with VWD with mild to moderate disease with factor VIII levels greater than 5% to maintain hemostasis during surgical procedures or traumatic injuries.

Vonvendi is the only non-plasma derived VWF replacement product approved for VWD. It is currently approved for BEs and peri-operative bleeding in all adults and for prophylaxis in adults with Type 3 VWD.

2.3 Safety and Efficacy of Pharmacologically Related Products

Wilate is effective in VWD for treating BE's, in perioperative management, and routine prophylaxis for patients ≥ 6. The most common adverse reactions are hypersensitivity, urticaria, chest discomfort, and dizziness.

Humate-P is effective in treating BE's and perioperative management in VWD. The most common adverse reactions are allergic-anaphylactic reactions postoperative wound and injection-site bleeding, and epistaxis.

Alphanate is effective in VWD for surgery management besides major surgery in severe Type 3. The most frequent AEs include respiratory distress, pruritus, rash, urticaria, face edema, paresthesia, pain, fever, chills, joint pain and fatigue.

Wilate, Humate-P, and Alphanate are all plasma-derived VWF containing products. In general, plasma-derived VWF products have associated risks of thromboembolism, infection transmission, infusion related reactions such as anaphylaxis and hypersensitivity, neutralizing antibody development, and intravascular hemolysis.

DDAVP has been shown to be effective in mild to moderate VWD if Factor VIII levels > 5%. It is not effective in Type 3 VWD and is contraindicated in Type 2B VWD. Significant side effects include transient headache, nausea, mild abdominal cramps, vulval pain, local erythema, swelling or burning pain, and facial flushing.

Reviewer's comment:

- *Treatment of severe VWD disease represents an unmet medical need due to lack of available licensed therapies, specifically lack of non-pd replacement products.*
- *The recombinant nature of Vonvendi significantly reduces the risk of transmission of infectious agents.*
- *Since Vonvendi does not contain blood group isoagglutinins (Anti-A and Anti-B), the risk of developing intravascular hemolysis in patients with blood groups A, B and AB is significantly reduced.*
- *Since Vonvendi does not contain FVIII, the risk of developing neutralizing antibodies to FVIII and thromboembolism is significantly reduced.*

2.4 Previous Human Experience with the Product (Including Foreign Experience):

- December 8th, 2015: Vonvendi approved in USA for treatment and control of BEs in adults with VWD.
- April 13, 2018: Vonvendi approved in USA for peri-operative management in adults with VWD.
- Jan 28, 2022: Vonvendi approved in USA for prophylaxis in adults with Type 3 VWD.
- Vonvendi is marketed under the trade name Vonvendi in the United States (US), Canada, and Japan.
- In the European Union, Switzerland, and Australia, it is marketed under the trade name VEYVONDI.

2.5 Summary of Pre- and Post-submission Regulatory Activity Related to the Submission:

- Vonvendi was granted orphan designation (#10-3222) in November 2010 for the treatment of VWD.
- Breakthrough therapy designation request denied (b) (4) " due to lack of clinical evidence of substantial improvement over available treatments.
- Vonvendi approved in US on December 2015 for OD treatment and control of BEs in adults with VWD.
- April 2018, Vonvendi approved in the US for perioperative management of bleeding in adults with VWD.
- In January 2022, Vonvendi approved in the US for prophylaxis in adult patients with Type 3 VWD
- In November 2023, WRO Type C meeting was held regarding evidence supporting the effectiveness and safety of Vonvendi for OD treatment and control of BEs, perioperative management of bleeding, and routine prophylaxis in children with VWD. Feedback provided regarding this planned sBLA submission to be reasonable for pediatric indications of OD treatment and perioperative management with acceptability of the data to be reviewed at the time of submission. Feedback also provided for planned pediatric prophylaxis study, specifically the decreased sample size proposed.
- In January 2024, WRO Type B meeting was held regarding the indication expansion of "Routine prophylaxis to reduce the frequency of BEs in adult patients with severe type 3 VWD receiving on-demand therapy" to include patients with severe type 1 and type 2 VWD. This included inclusion of two RWE studies to support this indication expansion. Per FDA request, in February 2024, protocol and SAP submitted for ATHN 9 and protocol, data analysis plan, and CSR submitted or TAK-577-4007. Feedback provided in consultation with the RWE team that the studies were reasonable as supporting studies to be included with this sBLA submission with the acceptability of the data to be reviewed at the time of the submission. However, the review would include only patients that met the pre-specified inclusion criteria in the clinical trials.

- In February 2024, the applicant requested feedback regarding an RWE study protocol to support the pediatric surgery indication. Per FDA request, the datasets and TLF's were submitted in November 2024. Feedback provided in consultation with the RWE team that the data package was reasonable to be included with sBLA submission with the acceptability of the data to be reviewed at the time of the submission. However, the review would include only patients that met the pre-specified inclusion criteria as well as surgery definitions and follow up period within the clinical trials.
- In March 2025, s-BLA submission to support the following:
  - To expand the current approved adult prophylaxis indication for type 3 VWD to include adults with type 1 and type 2 VWD and
  - To expand the use of Vonvendi to children (0 to <18 years of age) with VWD for on demand treatment and control of BEs and perioperative management of bleeding.
  - Priority review was granted.

2.6 Other Relevant Background Information

None

3. Submission Quality and Good Clinical Practices

3.1 Submission Quality and Completeness

The submission was sufficiently organized to allow complete clinical review without difficulty.

3.2 Compliance With Good Clinical Practices And Submission Integrity

Adequate without concerns regarding study conduct or data integrity.

3.3 Financial Disclosures

Covered clinical studies 071102, SHP 677-3040, and ATHN 9:
Was a list of clinical investigators provided? X Yes ☐ No (Request list from applicant)
Total number of investigators identified: 180
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 8 in 077102, 4 in SHP 677-304, and 0 in ATHN 9
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 12 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in sponsor of covered study: 0 Is an attachment provided with details of the disclosable financial interests/arrangements? X Yes ☐ No (Request details from applicant) Is a description of the steps taken to minimize potential bias provided? X Yes ☐ No (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3): 0 Is an attachment provided with the reason? ☐ Yes ☐ No (Request explanation from applicant)

Complete financial disclosures were provided for 071102, SHP 677-304, and ATHN 9. No financial disclosures were provided for CCR-2024-200475. Eight investigators for study 071102, 4 for study SHP 677-304, and 0 for ATHN 9 were noted to have disclosable financial interests including grants, advisory boards, fee for services, consulting, research, committees, meetings. All were not related to this trial.

4. Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry, Manufacturing, and Controls

Vonvendi is a purified rVWF expressed in Chinese hamster ovary (CHO) cells. It does not require the addition of human or animal materials for the final product. Proteins present in the final product contain trace amounts of mouse IgG (from the purification process), CHO protein, rFurin, and rFVIII. There were no significant CMC issues for this supplement. See CMC review memo for full review.

4.2 Assay Validation

There was no issue related to assay validation for this supplement.

4.3 Nonclinical Pharmacology/Toxicology

No new data were submitted to Pharmacology/Toxicology.

4.4 Clinical Pharmacology

In current submission, the clinical pharmacology of VONVENDI was evaluated in Study SHP-677-304 (adult patients with type 1 and type 2 VWD on prophylaxis) and Study 071102 (pediatric patients with VWD for on demand and surgery treatment). In addition, the Applicant conducted population pharmacokinetic (PK) and pharmacokinetic/pharmacodynamic (PK/PD) modeling analysis to better characterize the PK and PD properties of VONVENDI in targeted patient populations. The population PK model was developed using data from 6 clinical studies conducted in adult and pediatric patients (N=134). Exposure-response was also evaluated to support proposed dosing regimens with. There were no significant clinical pharmacology issues for this supplement.

4.4.1 Mechanism of Action

Vonvendi contains high molecular weight multimers (HMWM) and ultra large multimers (ULM) that function analogous to endogenous VWF. It mediates adhesion of platelets to sites of vascular injury at high shear rates forming a platelet plug for primary hemostasis. In addition, VWF is a carrier protein for Factor VIII which is an essential cofactor of secondary hemostasis that leads to fibrin clot formation. Since it is a recombinant product, it is not exposed to plasma protease ADATMTS13 during manufacturing, resulting in HMWM and ultra large multimers which are hemostatically very active contributing to the efficacy of Vonvendi.

4.4.2 Human Pharmacodynamics (PD)

Adult Patients with VWD Type 1 and Type 2 for Prophylaxis Treatment (Study SHP677-304)
Endogenous FVIII activity, the pharmacodynamic (PD) analyte of VONVENDI, was measured using the one-stage assay. PD samples were collected at pre-dose and at 0.25, 0.5, 1, 3, 6, 9, 24, 30-, 48-, 72-, and 96-hours post-dosing.

Individual patient pharmacokinetic (PK) parameters for FVIII:C are summarized in Table 4. Although slightly variable PK doses were administered during the initial PK assessments, this variation did not affect the PD evaluation. The PD exposure parameters for the three patients with type 2 von Willebrand disease (VWD) in Cohort 4 demonstrated consistency both between patients and between assessments, indicating sustained FVIII exposure following prophylactic treatment with VONVENDI.

Table 4 Summary of Individual Subject PK Parameters for FVIII:C

Assessment	Subject 2 (Cohort 4)	Subject 3 (Cohort 4)	Subject 4 (Cohort 4)	Subject 1 (Cohort 1)
Initial Assessment				
Actual dose (IU/kg)	50.21	43.70	47.00	-
Cmax (IU/dL)	41	58	39	-
Tmax (h)	23.72	28.32	23.92	-
AUC0-96 h (h*IU/dL)	2220.06	2986.745	2590.27	-
Cmax/Dose ((IU/dL)/(IU/kg))	0.81657	1.327231	0.829787234	-
AUC0-96 h/Dose ((h*IU/dL)/(IU/kg))	44.21549	68.34657	55.11212766	-
End of Study				
Actual dose (IU/kg)	-	-	-	81.74
Cmax, ss (IU/dL)	-	-	-	57
Cmin, ss (IU/dL)	-	-	-	0
Tmax, ss (h)	-	-	-	23.80
AUCtau (h*IU/dL)	-	-	-	3601.765
Cmax, ss/Dose ((IU/dL)/(IU/kg))	-	-	-	0.697333
AUCtau/Dose ((h*IU/dL)/(IU/kg))	-	-	-	44.06368

Source: Applicant. Study SHP-677-304 CSR.

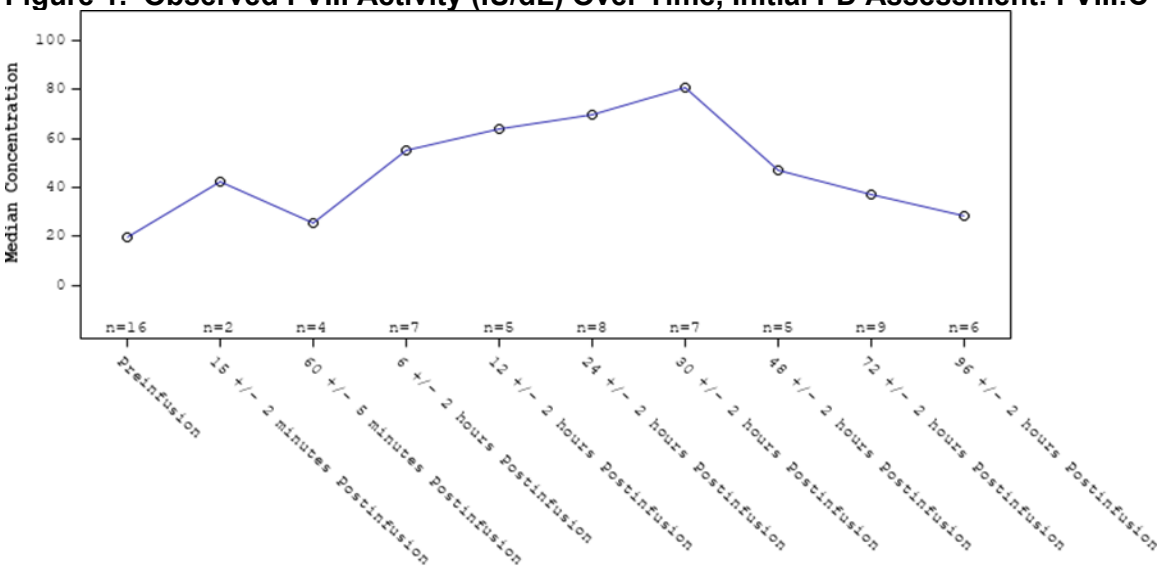
Results from population PK/PD modeling analysis indicate that VWD types have no effect on PD/FVIII:C (rate constant of degradation of FVIII, Kout) properties.

Pediatric Patients with VWD for On-demand Treatment (Study 071102)

The pharmacodynamic properties (PD) of VONVENDI, specifically FVIII activity, in pediatric patients receiving on-demand therapy for bleeding episodes and treatment for surgical bleeds were evaluated. The evaluation utilized sparse sampling across three age groups (less than 6 years old, 6 years to less than 12 years old, and 12 years to less than 17 years old).

Following a single infusion of VONVENDI at 50 (±5) IU/kg in pediatric patients, median levels of FVIII increased through the 30-hours assessment then a decease through the 96-hour assessment (Figure 1). The median baseline corrected C_{max} and AUC_{0-96} of FVIII:C were 64.5 IU/dL and 3379 IU*h/dL.

Figure 1. Observed FVIII Activity (IU/dL) Over Time, Initial PD Assessment: FVIII:C



Source: Applicant. Study 071102 CSR.

The baseline pre-dose FVIII:C activity was substantially higher in patients with type 1 and type 2 VWD than in patients with type 3 VWD. The mean (SD) values of FVIII:C were 37.0 (15.56), 31.0 (5.66), 59.0 (4.24) and 4.0 (4.24) IU/dL for patients with type 1 (n=2), type 2A (n=4), type 2B (n=2), and type 3 (n=8), respectively (Table 5).

Table 5 Summary of Observed Pre-PK Dose VWF and FVIII Activity (IU/dL) by VWD Type (PKPD Analysis Set)

	Predose			
VWD Type	**VWF:RCo**	**VWF:Ag**	**VWF:CB**	**FVIII:C**
Type 1				
n	2	2	2	2
<LLOQ [a]	0	0	0	0
Mean (SD)	13.75 (2.333)	13.5 (2.12)	12.30 (2.404)	37.0 (15.56)
Median	ND	ND	ND	ND
Min, Max	12.1, 15.4	12, 15	10.6, 14.0	26, 48
Type 2A				
n	4	4	4	4
<LLOQ [a]	4	0	0	0
Mean (SD)	BLQ (ND)	19.3 (6.85)	10.48 (5.773)	31.0 (5.66)
Median	BLQ	17.5	11.00	29.0
Min, Max	BLQ, BLQ	13, 29	4.1, 15.8	27, 39
Type 2B				
n	2	2	2	2
<LLOQ [a]	0	0	0	0
Mean (SD)	16.75 (5.162)	36.5 (4.95)	30.40 (0.141)	59.0 (4.24)
Median	ND	ND	ND	ND
Min, Max	13.1, 20.4	33, 40	30.3, 30.5	56, 62
Type 3				
n	8	8	8	8
<LLOQ [a]	8	7	8	0
Mean (SD)	BLQ (ND)	BLQ (ND)	BLQ (ND)	4.0 (4.24)
Median	BLQ	BLQ	BLQ	20
Min, Max	BLQ, BLQ	BLQ, 4	BLQ, BLQ	1, 13

Dose range for age cohort aged ≥12 to <18 years is 45.73 – 58.75 IU/kg. Dose range for age cohort aged ≥6 to <12 years is: 35.45 – 56.84 IU/kg. Dose range for age cohort aged < 6 years is 45.48-50.47 IU/kg.
[a]Number of values <LLOQ. LLOQ is equal to 8.0% for VWF:RCo, 2.5% for VWF:Ag and VWF:CB, and 1.0 IU/dL for FVIII:C, values <LLOQ were considered as zeros in descriptive statistics.
Source: Applicant. Study 071102 CSR.

Results from the population pharmacokinetic (PK) and PK/pharmacodynamic (PD) modeling analyses were consistent with clinical observations regarding baseline endogenous FVIII:C levels (IU/dL). Compared to patients with VWD type 3, patients with type 1 and type 2 VWD demonstrated higher baseline endogenous FVIII:C activity levels.

Following a single infusion of VONVENDI at 50 ± 5 IU/kg, the median baseline-corrected Cmax and AUC0-96 were 3216 IU*h/dL and 66 IU/dL, respectively. Please refer to Pharmacometrics Consult Review for details.

4.4.3 Human Pharmacokinetics (PK)

Pharmacokinetics of VONVENDI in Adult Patients with VWD Type 1 and Type 2 for Prophylaxis Treatment (Study SHP677-304)

The pharmacokinetics (PK) of VONVEND in adult patients with type 1 or type 2 von Willebrand disease (VWD) receiving prophylaxis treatment were evaluated in Study SHP677-304 Cohort 1 (continued prophylaxis treatment) and Cohort 4 (newly enrolled patients). PK samples were collected at pre-dose and at 0.25, 0.5, 1, 3, 6, 9, 24, 30-, 48-, 72-, and 96-hours post-dosing.

VWF activity was determined using three assays: von Willebrand factor ristocetin cofactor (VWF:RCo), von Willebrand factor antigen (VWF:Ag), and von Willebrand factor collagen binding activity (VWF:CB). One patient in Cohort 1 who completed the study underwent a full PK assessment at the end of study. Three patients in Cohort 4 completed the initial PK and PD assessment.

The individual patient PK parameter for VWF:RCo are summarized in Table 6. Although slightly variable PK doses were administered during the initial PK assessments, this variation did not affect the PK evaluation. The three patients with type 2 VWD in Cohort 4 demonstrated comparable maximum concentration (Cmax) values, expected Cmax incremental recovery (IR) values, and similar clearance (CL), exposure (AUC), and dose-normalized exposure values. The one patient in Cohort 1 who underwent PK assessment after receiving the prophylactic dose (81.74 IU/kg) showed similar PK parameters. Patients with VWD type 1 and type 2 had higher baseline VWF:RCo levels compared to patients with VWD type 3.

Table 6 Summary of Individual Subject PK Parameters for VWF:RCo

Assessment	Subject 2 (Cohort 4)	Subject 3 (Cohort 4)	Subject 4 (Cohort 4)	Subject 1 (Cohort 1)
Initial Assessment				
Actual dose (IU/kg)	50.21	43.70	47.00	-
C_{max} (IU/dL)	136	101	75.8	-
T_{max} (h)	0.47	0.48	0.33	-
IR at C_{max} ((IU/dL)/(IU/kg))	2.708624	2.311213	1.612766	-
$AUC_{0\text{-}96\ h}$ (h*IU/dL)	1802.067	2431.624	965.0875	-
C_{max}/Dose ((IU/dL)/(IU/kg))	2.708624	2.311213	1.612766	-
$AUC_{0\text{-}96\ h}$/Dose ((h*IU/dL)/(IU/kg))	35.8906	55.64356	20.53378	-
$AUC_{0\text{-}\infty}$ (h*IU/dL)	1853.454	2868.795	1188.86	-
$AUC_{0\text{-}\infty}$/Dose ((h*IU/dL)/(IU/kg))	36.91403	65.64747	25.29488	-
CL (dL/h/kg)	0.02709	0.015233	0.039534	-
V_{ss} (dL/kg)	0.466976	0.691849	0.950625	-
MRT (h)	17.23796	45.41811	24.04596	-
$t_{1/2}$ (h)	12.26208	30.9208	15.30891	-
End of Study				
Actual dose (IU/kg)	-	-	-	81.74
$C_{max, ss}$ (IU/dL)	-	-	-	144
$C_{min, ss}$ (IU/dL)	-	-	-	0
$T_{max, ss}$ (h)	-	-	-	0.42
IR at C_{max} ((IU/dL)/(IU/kg))	-	-	-	1.761683
AUC_{tau} (h*IU/dL)	-	-	-	2683.264
$C_{max, ss}$/Dose ((IU/dL)/(IU/kg))	-	-	-	1.761683
$C_{min, ss}$/Dose ((IU/dL)/(IU/kg))	-	-	-	0
AUC_{tau}/Dose ((h*IU/dL)/(IU/kg))	-	-	-	32.82681

AUC: area under the plasma concentration/time curve; AUC0-96 h: AUC from time 0 to 96 hours postinfusion dose; AUC0-∞: AUC from time 0 to infinity; AUCtau: AUC for a dosing interval; CL: clearance; Cmax: maximum plasma concentration; Cmax,ss: Cmax at steady state; Cmin,ss: minimum plasma concentration at steady state; IR: incremental recovery; MRT: mean residence time; PK: pharmacokinetic; t1/2: half-life; Tmax: minimum time to reach the maximum concentration; Tmax,ss: Tmax at steady state; Vss: apparent steady-state volume of distribution; VWF:RCo: recombinant von Willebrand factor:ristocetin cofactor.

Note: AUC_{tau} was calculated from time 0 to 96 hours post-dose at steady state (end of study assessment).

Source: Applicant. Study SHP-677-304 CSR.

PK Properties of VONCENDI in Adult Patients with Type 1, Type 2, and Type 3 VWD

The PK parameters of VONVENDI following single-dose infusion of 50 IU/kg (PK50) or 80 IU/kg (PK80) in adults (VWF:RCo) are summarized in Table 7.

Table 7 Pharmacokinetic Parameters of VONVENDI Following Single-Dose Infusion in Adults (VWF:RCo)

Parameter (unit)	PK_{50} VONVENDI with ADVATE[a] Mean (SD) Min; Max	PK_{50} VONVENDI Mean (SD) Min; Max	PK_{80} VONVENDI Mean (SD) Min; Max
$T_{1/2}$ (h)	19.3 (10.99) 10.8; 51.2	22.6 (5.34) 17.0; 37.2	19.1 (4.32) 11.8; 28.0
CL ([dL/kg]/h)	0.04 (0.028) 0.01; 0.16	0.02 (0.005) 0.02; 0.04	0.03 (0.009) 0.02; 0.05
IR ([IU/dL]/([IU/kg])	1.7 (0.62) 1.0; 3.6	1.9 (0.41) 1.2; 2.7	2.0 (0.39) 1.4; 2.9
$AUC_{0\text{-inf}}$ (IU*h/dL)	1541.4 (554.31) 173.8; 2862.0	2105.4 (427.51) 1334.0; 2813.3	2939.0 (732.72) 1507.8; 4121.1
$AUC_{0\text{-inf}}$/Dose ([IU*h/dL]/[IU/kg])	33.4 (13.87) 6.4; 70.4	42.1 (8.31) 27.8; 54.8	36.8 (8.97) 18.8; 50.4

$AUC_{(0\text{-inf})}$ = area under plasma concentration-time curve from time 0 hour to infinite time post-infusion; IR = incremental
Source: Applicant. IR response submitted on August 13, 2025.

The Applicant developed a population pharmacokinetic (PK) model using data from six clinical studies conducted in adult and pediatric patients (n=134) to characterize the PK profiles in both pediatric and adult patients with von Willebrand disease (VWD).

Results from the population PK analysis indicate that VWD type (types 1-2 versus type 3) has no effect on PK parameters, specifically clearance (CL) and volume of distribution (V). Patients with VWD types 1, 2, and 3 demonstrated similar PK properties for VWF:RCo. Differences in VWF:RCo exposure were attributed to differences in baseline levels across VWD types..

Baseline endogenous VWF:RCo levels (IU/dL) in patients with type 1 and type 2 VWD were higher than those in patients with type 3 VWD. The median (range) endogenous baseline VWF:RCo levels were:

Type 1 VWD: 12 IU/dL (0 - 30.5 IU/dL) • **Type 2 VWD:** 9 IU/dL (0 - 22 IU/dL)

Endogenous baseline VWF:RCo levels in patients with type 3 VWD were below the lower limit of quantification (LLOQ) of the assay in 93 out of 95 patients (97.9%).

Please refer to pharmacometrics consult review for details.

Incremental Recovery (IR)
Incremental recovery (IR) was estimated for subjects in Cohorts 1 and 4 who received prophylactic doses, using samples collected 30 minutes before and after dosing at each scheduled visit. IR was determined for VWF:RCo, VWF:Ag, and VWF:CB during the initial phase 3b continuation study prophylaxis visit and at follow-up visits at Months 1, 2, 3, 6, 9, and 12.

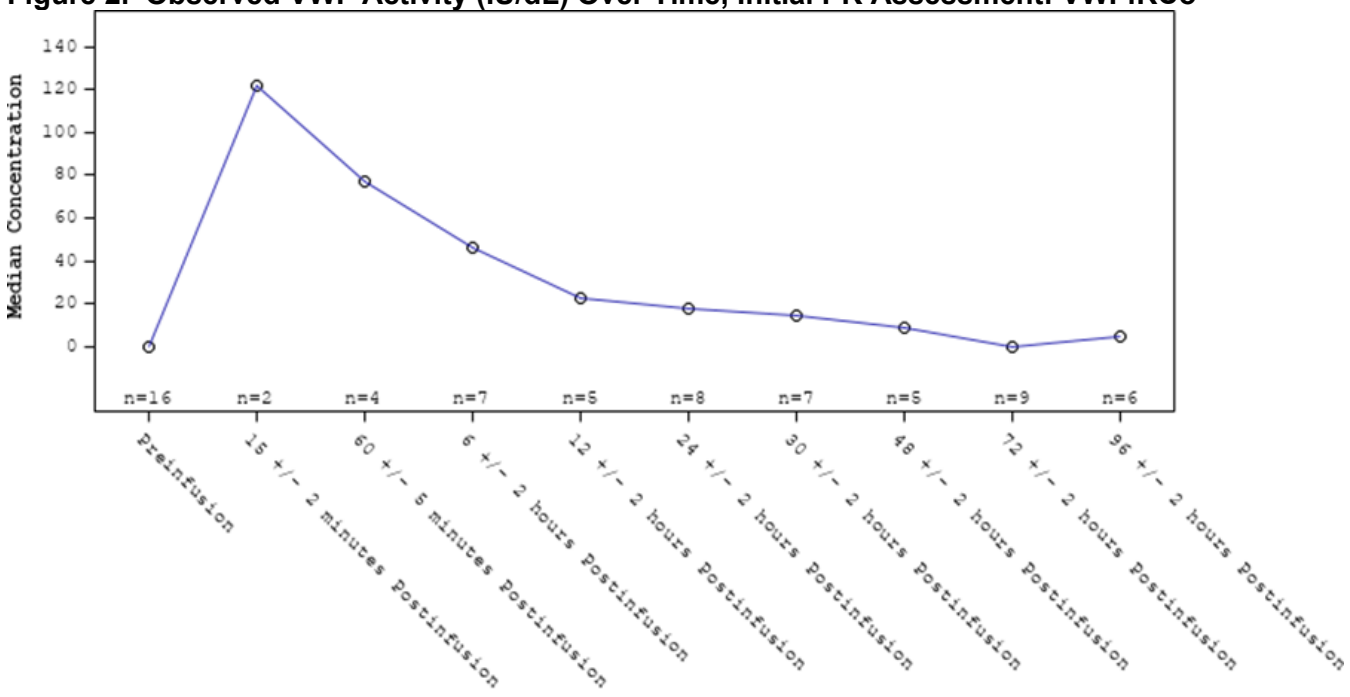
Based on available data, IR at 30 minutes post-dose was generally >1.0 throughout the first 12 months of prophylactic treatment. IRs for VWF:RCo remained consistent for the majority of subjects during the study, demonstrating sustainable exposure for continued prophylactic dosing of vonicog alfa in subjects with type 2 VWD.

Two patients in Cohort 4 demonstrated notable IR patterns: one patient had an IR value below 1.0 (0.271) at the Month 3 visit. At other visits, this patient's IR values ranged from 1.179 at Month 2 to 1.659 at Month 9. During the first 12 months of prophylactic treatment, the patient experienced a treated spontaneous annual bleeding rate of 0.96, representing a reduction from the historical spontaneous annual bleeding rate of 7.0 for treated bleeding episodes. Another patient had a lowest IR value of 0.591 at Month 2. This patient's IR values at other visits ranged from 2.13 to 4.31. The treated spontaneous annual bleeding rate during the first 12 months of prophylactic treatment was 2.99, representing a decrease from the historical annualized bleeding rate of 18.0, suggesting clinical benefit from prophylactic treatment.

Pharmacokinetics of VONVENDI in pediatric patients with VWD, for on-demand treatment (Study 071102)

In Study 071102, the PK/PD properties following single dose IV infusion of 50 ± 5 IU/kg VONVENDI were evaluated in pediatric subjects with VWD across 3 age groups: <6 years (n=5), ≥ 6 to < 12 years (n=10), and ≥ 6 to < 18 years (n=7). Sparse PK/PD samples were collected up to 96 hours post PK infusion at the baseline visit, according to the 3 sample collection sequences, with 4 samples planned per subject. The Applicant developed population PK model using data from 6 clinical studies conducted in adult and pediatric patients (n=134) to characterize the PK profiles in pediatric VWD patients and adult VWD type 1 and type 2 patients (please refer to pharmacometrics consult review for detailed information).

Figure 2. Observed VWF Activity (IU/dL) Over Time, Initial PK Assessment: VWF:RCo



Source: Applicant. Study 071102 CSR.

Baseline pre-dose VWF and FVIII:C activities were higher in subjects with type 1 and type 2 VWD than in subjects with type 3 VWD (Table 2).

Table 8 shows the estimated PK parameters of VWF:RCo in pediatric patients based on the PK modeling across 3 age groups.

Table 8. Pharmacokinetic Assessment of VWF:RCo Following Single-Dose Infusion in Pediatric Patients

Parameter (unit)	**PK50 VONVENDI Mean (SD) Min; Max**			
Age Range	**<6 yrs (n=5)**	**6 yrs to <12 yrs (n=10)**	**12 yrs to <17 yrs (n=6)**	**Total (n=21)**
$T_{1/2}$ (h)	12.4 (2.90) 8.96; 15.7	14.5 (1.47) 12.3; 16.7	14.5 (1.27) 13.0; 16.4	14.3 (2.03) 8.96; 17.4
CL([dL/kg]/h)	0.08 (0.041) 0.048; 0.141	0.05 (0.016) 0.032; 0.077	0.05 (0.008) 0.034; 0.055	0.05 (0.025) 0.032; 0.141
C_{max} (IU/dL)	69.4 (18.8) 51.0, 90.3	82.6 (20.8) 53.7, 122	80.8 (19.7) 65.7, 115	79.0 (19.9) 51.0, 122
IR at Cmax ([IU/dL]/[(IU/kg])	1.25 (0.378) 0.828; 1.78	1.54 (0.378) 1.06; 2.13	1.57 (0.279) 1.29; 2.06	1.49 (0.339) 0.828; 2.13
$AUC_{0\text{-}inf}$ (IU*h/dL)	1260 (654) 811; 2390	1630 (882) 697; 3360	1600 (867) 961; 2760	1540 (757) 697; 3360
$AUC_{0\text{-}inf}$/Dose ([IU*h/dL]/[IU/kg])	25.6 (12.8) 16.1; 47.9	32.5 (18.1) 13.5; 68.5	33.1 (17.6) 19.0; 55.6	31.1 (15.3) 13.5; 68.5

$AUC_{(0\text{-}inf)}$ = area under plasma concentration-time curve from time 0 hour to infinite time post-infusion; IR = incremental recovery; CL = clearance; $t_{1/2}$ = half-life.
Source: Applicant. IR response submitted on August 13, 2025.

Based on population PK (popPK) analysis results, the VWF:RCo median $AUC_{0\text{-}72}$ in pediatric patients was 48%, 26%, and 37% lower than in adults for VWD types 1, 2, and 3, respectively. The median Cmax for both VWF:RCo and FVIII:C was comparable (less than 25% difference) between adult and pediatric patients across all VWD types. According to the VONVENDI label, the cessation of minor and major bleeding episodes (on-demand indication) in adult and pediatric patients was associated with peak FVIII:C activity levels ≥30 and ≥60 IU/dL, respectively. Based on these results, a dose of 50 IU/kg is expected to effectively treat minor and major bleeding episodes in pediatric patients.

4.4.4 Exposure-Response Analysis

Exposure-Efficacy Response Analysis in Adult Patients with Type 1 and Type 2 VWD for Prophylaxis Treatment

The exposure-response (E-R) efficacy relationships between the efficacy endpoint of severe bleeding episodes (sBE) and VWF:RCo or FVIII:C exposure was explored. A significant relationship between sBE and VWF:RCo was identified: higher VONVENDI exposure was associated with lower bleeding risk. No significant relationship between sBE and FVIII:C was observed. VWD type did not impact the relationship between sBE and VWF:RCo.

The bleeding risk (hazard ratio) for patients with VWD types 1 and 2 receiving 50 IU/kg weekly (QW) and biweekly (BIW) regimens was 8% lower and 27% lower, respectively, relative to the reference treatment (VWD type 3, 50 IU/kg, BIW) (Table 9).

Table 9 Hazard Ratio for BIW and QW Dosing Regimen for rVWF in Patients with VWD Type 1-2 and 3

VWD	Regimen	N	Mean (Min, Max) Average VWF:RCo Activity at Steady State (IU/dL)	HR (95% CI)
1-2	No treatment	8	7.61 (6.31, 9.77)	1.21 (1.03 – 1.43)
	50 IU/kg QW	8	16.4 (12.0, 20.5)	0.92 (0.86 – 0.99)
	50 IU/kg BIW	8	25.1 (17.7, 32.0)	0.73 (0.56 – 0.96)
3	No treatment	18	0.500 (0.500, 0.500)	1.42 (1.05 – 1.90)
	50 IU/kg QW	18	7.61 (3.90, 15.5)	1.19 (1.03 – 1.38)
	50 IU/kg BIW	18	14.7 (7.30, 30.4)*	1.00 (1.00 – 1.00)*

HR=Hazard ratio. * Reference.

Source: Applicant. Population PK PKPD and ER of rVWF in Adult T1T2 VWD study report.

Regarding safety response, no E-R relationship was observed with VWD type 1 and 2. Patients with VWD type 3 presented higher proportion of infections and infestations for higher value of average concentration at steady state (Cave,ss) of VWF:RCo (3rd and 4th quartiles).

Exposure-Efficacy Response Analysis in Pediatric Patients with VWD for On-Demand and Surgery Treatment

For on-demand (OD) treatment, based on the exposure-response (ER) results and PK/PD properties, a 50 IU/kg dose is expected to achieve target FVIII:C exposure levels (peak FVIII:C activity levels ≥30 and ≥60 IU/dL) to maintain hemostasis and resolve minor and major bleeding episodes in all pediatric age groups.

The presence of minor surgery did not affect the AUC0-72 and Cmax of VWF:RCo in adult and pediatric patients. A 50 IU/kg dose for minor surgery achieved the targeted VWF:RCo levels (>60 IU/dL) in both adult and pediatric patients.

PK/PD data from major surgeries were available only in adults. The presence of major surgery did not affect the AUC0-72 and Cmax of VWF:RCo in adult patients. An 80 IU/kg dose for major surgery achieved the targeted VWF:RCo levels (>100 IU/dL) in adult patients.

No exposure-response (ER) relationship for safety was observed in either OD or surgery indications.

Please refer to Pharmacometrics Consult Review for detailed information.

4.4.5 Immunogenicity

Study patients were tested for the development of antibodies to VWF and FVIII, as well as trace proteins that might be present in the vonicog alfa drug product, including murine immunoglobulin (from immunoaffinity purification), host-cell (CHO) proteins, and rFurin (used to further process vonicog alfa).

Study SHP677-304
For adult patients with type 1 and type 2 VWD, none of the four subjects developed binding antibodies to VWF or FVIII, or to murine immunoglobulin, CHO protein, and/or rFurin. No confirmed neutralizing antibodies against human VWF or FVIII were reported during the study.

For pediatric patients, no patient developed binding antibodies to VWF or FVIII, or to murine IgG, CHO protein, and/or rFurin. No confirmed neutralizing antibodies against VWF or FVIII were reported.

Study 071102 (pediatric patients with VWD)
No pediatric patients developed neutralizing or binding antibodies to VWF, neutralizing antibodies to FVIII, or antibodies to murine IgG, CHO proteins, or rFurin.

4.5 Statistical

See statistical review memo.

4.6 Pharmacovigilance

See pharmacovigilance review memo

5. Sources of Clinical Data and Other Information Considered in the Review

5.1 Review Strategy

The clinical review of the submission is based on the results from the clinical trials 071301, 071102, and SHP677-304. The RWE studies ATHN 9 and CCR-2024-200475 provide supportive data. Datasets and study reports for 071301, 071102, SHP677-304 and study reports for ATHN 9 and CCR-2024-200475 were submitted in Module 5 of this BLA. The datasets for ATHN 9 and CCR-2024-200475 were submitted separately via ATHN in CBER Connect. The studies are described below in Section 5.3.

5.2 BLA/IND Documents That Serve as the Basis for the Clinical Review

Documents pertinent to this review are provided in BLS 125577/691.

5.3 Table of Studies/Clinical Trials

Table 10 Studies supporting prophylaxis indication expansion

Study	Phase	Title	Study Status
071301	3	A Prospective, Phase 3, Open-label, International Multicenter Study on Efficacy and Safety of Prophylaxis with Vonvendi in Severe VWD	Complete
SHP 677-304 (extension study)	3b	A Phase 3b, Prospective, Open-label, Uncontrolled, Multicenter Study on Long-term Safety and Efficacy of Vonvendi in Pediatric and Adult Patients with Severe VWD	Complete
RWE Study ATHN9	4	A Natural History Cohort study of the Safety, Effectiveness, and Practice of Treatment for People with severe VWD	Ongoing

*Source: Tabular Listing of all Clinical Studies

Reviewer's Comment:

- *Study SHP 677-304 ended January 30, 2025, with efficacy data cutoff date January 26, 2024. A safety update was submitted May 28, 2025, with updated safety data cutoff date January 3, 2025.*
- *ATHN 9 data cutoff date is August 31, 2024.*

Table 11 Studies supporting pediatric indication expansion

Study	Phase	Title	Study Status
071102	3	A Phase 3, Prospective, Multicenter, Uncontrolled, Open-Label Clinical Study to Determine the Efficacy, Safety, and Tolerability of Vonvendi with or without Advate in the Treatment and Control of BEs, the Efficacy and Safety of Vonvendi in Elective and Emergency Surgeries, and the Pharmacokinetics (PK) of Vonvendi in Children Diagnosed with Severe VWD	Complete
SHP 677-304 (extension study)	3b	A Phase 3b, Prospective, Open-label, Uncontrolled, Multicenter Study on Long-term Safety and Efficacy of Vonvendi in Pediatric and Adult Patients with Severe VWD	Complete
RWE Study CCR-2024-200475	4	A retrospective analysis of the Safety, Effectiveness of surgery management with recombinant von Willebrand Factor (Vonvendi) in children with VWD in the ATHNdataset	Complete

*Source: Tabular Listing of all Clinical Studies

Reviewer's Comment:
Study SHP 677-304 ended January 30, 2025, with efficacy data cutoff date January 26, 2024. A safety update was submitted May 28, 2025, with updated data cutoff January 3, 2025. Efficacy update also included for 2 additional pediatric surgery patients in 071102 with data cutoff date January 3, 2025.

5.4 Consultations

1. Drs. Hao Zhu, and Jiang Liu in CDER/OTS/OCP/Division Pharmacometrics (DPM) were consulted to assist with population PK study analyses.2. Whitney Steele, Tainya Clarke, and Stephen Chang from the RWE team were consulted to assisted with RWE study analyses.

5.4.1 Advisory Committee Meeting (if applicable)

NA

5.4.2 External Consults/Collaborations

NA

5.5 Literature Reviewed (if applicable)

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6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 Indication #1: To expand the current approved adult prophylaxis indication for type 3 VWD to include adults with type 1 and type 2 VWD. Studies 071301, SHP 677-304, and ATHN 9 were reviewed to evaluate this indication.

Study 071301:
A prospective, open-label, uncontrolled, non-randomized, international, multicenter, phase 3 study to evaluate efficacy and safety of routine prophylaxis with Vonvendi in adult patients with severe VWD. Patients could then continue onto Study SHP 677-304.

RWE Study ATHN 9:
Natural History Cohort Study of Safety, Effectiveness, and Practice of Treatment for People with Severe VWD.

6.1.1 Objectives (Primary, Secondary, etc.)

Primary:
Primary Objective (071301): prospectively evaluate the sABR while on prophylactic treatment with Vonvendi compared to the patient's historical sABR.

Primary Objective (RWE Study ATHN 9):
To assess the safety of Vonvendi treatment regimens for prophylaxis in patients with VWD who were treated with continuous prophylaxis on Vonvendi.

Secondary:
Secondary Objectives (071301):
- Additional efficacy of prophylactic treatment with Vonvendi.
- Safety of Vonvendi, including immunogenicity, thrombogenicity and hypersensitivity.
- PK and PD of Vonvendi as measured in FVIII activity.

Secondary Objectives (RWE Study ATHN 9):
- Enrich and analyze the data from currently enrolled patients in the ATHNdataset with VWD treated with Vonvendi prophylaxis including (b) (4) based VWF activity assay and genetic sequence analysis of VWF coding regions and adjacent non-coding regions.
- Establish a platform for sub-studies for patients with congenital severe VWD treated with Vonvendi.
- Evaluate the use of Vonvendi replacement as prophylaxis in patients over 6- month time periods.
- Describe bleeding events, changes in overall bleeding and ABR over the course of the study.
- Describe real-world effectiveness of VWD treatment.

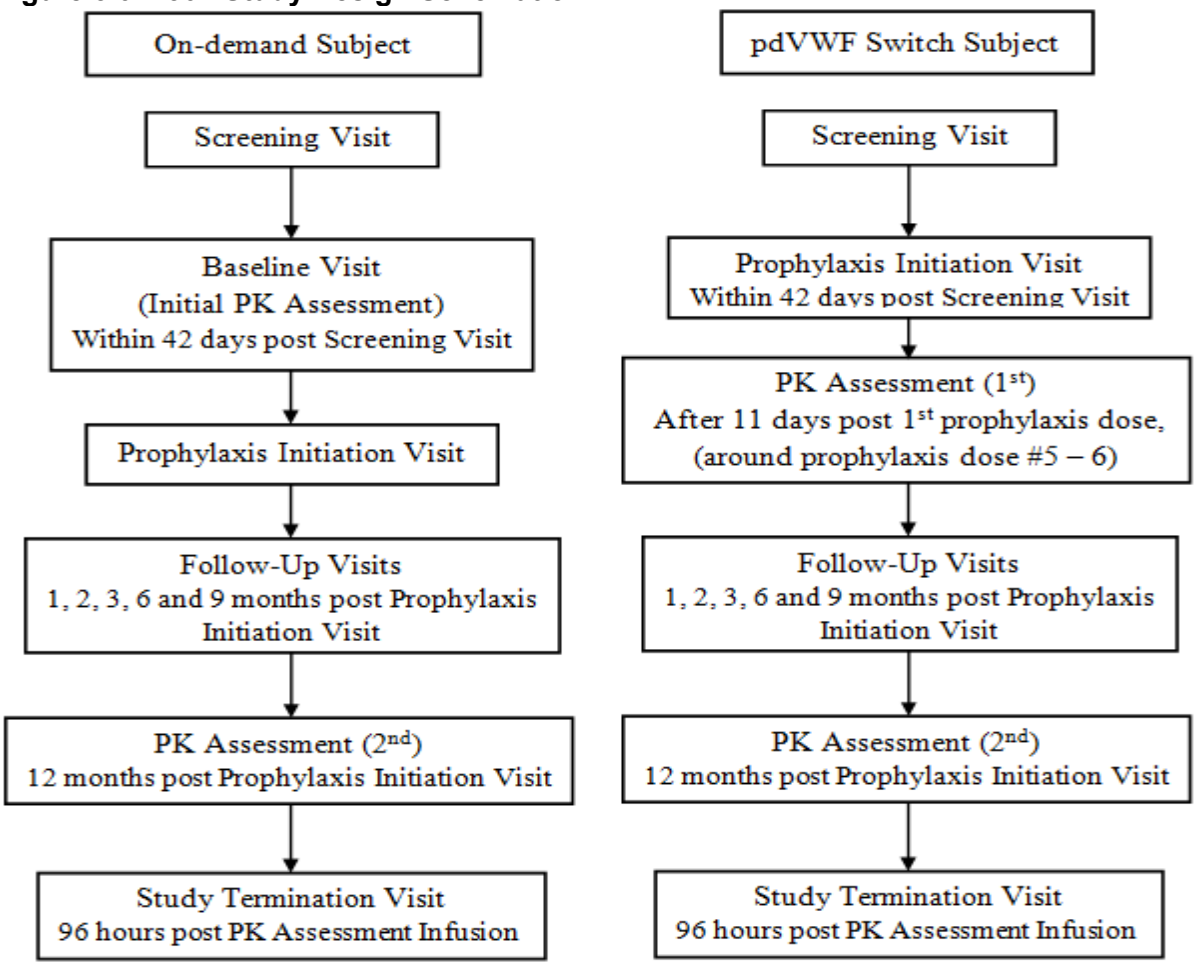
Exploratory:
Exploratory Objectives (071301):
- Efficacy of the treatment of BEs (spontaneous and traumatic).
- Efficacy of perioperative bleeding management.
- HRQoL: EQ-5D (EuroQol-5 Dimension), Short Form (36) Health Survey (SF-36) and Von Willebrand Impact Questionnaire (V-WIQ).
- Pharmacoeconomics: health resource utilization (HRU) and productivity: Number and duration of hospitalizations, emergency room visits, urgent care physician visits, days missed from school or work.

Reviewer's Comment:

- *The objectives for continuation study SHP 677-304 aligned with 071301 with differences including:*
  - *PK/PK were secondary objectives in 071301 and exploratory in SHP 677-304.*
  - *SHP 677-304 secondary objectives included efficacy of different prophylaxis dose regimens.*
  - *Efficacy for OD BE's treatment was secondary in SHP 677-304 and exploratory in 071301.*
- *There were no exploratory objectives for RWE study ATHN 9.*

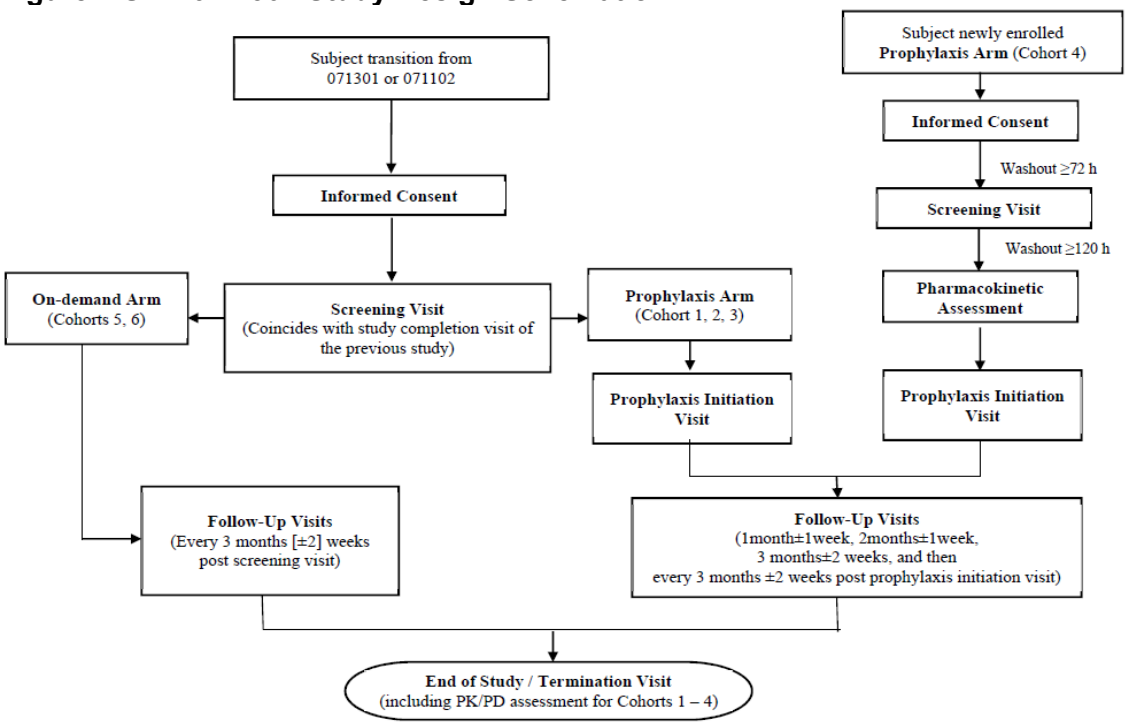
6.1.2 Design Overview

Figure 3 071301 Study Design Schematic



*Source: Study 071301 CSR page 32

Figure 4 SHP 677-304 Study Design Schematic



*Source: Study SHP 677-304 Protocol page 29

Two groups of patients were enrolled in 071301:

- Prior OD group: Vonvendi prophylaxis was initiated twice weekly at 50±10 IU/kg.
- Switch group: The initial prophylaxis regimen with Vonvendi was based on matching (±10%) of the weekly pdVWF dose of their prior pdVWF prophylaxis regimen.

There were 6 cohorts in SHP 677-304. Cohorts 1 through 4 included prophylaxis patients and cohorts 5 and 6 included OD cohorts. All cohorts besides Cohort 4 were patients transitioning from 071301 or 071102. Cohorts 1 and 4 were pertinent to the prophylaxis indication expansion:

1. Cohort 1: Adult patients transitioning from 071301 on the same prophylactic dose as in 071301.
2. Cohort 4. Newly enrolled adult and adolescent (aged 12 to <18 years) patients switching from OD treatment with VWF products who started 1× per week prophylaxis with Vonvendi.

Reviewer's comment:
This review will focus on 1 patient from Cohort 1 and 3 patients from Cohort 4 with Type 1 and Type 2 VWD.

Duration of Treatment (071301/SHP 677-304):
The planned duration for 071301 was at least 12 months. Longer duration was permitted for sites that did not have SHP677-304 initiated by the time a patient finished Month 12. Patients in SHP 677-304 had planned duration of at least 12 months and up to 3 years. Infusions were allowed either at the study site or at home.

Assessments:

- Efficacy and safety were assessed throughout the study.
- Initial PK/PD assessment:
  - Prior OD patients: PK/PD were assessed before the start of prophylaxis
  - Switch patients: PK/PD were assessed after the first 5 to 6 prophylactic doses
- Final PK/PD assessment was conducted at study completion for both groups.

After completing 071301, patients could continue into SHP677-304 to continue prophylaxis or switch to OD.

An electronic patient diary was provided to each patient at the screening visit to record the following:

- Vonvendi infusions including date, start and stop times of the infusion, number of vials utilized, and infusion volume for prophylactic treatment or treatment of spontaneous and traumatic BE's.
- Details of BEs (site, type, severity and date/time of bleeding and response to treatment).
- Patientive hemostatic efficacy assessments.
- Untoward events/unwanted experiences.
- Concomitant medications (including immunizations) and non-drug therapies.
- Patient Reported Outcomes (PROs).

Study Design (RWE Study ATHN 9): This is a longitudinal, observational cohort study being conducted at ATHN affiliated sites. Patients will be followed for 2 years. The total study duration is 3 years.

- All study visits were timed to coincide with routine, scheduled follow up for their VWD when possible.
- Study enrollment occurred at the baseline visit with biannual follow up visits to occur in person or by phone.
- Ad hoc follow up as needed.
- Study exit visit at 2 years unless withdrawn prior.

6.1.3 Population:

Key Inclusion Criteria (071301/SHP 677-304):

1. Age ≥18 years old at screening.
2. History of diagnosis of severe VWD (VWF:RCo <20 IU/dL) requiring VWF concentrate to control bleeding.
3. Confirmed diagnosis by genetic testing and multimer analysis.
4. For Switch group, patient receiving prophylactic treatment of pdVWF products for at least 12 months.
5. For Prior OD group, patient had ≥3 documented spontaneous bleeds, excluding menorrhagia, requiring VWF treatment during past 12 months.

Exclusion Criteria (071301/SHP 677-304):

1. Type 2N VWD, pseudo VWD, or another hereditary or acquired coagulation disorder other than VWD.
2. Prophylactic treatment of more than 5 infusions per week.
3. Prophylactic treatment with a weekly dose exceeding 240 IU/kg.
4. History or presence of a VWF inhibitor.
5. History or presence of a FVIII inhibitor; titer ≥0.4 Bethesda units (BU) (by Nijmegen modified Bethesda assay) or ≥0.6 BU (by Bethesda assay).
6. Medical history of immunological disorders except allergies.
7. Medical history of a thromboembolic event.
8. HIV positive with an absolute Helper T cell (CD4) count <200/mm3.
9. Significant liver disease defined as:
    a) serum ALT greater than 5 times the ULN
    b) hypoalbuminemia
    c) portal vein hypertension
10. Renal disease, with a serum creatinine level ≥2.5 mg/dL.
11. Platelet count <100,000/mL.

12. Treatment with immunomodulatory drugs within 30 days.
13. Pregnancy and lactation.
14. Cervical or uterine conditions causing menorrhagia or metrorrhagia.

Inclusion Criteria ATHN Study ATHN 9:
1. Severe VWD with Type 3 VWD, VWF:RCo, VWF:(b) (4), VWF:Ag ≤30%, or clinically severe VWD defined as VWF:RCo or VWF:Ag ≤40% with severe bleeding defined as requiring use of recurrent factor concentrates.
2. Co-enrollment in the ATHNdataset.

Patients for the subgroup analysis were required to meet the following additional inclusion criterion:
1. Severe VWD, defined as VWF activity <20% as measured by VWF:(b) (4), VWF:CB, or VWF:Ag.

Reviewer's Comment:
This review includes 10 patients in the subgroup with the pre-specified criteria of severe VWD in the clinical trials, 071301 and SHP 677-304.

Exclusion Criteria ATHN Study ATHN 9:
1. Diagnosis of platelet-type VWD.
2. Diagnosis of acquired VWD.

6.1.4 Study Treatments or Agents Mandated by the Protocol (071301/SHP 677-304):

Dose and dose adjustments for prophylaxis:
In 071301, Vonvendi intravenous (IV) infusions were as follows:

- OD patients: 1 to 3 times a week at 50±10 IU/kg per dose (up to 80 IU/kg allowed).
- Switch patients: 1 to 3 times a week with total weekly dose based on the pdVWF regimen used before study with limit of 80 IU/kg per dose.

In SHP 677-304, Cohort 1 patients continued the same prophylactic regimen from 071301. Cohort 4 patients were newly enrolled and previously treated with VWF products for BEs, with at least 3 BEs, excluding menorrhagia, over the past 12 months. They were initiated on Vonvendi prophylaxis at 50 IU/kg weekly.

Reviewer's Comment:
The one Switch patient in Cohort 1 who rolled over from 071301 to SHP 677-304 was on 80 IU/kg weekly.

Initial prophylaxis dose of 40 to 60 IU/kg was based on recommended dosing for pd-VWF products and Vonvendi doses investigated in the completed Phase 1 (070701, 071104) and Phase 3 (071001, 071101) studies. Dosage could be individualized and increased up to 80 IU/kg 3 times weekly based on historical PK data, VWD type, and severity of BEs with monitoring of appropriate clinical and laboratory measures.

Reviewer's Comment:

- *Based on published data with pdVWF, the relative long t1/2 and mean residence time (MRT) for Vonvendi, the proposed dose escalation up to 80 IU/kg VWF:RCo and administration intervals were reasonable.*
- *In 071301, 2 patients from Prior OD group and one Switch patient received prophylaxis dose of 50 IU/kg twice weekly. One Switch patient received 80 IU/kg weekly. No dose changes occurred.*
- *In SHP 677-304, the 3 newly enrolled OD patients started at 50 IU /kg weekly:*
  - *2 switched to twice weekly after 12 months.*
  - *1 switched to every 4 days at about 10 months and then back to weekly at 12 months.*

BE dosage (071301 and SHP 677-304):
Dosage was individualized based on the patient's weight, type and severity of BE and monitoring of clinical and laboratory measures. In general, an initial dose of 40-60 IU/kg Vonvendi with or without 30-45 IU/kg Advate. Advate recommended if plasma FVIII levels fell below 30 IU/dl or were unknown. In cases of major BEs, a dose of up to 80 IU/kg Vonvendi could be infused. Subsequent doses, if necessary, could be administered with or without Advate to maintain VWF:RCo and FVIII levels for as long as deemed necessary by the investigator.

Surgery dosage (071301 and SHP 677-304):
For both elective and emergency surgery, loading dose of 40 to 60 IU/kg Vonvendi was recommended within 3 hours prior to surgery. Advate could be administered 12-24 hours prior to surgery to raise FVIII:C levels to recommended levels at a dose of 30 to 45 IU/kg, preferably within 10 minutes after the Vonvendi infusion in patients whose FVIII plasma levels already are (or are highly likely to be) less than 40 to 50 IU/dL for minor/oral surgery or 80 to 100 IU/dL for major surgery. At the discretion of the investigator, the Advate dose could be increased in patients requiring emergency surgery who did not receive a preoperative priming dose. The peri- and postoperative regimen was individualized according to PK results, intensity, and duration of the hemostatic challenge, and the institution's standard of care.

Reviewer's Comment:
- *No Type 1/Type 2 patients had surgery in 071301. In SHP 677-304, Patients* (b) (6) *all had at least 1 surgery each.*
- *Advate replacement for BEs was slightly different in 071301 and SHP 677-304*:
    - *For 071301 "In general, an initial dose of 40-60 IU/kg VWF:RCo with 30-45 IU rFVIII [Advate]/kg) is recommended (Vonvendi:rFVIII ratio of 1.3:1: ±0.2). In cases of major BEs, a dose of up to 80 IU/kg VWF:RCo may be infused. Subsequent doses, if necessary, will be administered with or without Advate to maintain VWF:RCo and FVIII levels for as long as deemed necessary by the investigator. In general, the aim of the initial dose should be full replacement of VWF with VWF:RCo levels of > 0.6 IU/ml (60%) and FVIII:C of > 0.4 IU/mL (40%). Re-dosing with Vonvendi in combination with Advate using the same (initial) dose and adaptation of the dosing frequency should be considered until cessation of the bleed, if the FVIII and/or VWF:RCo levels drop below 30%-50% depending on bleeding severity."*
    - *For SHP 677-304 "However, if endogenous FVIII is below 30% or is unknown and cannot be estimated from the patient's PK study, an infusion of Vonvendi: Advate at an Vonvendi: Advate ratio of (1.3± 0.2): 1 should be administered initially. Subsequent infusions should be with Vonvendi:RCo 40 to 60 IU/kg with or, in many cases, without Advate (30 to 45 IU/kg, only to be administered if plasma FVIII levels fall below 30 IU/L during the treatment period)."*

Study Treatment RWE Study ATHN 9:
All treatment regimens were at the discretion of the patient's healthcare providers. Informed consent stated that clinical care and participation in the study is not determined based on their selection of clotting factor replacement or non-factor products. No treatment provided by the study.

6.1.5 Directions for Use (071301/SHP 677-304):

Vonvendi is provided as lyophilized powder in single use vials containing nominally 650-1300 international units for intravenous use.

Advate is provided as lyophilized powder in single use vials containing nominally 250, 500, 1000, 1500, 2000, 3000 or 4000 IU for intravenous use.

6.1.6 Sites and Centers
071301's subset included in this analysis conducted at 5 sites in 3 countries (Italy, Russia, and Spain). SHP 677-304's subset included in this analysis conducted at 4 sites in 4 countries (Italy, Russia, Spain, and US).

RWE Study ATHN 9's included in this analysis was conducted at 6 districts within ATHN in the US.

6.1.7 Surveillance/Monitoring

Table 12 Schedule of Study Procedures and Assessments for Prior OD Patients 071301

Procedures/ Assessments	Screening Visit	Baseline Visit (PK-assessment visit)			Prophylaxis Initiation Visit	Interval/Follow-Up Study Visits					PK Assessment at Study Completion			Termination Visit
		Pre-infusion[g]	Infusion	Post-infusion[g]		1 month ± 1 week	2 month ± 1 week	3 month ± 2 weeks	6 month ± 2 weeks	9 month ± 2 weeks	Pre-infusion[g]	Infusion	Post-infusion[g]	Conducted at the 96 hour postinfusion PK Assessment
											12 month ± 2 weeks			
Informed Consent [a]	X													
Eligibility Criteria	X													
Medical History[b]	X													
Concomitant Medications[c]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Non-drug Therapies[c]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical Exam	X	X			X	X	X	X	X	X	X			X
Adverse Events		X	X	X	X	X	X	X	X	X	X	X	X	X
Bleeding Episodes and Treatment and Hemostatic Efficacy	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratories	X	X		X	X[h]	X	X	X	X	X	X		X	X
Vital Signs[d]	X	X		X	X	X	X	X	X	X	X		X	X
ECG	X								X					X
IP Treatment[e]			X		X	X	X	X	X	X		X		
IP Consumption / Treatment Compliance						X	X	X	X	X				
Subject Diary					X	X	X	X	X	X				
HRQoL	X[f]								X					X

*Source: 071301 protocol page 114

Table 13 Schedule of Study Procedures and Assessments for Switch Patients 071301

Procedures/ Assessments	Screening Visit	Prophylaxis Initiation Visit	PK Assessment (at prophylaxis dose #5-6)			Interval/Follow-Up Study Visits					PK Assessment at Study Completion			Termination Visit
			Pre-infusion[g]	Infusion	Post-infusion[g]	1 month ± 1 week	2 month ± 1 week	3 month ± 2 weeks	6 month ± 2 weeks	9 month ± 2 weeks	Pre-infusion[g]	Infusion	Post-infusion[g]	Conducted at the 96 hour postinfusion PK Assessment
											12 month± 2 weeks			
Informed Consent [a]	X													
Eligibility Criteria	X													
Medical History[b]	X													
Concomitant Medications[c]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Non-drug Therapies[c]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical Exam	X	X	X			X	X	X	X	X	X			X
Adverse Events		X	X	X	X	X	X	X	X	X	X	X	X	X
Bleeding Episodes and Treatment and Hemostatic Efficacy	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratories	X	X	X		X	X	X	X	X	X	X		X	X
Vital Signs[d]	X	X	X		X	X	X	X	X	X	X		X	X
ECG	X								X					X
IP Treatment[e]		X		X		X	X	X	X	X		X		
IP Consumption / Treatment Compliance						X	X	X	X	X				
Subject Diary		X				X	X	X	X	X				
HRQoL	X[f]								X					X

*Source: 071301 protocol page 116

Table 14 Schedule of Study Procedures and Assessments for Cohort 1 Patients SHP 677-304

Procedures/ Assessments	Screening Visit [a]	Prophylaxis Initiation Visit [a]	Follow-Up Study Visits							End of Study Visit
			1 month (±1) week	2 months (±1) week	3 months (±2) weeks	6 months (±2) weeks	9 months (±2) weeks	12 months (±2) weeks	Every 3 months (±2) weeks	
Informed Consent [b]	X									See Table 9
Eligibility Criteria	X									
Medical History	*									
Physical Exam	*	X	X	X	X	X	X	X	X	
Vital Signs [c]	*	X	X	X	X	X	X	X	X	
IP Treatment [d]		X	X	X	X	X	X	X	X	
Concomitant Medications and Nondrug Therapies [e]	*	X	X	X	X	X	X	X	X	
Adverse Events [e]	*	X	X	X	X	X	X	X	X	
Bleeding Episodes and Treatment [e]	*	X	X	X	X	X	X	X	X	
Investigator Assessment of Hemostatic Efficacy [e]	*	X	X	X	X	X	X	X		
IR Determination [d]		X	X	X	X	X	X	X		
Laboratories (See Table 6)	*	X	X	X	X	X	X	X	X	
ECG	*					X		X		
Subject Diary [f]	X	X	X	X	X	X	X	X	X	
PROs (HRQoL, TSQM-9 etc.)		X				X		X		

*Source: SHP 677-304 protocol page 32

Table 15 Schedule of Study Procedures and Assessments for Cohort 4 Patients SHP 677-304

Procedures/ Assessments	Screening Visit	PK Assessment [h]			Prophylaxis Initiation Visit[i]	Follow-Up Study Visits							End of Study Visit
		Pre-infusion [g]	Infusion	Post-infusion [g]		1 month (±1) week	2 months (±1) week	3 months (±2) weeks	6 months (±2) weeks	9 months (±2) weeks	12 months (±2) weeks	Every 3 months (±2) weeks	
Informed Consent [a]	X												See Table 10
Eligibility Criteria	X												
Medical History [b]	X												
Physical Exam	X	X			X	X	X	X	X	X	X	X	
Vital Signs [c]	X	X		X	X	X	X	X	X	X	X	X	
IP Treatment [d]			X		X	X	X	X	X	X	X	X	
Concomitant Medications and Non-drug Therapies [e]	X	X	X	X	X	X	X	X	X	X	X	X	
Adverse Events [e]		X	X	X	X	X	X	X	X	X	X	X	
Bleeding Episodes and Treatment [e]	X	X	X	X	X	X	X	X	X	X	X	X	
Investigator Assessment of Hemostatic Efficacy [e]	X	X	X	X	X	X	X	X	X	X	X		
Laboratories (See Table 7)	X	X		X		X	X	X	X	X	X	X	
IR Determination					X	X	X	X	X	X	X		
ECG	X								X		X		
Subject Diary [f]	X				X	X	X	X	X	X	X	X	
PROs (HRQoL, TSQM-9, etc.)					X[j]				X		X		

*Source: SHP 677-304 protocol page 34

Table 16 RWE Study ATHN 9 assessments:

Visit	Assessments	Lab Assessments
Baseline	1. Informed consent 2. Co-enrollment in the ATHNdataset 3. Review of medical/bleeding disorder history 4. Review of bleeding events and treatment plan 5. Completion of ISTH BAT. PBAC 6. Completion of PROs (PROMIS and V-WIQ)	1. Baseline diagnostic VWD testing 2. Lab assessments, including VWF inhibitor testing
6 months	1. Review of medical/bleeding disorder history 2. Review of bleeding events and treatment plan 3. Completion of PBAC, if applicable	
12 months	1. Review of medical/bleeding disorder history 2. Review of bleeding events and treatment plan 3. Completion of PBAC, if applicable 4. Completion of PROs (PROMIS Profile and V-WIQ)	Laboratory assessments, as applicable
18 months	1. Review of medical/bleeding disorder history 2. Review of bleeding events and treatment plan 3. Completion of PBAC, if applicable	
24 months	1. Review of medical/bleeding disorder history 2. Review of bleeding events and treatment plan 3. Completion of ISTH BAT and PBAC if applicable 4. Completion of PROs (PROMIS Profile and V-WIQ)	Laboratory assessments, as applicable
Ad Hoc	1. AE reconciliation 2. Review of medical/bleeding disorder history 3. Review of bleeding events and treatment plan	VWF inhibitor testing if inhibitor development is suspected

*Source: Reviewer summary from ATHN 9 protocol pages 12-13.

Lab Assessments RWE Study ATHN 9:

- VWF inhibitor testing at baseline, at time of suspected inhibitor development, and within 10 days for previously elevated results.
- FVIII Activity.
- VWF Antigen.
- VWF:(b) (4) Activity Assay.
- Genetic sequence analysis of VWF .

6.1.8 Endpoints and Criteria for Study Success

Primary Endpoint:

Primary endpoint (071301):
sABR for BEs during prophylactic treatment with Vonvendi compared to the patients' historical sABR during OD treatment or prior prophylaxis with pd-VWD.

Primary endpoint (RWE study ATHN 9):
Number of AE's related to various VWF treatment regimens in adult and pediatric patients with clinically severe congenital VWD. Safety was measured by the number of reported events defined by the EUHASS program.

Secondary Endpoints (071301):

- Categorized spontaneous ABR defined as 0, 1-2, 3-5, or >5 BEs during the prophylaxis.
- Total number of infusions and the average number of infusions per week during prophylaxis.
- Total weight adjusted consumption of Vonvendi during prophylactic treatment.
- sABR by location of bleeding while on prophylactic treatment with Vonvendi.
- ABR percent reduction success for OD patients defined as at least 25% reduction of sABR during prophylaxis relative to the patient's own historical ABR during OD treatment.
- ABR preservation success for pdVWF switch patients defined as achieving an sABR no greater than the patient's own historical ABR during prophylactic treatment with pdVWF.

Secondary endpoints (RWE study ATHN 9):

- Collection of (b) (4) based VWF activity assay, and genetic sequence analysis of VWF coding regions and adjacent non-coding regions.
- Establishment of the platform for patients with congenital severe VWD.
- Clinical outcomes of prophylaxis in patients over 6-month time periods.
- Measurement of individual bleeding components, calculated per ISTH Bleed Assessment Tool (ISTH BAT), and if applicable, the Pictorial Bleeding Assessment Chart (PBAC).
- Health care utilization: measured by number and type of visit and hospitalizations per year.
- Health-related QOL (Quality of Life): measured annually by the PROMIS Profile and V-WIQ.

Safety Endpoints:

Safety Endpoints (071301):

- Adverse events (AEs): incidence, severity, causality.
- Thromboembolic events.
- Hypersensitivity reactions.
- Development of neutralizing antibodies to VWF and FVIII.
- Development of total binding antibodies to VWF and FVIII.
- Development of binding antibodies to Chinese hamster ovary (CHO) proteins, mouse immunoglobulin G (IgG) and rFurin.
- Clinically significant changes in vital signs and clinical laboratory parameters relative to baseline.

Exploratory Endpoints:

Exploratory Endpoints (071301):

Efficacy of Treatment of BEs:

- Number of infusions of Vonvendi and Advate per spontaneous BE.
- Number of infusions of Vonvendi and Advate per traumatic BE.
- Weight-adjusted consumption of Vonvendi and Advate per spontaneous BE.
- Weight-adjusted consumption of Vonvendi and Advate per traumatic BE.
- Overall hemostatic efficacy rating at resolution of bleed.

Reviewer's Comment:

- *The endpoints for continuation study SHP 677-304 aligned with 071301 with differences including:*
  - *071301 had additional secondary endpoints of sABR reduction success in OD patients and preservation in Switch patients.*
  - *SHP 677-304 had additional secondary endpoints of time to first bleeding event on prophylaxis and transfusion free maintenance of hemoglobin and ferritin.*
- *There were no exploratory endpoints for RWE study ATHN 9.*

Table 17 Hemostatic Efficacy Rating for BE's in 071301/SHP 677-304

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

*Source: 071301 (page 74) and SHP 677-304 (pages 97-98) protocols

Efficacy of treatment of perioperative bleeding management, if surgery is required:

- Intraoperative actual versus predicted blood loss at completion of surgery.
- Intraoperative hemostatic efficacy score at completion of surgery.
- Overall assessment of hemostatic efficacy 24 hours after last perioperative infusion of Vonvendi or at post-op day 14, whichever occurs first.
- Daily intra- and postoperative weight-adjusted dose of Vonvendi +/- Advate through post-op day 14.

Table 18 Hemostatic Efficacy Rating in Perioperative Setting in 071301/SHP 677-304

RATING	Overall Assessment of Hemostatic Efficacy 24 Hours After the Last Perioperative rVWF Infusion
Excellent (1)	Intra- and post-operative hemostasis achieved with vonicog alfa with or without ADVATE was as good or better than that expected for the type of surgical procedure performed in a hemostatically normal subject
Good (2)	Intra- and post-operative hemostasis achieved with vonicog alfa with or without ADVATE was probably as good as that expected for the type of surgical procedure performed in a hemostatically normal subject
Moderate (3)	Intra- and post-operative hemostasis with vonicog alfa with or without ADVATE was clearly less than optimal for the type of procedure performed but was maintained without the need to change the vonicog alfa concentrate
None (4)	Subject experienced uncontrolled bleeding that was the result of inadequate therapeutic response despite proper dosing, necessitating a change of vonicog alfa concentrate

*Sources: 071031 (page 75) and SHP 677-304 (page 98) protocols

Health related Quality of Life (071301 and SHP 677-304):
HRQoL using Questionnaires for the Assessments: EQ-5D, SF-36 and V-WIQ.

6.1.9 Statistical Considerations & Statistical Analysis Plan

Please see statistical review memo.

6.1.10 Study Population and Disposition

6.1.10.1 Populations Enrolled/Analyzed (071301 and SHP 677-304):

Analysis sets were the following:

- Safety Analysis Set (SAF) consisted of patients who received at least one dose of Vonvendi including PK.
- Full Analysis Set (FAS) consisted of all patients who received Vonvendi prophylaxis (primary analysis set).

In 071301, a total of approximately 22 eligible adult patients were planned for enrollment with ≥8 patients in each of the 2 groups (Prior OD and Switch) and with a total of at least 5 patients with Type 3 VWD. There were 4 patients included in the FAS with Type 1 and Type 2 VWD: 2 prior OD patients and 2 Switch patients.

Populations Enrolled/Analyzed (RWE Study ATHN 9):

Target enrollment was at least 30 patients at up to 30 sites. At data cut off, the sample size was 11 with 10 in the subset of severe Type 1 and 2 VWD included in both FAS and SAF with mean follow up time of 1.6 years.

Table 19 Prophylaxis regimens in RWE Study ATHN 9

	6-month Follow-up	12-month Follow-up	18-month Follow-up	24-month Follow-up
Subgroup	**N=8**	**N=8**	**N=6**	**N=6**
Vonicog Alfa Dosage (IU/kg)				
Mean (SD)	53.7 (9.86)	52.0 (12.64)	52.8 (12.01)	52.8 (12.01)
Median	56.2	56.2	56.8	56.8
Min, Max	(36.6, 67.5)	(30.2, 67.5)	(30.2, 61.6)	(30.2, 61.6)
Dose Frequency per Week, n (%)				
Mean (SD)	1.9 (0.78)	1.9 (0.78)	2.3 (1.13)	1.8 (0.65)
Median	2.0	2.0	2.0	2.0
Min, Max	(1.0, 3.5)	(1.0, 3.5)	(0.5, 3.5)	(0.5, 2.3)

* Source: ATHN 9 CSR page 35

*N in table 19 is the number of patients who attended the visit at each timepoint.

Reviewer's Comment:

Prophylaxis regimen was consistent with 071301 and with the label of 50 IU/kg twice weekly at a mean dose frequency of 1.9 to 2.3 times weekly and mean dose of 52 to 53.7 IU/kg.

6.1.10.1.1 Demographics:

Please see tables in section 1.1.

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population:

All patients had multimer analysis and/or genetic testing confirming their severe VWD diagnosis and type.

6.1.10.1.3 Patient Disposition

Table 20 Patient Disposition of 071301 patients supporting prophylaxis indication expansion

Patient	Arm	VWD Type	Study Status	Analysis Set
071301-(b) (6)	OD	Type 2B	Discontinued at Day 222	FAS, SAF
071301-(b) (6)	OD	Type 1	Completed	FAS, SAF
071301-(b) (6)	OD	Type 1	Discontinued at Day 59	SAF only
071301-(b) (6)	Switch	Type 1	Discontinued at Day 155	FAS, SAF
071301-(b) (6)	Switch	Type 2A	Completed and continued in SHP 6773-304	FAS, SAF

*Source: 071301 CSR and ADSL dataset

Table 21 Duration of prophylactic treatment 071301 (FAS)

Duration	Prior OD (N = 2) n (%)	Prior Switch (N = 2) n (%)	Total (N = 4) n (%)
≥ 1 month	2 (100)	2 (100)	4 (100)
≥ 3 months	2 (100)	2 (100)	4 (100)
≥ 6 months	2 (100)	1 (50)	3 (75)
≥ 9 months	1 (50)	1 (50)	2 (50)
≥ 12 months	1 (50)	1 (50)	2 (50)

*Source: 071301 CSR

Reviewer's Comment:
- *Patient* (b) (6) *excluded from FAS as patient only received 2 days of prophylaxis treatment.*
- *Patients* (b) (6) *discontinued early due to the need for prohibited medications (steroids).*
- *The mean duration of prophylaxis for patients in FAS was 8.6 months; 6.9 months for the safety set.*
- *None of these patients received Advate during the study.*
- *Mean compliance of 84 % with prophylaxis regimens for patients with Type and Type 2 in 071301 in FAS.*

In SHP 677-304, a planned total of up to 22 adult patients transitioning from study 071301 and 7-15 newly enrolled adult and pediatric/adolescent patients on prior OD with VWF products.

Table 22 Patient disposition in SHP 677-304 supporting prophylaxis indication expansion (FAS/SAF)

Patient	Cohort	VWD Type	Study Status
(b) (6)	1 (Switch)	Type 2A	Completed
(b) (6)	4 (OD)	Type 2A	Completed
(b) (6)	4 (OD)	Type 2A	Completed
(b) (6)	4 (OD)	Type 2A	Completed

*Source: SHP 677-304 CSR and ADSL dataset

Reviewer's Comment:
- *Patient* (b) (6) *completed 071301 Switch group prior to enrollment on SHP 677-304.*
- *3 patients were on OD treatment prior to enrolling in SHP 677-304 for Vonvendi prophylaxis.*
- *In SHP 677-304, mean compliance was 100% with mean duration of 35.8 months.*

- *While the label recommends 50 IU/kg twice weekly, SHP 677-304 evaluated 50 IU/kg weekly prophylactic dosing. The justification was based on experience with pd-VWF and mean residence time (MRT) of Vonvendi to evaluate a wider dosing range.*

Table 23 Patient disposition in ATHN 9 supporting prophylaxis indication expansion (FAS/SAF)

# Patients	Type	Study Status
1	Type 1	Lost to follow up
8	Type 2A	5 completed 2 remain on study 1 discontinued
1	Type 2B	Completed

* Source: ATHN 9 CSR and datasets

6.1.11 Efficacy Analyses

6.1.11.1 Analyses of Primary Endpoint(s)

Primary endpoint (071301):
sABR during prophylactic treatment with Vonvendi and the patients' historical sABR during on-demand treatment. sABR is the number of spontaneous BEs (treated and untreated) divided by the observation period in years. The historic control period ABR is the number of spontaneous (treated and untreated) reported in the 12 months prior to the first dose of Vonvendi. ABR is the number of spontaneous and traumatic bleeds (treated and untreated) divided by the observation period in years. The on-study observation period (years) is calculated as the earlier of the date of Month 12 visit or date of termination from study – date of first dose + 1 / 365.2425. The historic control period ABR is calculated as the number of spontaneous and traumatic BEs (treated and untreated) reported in 12 months prior to the first dose of Vonvendi.

Reviewer's Comment:
While sABR was the primary endpoint, this review does include analysis of total ABR (spontaneous and traumatic) discussed in this section 6.1.11.1 below.

Total ABR analysis in patients with severe Type 1 and Type 2 VWD (071301):
- Prior OD group (N =2): Both patients in prior OD group had a 100% decrease from historical to on-study ABR from 3.5 to 0.
- Switch group (N=2): There was an increase in bleeds on study due to 1 minor, non-treated, skin BE secondary to injury.

Table 24 Treated and Untreated ABR (spontaneous and traumatic) in 071301 FAS (N=4)

	OD N = 2	Switch N = 2	Total N = 4
Historic			
Mean	3.5	0	1.8
Median	3.5	0	1.5
Min, Max	3, 4	0, 0	0, 4
On study			
Mean	0	1.6	0.8
Median	0	1.6	0
Min, Max	0, 0	0, 3.2	0, 3.2

* Source: 071301 ADBE dataset and table 2.1.3.1.A in integrated CSR

Table 2518 Treated ABR (spontaneous and traumatic) in 071301 FAS (N =4)

	OD N = 2	Switch N = 2	Total N = 4
Historic			
Mean	3	0	1.5
Median	3	0	1.5
Min, Max	3, 3	0, 0	0, 3
On study			
Mean	0	0	0
Median	0	0	0
Min, Max	0, 0	0, 0	0, 0

*Source: 071301 ADBE dataset and table 2.1.6.2.A in integrated CSR

Reviewer's Comment:

- *Patient* (b) (6) *had one minor skin bleed secondary to injury on study that didn't require treatment.*
- *There were no other bleeds on study, spontaneous or traumatic. No bleeds were treated on study.*
- *For study 071301, the 2 patients in the OD group didn't have significant historic sABR. The inclusion criteria for OD mandated that patients had ≥ 3 spontaneous bleeds during the 12 months prior to enrollment. Both had 3 historic treated spontaneous bleeds, just meeting that inclusion requirement.*
- *Subjects in the prophylaxis group were well controlled pre-study. When subjects with low ABR are included in the trial, it is difficult to assess the treatment effect of the product because it may well be that these patients were not prone to excess bleeding and no change in (the switch group) may be the result of the underlying phenotype and this is particularly challenging to interpret in a single arm study. However, the data does support that Vonvendi prophylaxis is efficacious at preventing bleeding.*
- *This demonstrates that prophylaxis with Vonvendi was efficacious across all bleeding sites assessed (joint, mucosal, oral, GI, muscle, and other) for both spontaneous and traumatic BE's. There were no females in the FAS for 701301 in patients with Type 1 and 2 so menstrual bleeding not assessed. Per the CSR of 071301, which included Type 3 patients not included in this analysis, there were 11 female patients, 6 with child-bearing potential. There was 1 subject (071301-*(b) (6)*) with 5 treated BE's that were genital tract bleeding. On prior OD therapy, the patient had 1 episode of menorrhagia historically. On study, she had 1 severe episode of "other" bleeding documented as "bleeding menses", 2 episodes of moderate menorrhagia, and 2 episodes of moderate menstrual bleeding. Each required 1-2 infusions of Vonvendi: all with excellent or good hemostatic efficacy ratings. She received 1 infusion of Advate for 4 of these 5 BE's.*

Spontaneous Annualized bleeding rate (sABR) analysis in patients with severe Type 1 and Type 2 VWD:

- Prior OD group (N =2): Both patients in prior OD group had a 100% decrease from historical to on-study sABR from 3.5 to 0.
- Switch group (N=2): Both patients maintained and sABR of 0 in both the historical and on-study periods.

Table 26 Treated and Untreated sABR in 071301 FAS (N=4)

	OD N = 2	Switch N = 2	Total N = 4
Historic			
Mean	3.5	0	1.8
Median	3.5	0	1.5
Min, Max	3, 4	0, 0	0, 4
On study			
Mean	0	0	0
Median	0	0	0
Min, Max	0, 0	0, 0	0, 0

*Source: 071301 ADBE dataset and table 2.1.6.1.A in integrated CSR

Table 19 27 Treated sABR in 071301 FAS (N=4)

	OD N = 2	Switch N = 2	Total N = 4
Historic			
Mean	3	0	1.5
Median	3	0	1.5
Min, Max	3, 3	0, 0	0, 3
On study			
Mean	0	0	0
Median	0	0	0
Min, Max	0, 0	0, 0	0, 0

*Source: 071301 ADBE dataset and table 2.1.4.1.A in integrated CSR

Reviewer's Comment:

- *All 4 patients in 071301 achieved success, defined as > 25% reduction in sABR.*
- *Both OD patients had 3 historic treated spontaneous BE's.*
- *All historic bleeds were mucosal (4 gastric and 3 nasal). The on study sABR for each location was < 1.*
- *No spontaneous bleeds were treated on study.*
- *In SHP 677-304, all 4 patients achieved success with ≥ 25% reduction in sABR:*
    - *For total ABR (spontaneous and traumatic), the Switch patient in Cohort 1 had 0 historical bleeds and 1 minor GI bleed secondary to injury on study that required treatment. The 3 prior OD patients had significant reduction in ABR from a mean of 14.3 (12.3 treated) to 4 (3.4 treated) during first 12 months of study and to 3.1 (2 treated) until the cutoff date.*
    - *For sABR, the Switch patients in Cohort 1 had 0 sABR, both historical and on study. The 3 prior OD patients had a mean historical sABR of 10 (9.3 treated) that decreased to 2.4 (2.4 treated) the first 12 months of study and to 2.3 (1.5 treated) until the cutoff date.*
    - *Historically, there were a total of 28 treated BE's including 14 mucosal (10 oral and 4 nasal), 8 joint, 2 menstrual, 3 GI, and 1 other. On first 12 months of study, there were 8 treated BE's including 2 mucosal (oral), 1 joint, 1 muscle, 2 GI, 1 menstrual, and 1 other. Through data cutoff date, there were 14 treated BE including 5 mucosal (4 oral and 1 nasal), 2 joint, 1 muscle, 2 GI, 3 menstrual, and 1 other.*

Primary Endpoint (RWE Study ATHN 9):

The number of Adverse events (AEs) related to various VWF treatment regimens in adult and pediatric patients with clinically severe congenital VWD. Safety was measured by the number of reported events defined by the European Haemophilia Safety Surveillance (EUHASS) program. In addition, although not specifically defined by EUHASS, treatment-emergent side effects of therapy will be included as reportable events.

a. Hypersensitivity/Allergic reactions
b. Thrombotic events
c. VW Factor inhibitor development
d. Treatment-emergent side effects of therapy
e. Transfusion-transmitted infections
f. Malignancy
g. Cardiovascular events
h. Neurological

One patient in ATHN 9 had 9 AE's: 1 thrombosis, 2 acute respiratory failure, 2 metabolic encephalopathies, and 1 acute exacerbation of COPD, anemia, closed fracture of humerus, and GI hemorrhage.

Reviewer's Comment:
The 9 AE's reported were in 1 patient with multiple co-morbidities. The thrombosis was reported during a hospitalization with multiple complications and risk factors with the last dose of Vonvendi 9 days prior. Based on timing of thrombosis and last dose of Vonvendi, this reviewer concurs that the thrombosis was not related to Vonvendi and most likely related to risk factors associated with hospitalization.

6.1.11.2 Analyses of Secondary Endpoints

Secondary Endpoints (071301):
Categorized sABR defined as 0, 1-2, 3-5, or >5 BEs during the prophylactic treatment with Vonvendi:
All patients had 0 sABR on study 071301.

Reviewer's Comment:
In SHP 677-304:
- *The Switch Patient had 0 sABR throughout the study.*
- *1 OD patient within first 12 months and 2 OD patients through data cutoff had >0 to ≤2 bleeds/year.*
- *2 OD patients within first 12 months and 1 OD patient through data cutoff had >2 to ≤5 bleeds/year*.

Total number of infusions, average number of infusions, and total weight adjusted consumption of Vonvendi per week during prophylactic treatment:

In 071301, there were 196 prophylactic Vonvendi infusions with a mean of 49 (median 49; range 31-67) per patient at a mean dose of 58 IU/kg (median 52; range 51-79) and mean number of 1.5 (median 1.6; range 0.8-2) infusions per week over a mean of 8.6 months.

Reviewer's comment:
- *No on-demand usage of Vonvendi or Advate on study 071301 in Type 1 and Type 2 VWD patients.*
- *In SHP 677-304, there were 691 prophylactic Vonvendi infusions with a mean of 173 (median 160; 154-217) per patient at a mean dose of 59 IU/kg (median 53; range 48-80) and mean number of weekly infusions of 1 (median 1; range 1-1) over a mean of 35.8 months.*

sABR by location of bleeding (Gastrointestinal [GI], epistaxis, joint bleeding, menorrhagia, oral and other mucosa, muscle and soft tissue, etc.) while on prophylactic treatment with Vonvendi:

This was not assessed in 071301 as there was no spontaneous bleeding to assess.

Reviewer's Comment:
- *In SHP 677-304, treated sABR for was < 1 for mucosal, muscle, joint, GI, menstrual, and other bleeding and was 0 for CNS, skin, soft tissue, and body cavity*.
- *sABR data by location demonstrates Vonvendi prophylaxis is effective across all locations.*

ABR percent reduction success for OD patients defined as at least 25% reduction of ABR for spontaneous BEs during Vonvendi prophylaxis relative to the patient's own historical ABR during on-demand treatment:

This was achieved in all Type 1 and Type 2 OD patients in Study 071301.

ABR preservation success for pdVWF switch patients defined as achieving an sABR for during Vonvendi prophylaxis that is no greater than the patient's own historical ABR during prophylactic treatment with pdVWF:

This was achieved in all Type 1 and Type 2 Switch patients in Study 071301.

Reviewer's Comment:
Additional secondary endpoints of SHP 677-304 included categorized weekly number of infusions defined as 1, 2 or = 3 during prophylactic treatment with Vonvendi and time to first bleeding event under each prophylaxis regimen:

- *All 4 patients received started with once weekly infusions. The patient in cohort 1 stayed on 80 IU/kg weekly regimen throughout the study. All patients in cohort 4 had dose adjustments:*
  - *Patient* (b) (6) *switched from 50 IU/kg weekly to twice weekly at day 805.*
  - *Patient* (b) (6) *switched to 50 IU/kg weekly to every 4 days on day 297 and then back to weekly on day 365.*
  - *Patient* (b) (6) *switched from 50 IU/kg weekly to twice weekly at day 717.*
  - *The median time to first spontaneous bleeding event (excluding 1 subject with 0 BE's) was 110 days (9, 137). All patients were on once weekly prophylaxis at the time of their first BE.*

Secondary endpoints (RWE study ATHN 9):

Collection of laboratory data consisting of a standardized diagnostic battery using an (b) (4) based VWF activity assay, and genetic sequence analysis of VWF coding regions and adjacent non-coding regions:

All patients had baseline (b) (4) based VWF activity assay and genetic testing done.

Establishment of the platform for patients with congenital severe VWD:

Optional sub-study modules (SSMs) were incorporated to support the study's objectives and serve as a platform for sub-studies in cohorts of patients with VWD.

Clinical outcomes of prophylaxis in patients over 6-month time periods:

Table 28 Treated BE's in ATHN 9

Bleed Cause	**Number of patients (N = 10) n (%)**	**Number of Treated BE's (N = 22) n (%)**
Spontaneous	4 (40)	8 (36)
Unknown	2 (20)	12 (54)
Activity/exercise without known trauma	1(10)	1 (5)
Trauma injury	1 (10)	1 (5)
Bleed Location		
GI	3 (30)	18 (82)
Joint	2 (20)	2 (9)
Head – extracranial	1 (10)	1 (4)
Oral/Nasal	1 (10)	1 (4)

*Source: ATHN 9 CSR and ADBE dataset
*Bleed locations Genitourinary, head – intracranial, tissue, and other all had 0 BE's reported.

Mean ABR ranged from 1 to 4.5: 1 at 6 months (N=9), 1.3 at 12 months (N=9), 1 at 18 months (N=7), and 4.5 at 24 months (N = 7).

Mean treated ABR ranged from 0.4 to 4.1: 0.4 at 6 months (N=9), 0.2 at 12 months (N=9), 1 at 18 months (N=7), and 4.1 at 24 months(N=7).

Reviewer's Comment:

- *Mean ABR values in ATHN 9 for the 24-month follow-up visit were higher than the previous timepoints due to one patient experiencing a high number of bleeds during that time.*
- *2 patients in ATHN 9 didn't start prophylaxis with Vonvendi until after enrollment. One started between 12 and 18 months and one had only 3 exposure dates documented during the 24-month period.*

Measurement of individual bleeding components, calculated per ISTH Bleed Assessment Tool (ISTH BAT), and if applicable, the Pictorial Bleeding Assessment Chart (PBAC):

- ISTH BAT scores remained unchanged; 12 at baseline (N=8) and 11 at 24 months (N=5).
- PBAC assessments were minimal; 2 patients at baseline and 1 at 24 months.

Reviewer's Comment:

- *The ISTH BAT comprises 14 categories for assessing bleeding symptoms retrospectively. Each of the 14 variables is scored from 0-4. A composite of all the variables has a score of 0 to 56; 0 is little to no bleeding symptoms or treatment needed to 56 meaning significant bleeding symptoms/treatment needed. The questionnaire was collected and entered into the ATHN database by the treating provider.*
- *The PBAC is a pictorial assessment of menorrhagia with > 100 suggesting significant blood loss.*
- *Both assessments with low numbers and difficult to assess meaningful outcomes.*

Health-related QOL (Quality of Life): measured annually by the PROMIS Profile and V-WIQ:

- PROMIS remained unchanged throughout study (baseline N=9 and 24 months N=5):
    - Physical Function: 43 at baseline and 41 at 24 months
    - Anxiety: 51 at baseline and 49 at 24 months
    - Depression: 47 at baseline and 47 at 24 months
    - Fatigue: 52 at baseline and 50 at 24 months
    - Sleep Disturbance: 54 at baseline and 55 at 24 months
    - Social Roles: 49 at baseline and 49 at 24 months
    - Pain: 56 at baseline and 60 at 24 months
- V-WIQ scores remained steady or decreased throughout the study. N = 9 at baseline and 5 at 24 months.

Reviewer's Comment:

- *PROMIS is an adult assessment of health related QOL, including physical and mental health assessing 7 domains of depression, anxiety, physical function, pain interference, fatigue, sleep disturbance, and ability to participate in social roles and activities.*
- *V-WIQ assesses the physical and emotional well-being of adults with VWD by assessing 16 questions.*
- *Both assessments with lower numbers and difficult to assess meaningful outcomes.*

6.1.11.3 Subpopulation Analyses

NA

6.1.11.4 Dropouts and/or Discontinuations

2 patients with Type 1 and 1 patient with Type 2B VWD in 071301 discontinued before the end of study. All patients completed SHP 677-304. In ATHN 9, 1 patient was lost to follow up (at 0.4 years) and 1 discontinued (at 1.8 years).

Reviewer's comment

- *For 071301, the ABR of the dropouts and discontinuations was calculated up to the last visit for FAS.*
- *Patient* (b) (6) *received only 2 doses of Vonvendi and therefore was not included in the efficacy analysis.*
- *Patients* (b) (6) *discontinued due to the need for steroids, which was a prohibited medication.*

6.1.11.5 Exploratory and Post Hoc Analyses

Exploratory Endpoints (071301):

Efficacy of Treatment of BEs including:

- Number of infusions of Vonvendi and Advate (rFVIII) per spontaneous BE
- Number of infusions of Vonvendi and Advate (rFVIII) per traumatic BE
- Weight-adjusted consumption of Vonvendi and Advate (rFVIII) per spontaneous BE
- Weight-adjusted consumption of Vonvendi and Advate (rFVIII) per traumatic BE
- Overall hemostatic efficacy rating at resolution of bleed

There were no treated bleeds on 071301 and no Advate used in 071301 so these were not assessed.

Reviewer's Comment:

- *For study 071301, the 2 patients in the OD group didn't have significant historic sABR. The inclusion criteria for OD mandated that patients had ≥ 3 spontaneous bleeds during the 12 months prior to enrollment. Both had 3 historic treated spontaneous bleeds, just meeting that inclusion requirement.*
- *The 2 patients in the Switch group were well controlled pre-study with 0 spontaneous BE's historically.*

Reviewer's Comment:
In SHP 677-304:

- *Mean of 2.2 Vonvendi (median 1; range 1-8) infusions and 1 Advate (median 1; range 1-1) infusions with weight-adjusted consumption of 48 IU/kg (median 50; range 37-61) of Vonvendi and 39 IU/kg (median 39 (37-41) of Advate per spontaneous bleed.*
- *Mean of 1.4 Vonvendi (median 1; range 1-2) infusions and 1.3 Advate (median 1; range 1-2) infusions with weight-adjusted consumption of 55 IU/kg (median 63; range 38-78) of Vonvendi and 31 IU/kg (median 37; range 9-41) of Advate per traumatic bleed.*

- *Two patients in the OD group of SHP 677-304 received at least one dose of Advate during the study:*
  - (b) (6) *with baseline Factor VIII of 31% had 4 BE's treated with Advate:*
    - *Moderate(investigator)/major (patient) mucosal gum bleed secondary to injury on day 359 treated with Vonvendi 63 IU/kg x 1 and Advate 41 IU/kg x 1 with good outcome.*
    - *Moderate, spontaneous mucosal gum and mouth bleed on day 410 treated with Vonvendi 38 IU/kg x 1 and Advate 41 IU/kg x 1 with excellent outcome.*
    - *Major right knee joint/muscle bleed secondary to injury on day 747 treated Vonvendi x 2 at total dose of 127 IU/kg and Advate x 2 at total dose of 73 IU/kg with good outcome.*
    - *Major (investigator), moderate (patient) spontaneous right ankle and knee joint bleeds on day 842 with Vonvendi x 2 at total dose of 90 IU/kg and Advate 37 IU/kg x 1 with excellent outcome.*
  - (b) (6) *with baseline Factor VIII of 19% had 1 mild (investigator)/moderate (patient) skin/soft tissue bleed due to injury at day 267 treated with Vonvendi x 2 at total dose of 76 IU/kg and Advate 9 IU/kg x 1 with excellent outcome.*
- *In SHP 677-304, there were 28 total BE's in 4 patients: 19 spontaneous, 8 secondary to injury and 1 missing cause. 18 BE's were treated; 13 (72%) spontaneous and 5 (28%) secondary to injury; 16 (89%) with excellent outcome and 2 (11%) with good outcome.*

Efficacy of treatment of perioperative bleeding management, if surgery is required:

- Intraoperative actual versus predicted blood loss at completion of surgery.
- Intraoperative hemostatic efficacy of excellent, good, moderate or none at completion of surgery.
- Overall assessment of hemostatic efficacy 24 hours after the last perioperative infusion of Vonvendi.
- Daily intra- and postoperative weight-adjusted dose of Vonvendi +/- Advate through postop day 14.

No Type 1/Type 2 patients had surgery in 071301 so above not assessed.

Reviewer's Comment:
In SHP 677-304:

- (b) (6) *had minor surgery of sphincterotomy with moderate overall hemostatic efficacy. No intraop or blood loss assessments reported. 1 dose of Vonvendi (78 IU/kg) given one day prior to surgery and pre-op on day of surgery (59 IU/kg) then 2 post-op doses given on day 1 at 59 IU/kg and day 14 at 84 IU/kg.*

- (b) (6) *had major surgery of ACL repair arthroscopically with excellent overall hemostatic efficacy post-op and intraop hemostatic efficacy. Predicted blood loss was 0 with actual of 25 ml. 1 dose of Vonvendi (39 IU/kg) given one day prior to surgery and pre-op on day of surgery (38 IU/kg) then post-op day 0 and 1 at 38 IU/kg then days 4, 6, 8, 10, 12, and 14 at 24-25 IU/kg.*

- (b) (6) *had minor surgery of colonoscopy without outcomes reported. 1 dose of Vonvendi (37 IU/kg) was given pre-op and 1 dose of Advate (18 IU/kg) given pre-op for the colonoscopy with baseline Factor of 19%. No post-op doses of Vonvendi or Advate given. This patient also had major surgery of repair of displaced fracture of right fibula and tibial malleolus with good overall hemostatic efficacy. 1 dose of Vonvendi (49 IU/kg) given one day prior to surgery and pre-op on day of surgery (25 IU/kg) then daily post-op at 25 IU/kg starting day 1 through day 16. No intraoperative or blood loss assessments reported.*

- *It is difficult to draw meaningful conclusions with the small number of procedures and limited data regarding peri-operative management in these patients. Within Study 071101 that evaluated peri-operative management in adults with Vonvendi, 15 patients had surgeries with 10 major and 1 minor. Overall hemostatic efficacy was excellent for 60% of surgeries and good for 40%. Intraoperative hemostatic efficacy was excellent for 73% of surgeries and good for 27%.*

Patients' self-assessments, on the 5-level EuroQol-5-Dimension (EQ-5D-5L) of their overall health status:

Assessments used were EQ-5D, SF-36, and V-WIQ. All are validated tools. Patients were given a diary to document bleeding events, Vonvendi, and Advate infusions, other concomitant medications, and treatment response. Patients' HR QoL in the assessed dimensions at each assessed timepoint were collected. HRU was also assessed including hospitalizations, emergency room visits, and doctor's office visits. Number of days missed from school and work was assessed. Finally, treatment satisfaction was also assessed in adults including effectiveness, convenience, and global satisfaction.

Because EQ-5D was only applicable starting with Protocol Amendment 6 and therefore, some patients may not have data from all timepoints. There is no baseline data for OD patients due to this. For the Switch group, general health appeared to be moderate from baseline through study termination. There was a trend toward increased mental component summary in SF-36 overall in OD and Switch patients. For V-WIQ, there was low overall impact of VWD at baseline in both OD and Switch patients. There was a potential trend toward reduced impact of VWD at end of study. For all assessments, statistical significance of change from baseline was not tested with descriptive statistical analysis performed at each assessed timepoint. There was low HRU overall.

Reviewer's Comment:

- *EQ-5D measures mobility, self-care, usual activities, pain/discomfort, and anxiety/depression.*
- *SF-36 measures physical, emotional, and social functioning. It examines physical functioning, role limitations due to physical problems, bodily pain, general health, vitality, and social functioning, role limitations due to emotional problems and mental health.*
- *V-WIQ assesses the physical and emotional well-being of adults with VWD by assessing 16 questions.*

- *Similar results were seen in SHP 677-304 with no significant difference from baseline to end of study for EQ-5D, SF-36, or V-WIQ. There was 1 rollover patient from 071301 and 3 unique patients again making it difficult to draw conclusions, limiting the value of these tools to be included in the label.*
- *The patient-reported, QOL data was evaluated as part of the application review but not included in the USPI, given the limitations of QOL assessments in uncontrolled, open-label trials. As with time-to-event endpoints, interpretation of patient-reported outcomes is challenging in uncontrolled clinical trials, because it is unclear to what extent the outcomes can be ascribed to the treatment effect of studied regimen versus to underlying disease and patient characteristics.*
- *Low HRU was also seen in SHP 677-304.*

6.1.12 Safety Analyses

Safety Endpoints (071301):

- Adverse events (AEs): incidence, severity, causality
- Thromboembolic events
- Hypersensitivity reactions
- Development of neutralizing antibodies to VWF and FVIII
- Development of total binding antibodies to VWF and FVIII
- Development of binding antibodies to Chinese hamster ovary (CHO) proteins, mouse immunoglobulin G (IgG) and rFurin
- Clinically significant changes in vital signs and clinical laboratory parameters relative to baseline

Reviewer's Comment:
The safety endpoints were the same in SHP 677-304.

Safety was primary endpoint for RWE Study ATHN 9. See section 6.1.11.1 Analyses of Primary Endpoint(s).

6.1.12.1 Methods

Eight patients with Type 1 and Type 2 VWD were included in the SAF from 071301 and SHP 677-304. Safety was assessed through TEAEs, development of antibodies to VWF, FVIII, and trace proteins in the Vonvendi product; and clinical lab assessments, vital signs, and electrocardiograms (ECGs). All adverse events were either observed by the investigator or reported by the patient.

Ten patients were included in the SAF from RWE Study ATHN 9. Reportable events included allergic/hypersensitivity reactions including injection site reactions, treatment emergent side effects, transfusion-transmitted infections, inhibitor development, thromboses and cardiovascular events, malignancies, neurologic events, and deaths.

6.1.12.2 Overview of Adverse Events

There was a total of 7 TEAE's in 3 patients in 071301. Overall, the majority of TEAE's were mild in severity with 1 TEAE's in 1 patient considered severe: 1 SAE in 1 patient. None related to study drug. There was 1 TEAE of rash pruritic (local) identified as a potential hypersensitivity reaction in 1 patient which was nonserious, mild in severity, and not related to study drug. No thromboembolic, serious hypersensitivity, or anaphylaxis. No deaths or TEAE's resulting in discontinuation of study or study drug.

Reviewer's Comment:
SHP 677-304 had similar safety profile with 54 TEAE's in 3 patients. Overall, the majority of TEAE's were mild in severity with 3 TEAE's in 2 patients considered severe: 4 SAE's in 2 patients. None related to study drug. No thromboembolic, serious hypersensitivity, or anaphylactic TEAE's reported. No deaths or TEAE's resulting in discontinuation of study or study drug.

See section 6.1.11.1 analysis of primary endpoints for adverse events for RWE Study ATHN 9.

See section 8 for the integrated safety analysis.

6.1.12.3 Deaths

No deaths occurred in 071301, SHP 677-304, or RWE Study ATHN 9.

6.1.12.4 Nonfatal Serious Adverse Events

There was 1 SAE reported in 1 patient in 071301 of rheumatoid arthritis, not related to study drug.

Reviewer's Comment:
There were 4 SAE's reported in 2 patients in SHP 677-304 of post-procedural hemorrhage, pneumonia, fibula fracture, and tibia fracture. None related to study drug.

6.1.12.5 Adverse Events of Special Interest (AESI)

One TEAE in 071301 of a rash and considered potential hypersensitivity reaction. It was nonserious, mild in severity, and considered not related to study drug. This was a mild local reaction, and this reviewer concurs with the Applicant's assessment that this event was non-serious and mild, not related to study drug, and resolved with no action taken regarding the study treatment.

6.1.12.6 Clinical Test Results

The clinical laboratory testing in in 071301, SHP 677-304, and RWE Study ATHN 9 did not identify any clinically important results.

6.1.12.7 Dropouts and/or Discontinuations

No TEAE's resulting in discontinuation from treatment or study.

6.1.13 Study Summary and Conclusions

Study 071301 demonstrated that Vonvendi is safe and effective in patients with Type 1 and Type 2 VWD with 100% decrease in sABR in prior OD patients and Switch patients on prior prophylaxis with pd-VWF maintaining 0 sABR. There were no significant safety concerns in this study.

The continuation study SHP 677-304 showed similar results.

The ATHN 9 data was used as supportive evidence, and also showed that this product is safe and effective in patients with Type 1 and Type 2 VWD.

Reviewer's Comment:
RWE team consult completed by Whitney Steele, Tainya Clark, and Stephen Chang states: "The results of the real-world data (RWD)/ RWE studies (ATHN 9 and CCR-2024-200475) support the findings of the clinical studies that Vonvendi [von Willebrand factor (recombinant)] is safe and effective for the proposed indication(s). Overall ATHN 9 supported the clinical studies that found Vonvendi to be safe and effective when used as routine prophylaxis to reduce the frequency of BEs in adults with type 1 and type 2 von Willebrand disease (VWD). For these RWE studies to be used alone as evidence of safety and effectiveness, they would have required a more robust methodological approach that addressed the potential biases and confounders that are inherent in RWD. These limitations as well as the small sample sizes, absence of control groups, limited to no confirmatory statistics, and misalignments with the pivotal clinical trial population, prevent the use of the RWE studies on the label. Given these limitations, the RWE review team concludes that as stand-alone studies ATHN 9 and CCR-2024-200475 do not demonstrate the safety or effectiveness of Vonvendi [von Willebrand

factor (recombinant) and therefore should not be cited on the label. We support the removal of the text with specific references to the RWD/RWE studies from lines 510-522, 600-623 of the current labeling document (with markup).”

6.2 Indication # 2: To expand the use of Vonvendi to children (0 to <18 years of age) with VWD for on demand treatment and control of BEs and perioperative management of bleeding

Study 071102:
A Phase 3, prospective, multicenter, uncontrolled, open-label clinical study to determine the efficacy, safety, and tolerability of Vonvendi with or without Advate in the treatment and control of BEs, the efficacy and safety of Vonvendi in elective and emergency surgeries, and the pharmacokinetics (PK) of Vonvendi in children diagnosed with severe VWD. Patients could then continue onto Study SHP 677-304.

RWE Study CCR-2024-200475:
A retrospective analysis of the safety, effectiveness of surgery management with recombinant Vonvendi in children with VWD in the ATHN dataset.

6.2.1 Objectives (Primary, Secondary, etc.)

Primary:
Primary Objective (071102): To evaluate the hemostatic efficacy and safety of Vonvendi, with or without Advate, in the treatment and control of nonsurgical bleeding events in pediatric patients (<18 years of age) diagnosed with severe, hereditary VWD.

Primary Objective (CCR-2024-200475):
To describe the effectiveness and safety of Vonvendi in perioperative setting (prior, during and after surgery) for the prevention or treatment of surgical bleeding in pediatric (aged <18years) patients with VWD, across pediatric age cohorts (Aged < 6 years, ≥6 to <12 years, ≥12 to <18 years).

Secondary:
Secondary Objectives (071102):
- Elective or emergency surgery: to evaluate hemostatic efficacy after the last perioperative infusion
- To evaluate the safety of Vonvendi
- To evaluate the PK of Vonvendi

Secondary Objective (CCR-2024-200475):
- To describe demographic and clinical characteristics of pediatric patients with VWD treated with Vonvendi in the perioperative setting.
- To describe preoperative levels (baseline and post infusion) of disease markers.
- Describe the hemostatic control with Vonvendi in the perioperative and postoperative setting.

Exploratory:
Exploratory Objectives (071102):
- Health-related Quality of Life (HRQoL) variables
- Health resource use

Reviewer’s Comment:
The objectives for continuation study SHP 677-304 aligned with 071102 with differences including:
- *The primary objective for study SHP 677-304 was not pertinent to the pediatric indication.*
- *Hemostatic efficacy in OD BE’s was a primary objective in 071102 vs. secondary in SHP 677-304.*
- *Perioperative management was a secondary objective in 071102 vs. exploratory in SHP 677-304.*

- *PK and PD assessment was a secondary objective in 071102 vs. exploratory in SHP 677-304.*
- *There were no exploratory objectives in RWE Study CCR-2024-200475.*

6.2.2 Design Overview

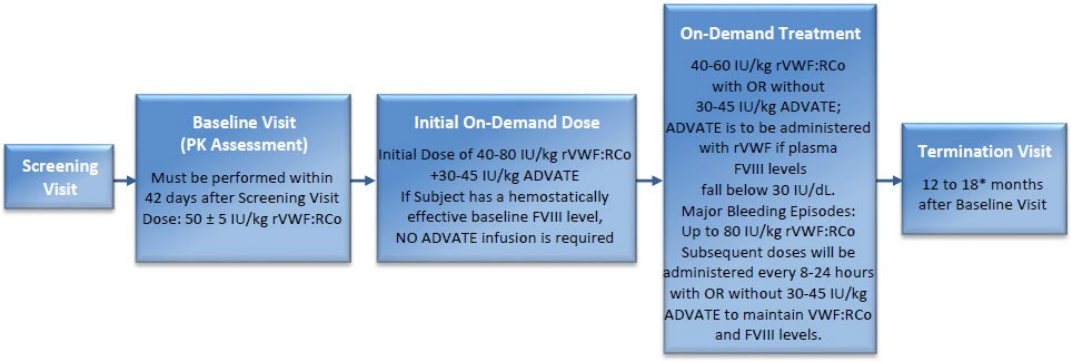
In 071102, 4 previously treated patients (PTP) were initially treated with Vonvendi before allowing enrollment of previously untreated patients (PUP).

Study 071102 consisted of 3 treatment arms: OD, elective surgery, and emergency surgery with 3 age cohorts (8 evaluable patients originally targeted in each cohort):
• Cohort 1: ≥12 to <18 years of age.
• Cohort 2: ≥6 to <12 years of age.
• Cohort 3: <6 years of age (including at least 3 patients with a diagnosis of type 3 VWD).

Reviewer's Comment:
Enrollment in subsequent cohort permitted following review of the PK results by the DMC from prior cohort.

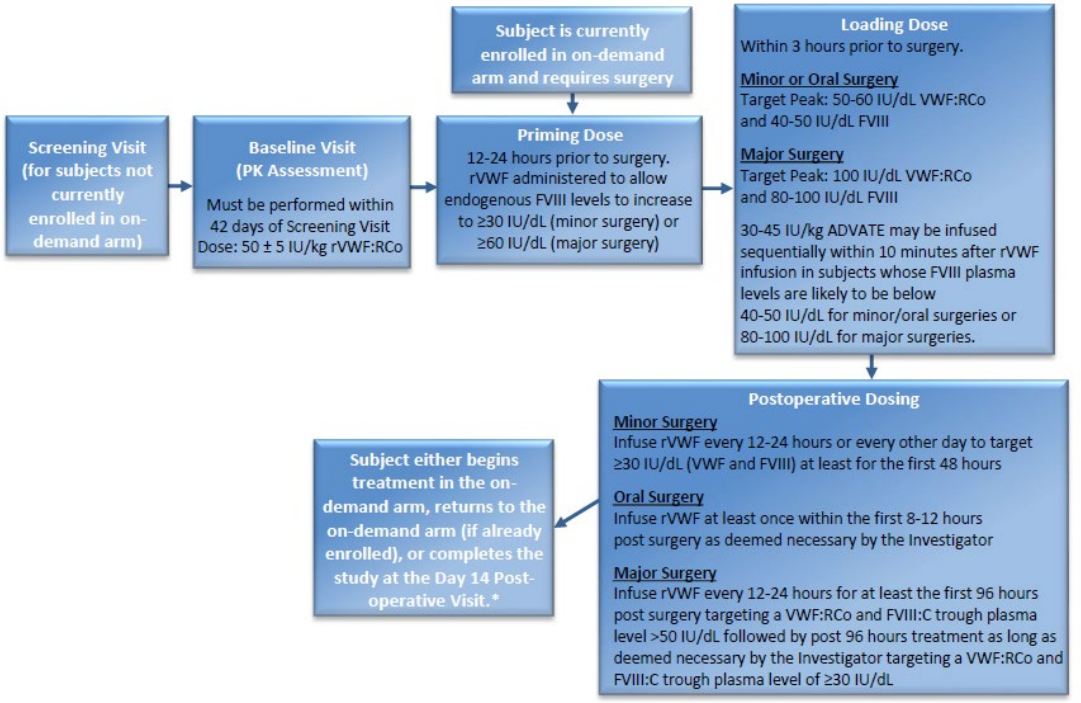
Elective and Emergency Surgical Procedures:
1. Cohort 1: ≥12 to <18 years of age: ≥ 3 patients and at least 1 major surgery in 1 patient with type 3 VWD.
2. Cohort 2: ≥6 to <12 years of age: ≥ 3 patients and at least 1 major surgery in 1 patient with type 3 VWD.
3. Cohort 3: <6 years of age: ≥ 3 patients (minimum 1 patient with type 3 VWD) with at least 1 major surgery. (At least 1 patient <2 years of age.)

Figure 5 Study Design for Takeda Clinical Study 071102; OD Treatment Arm:



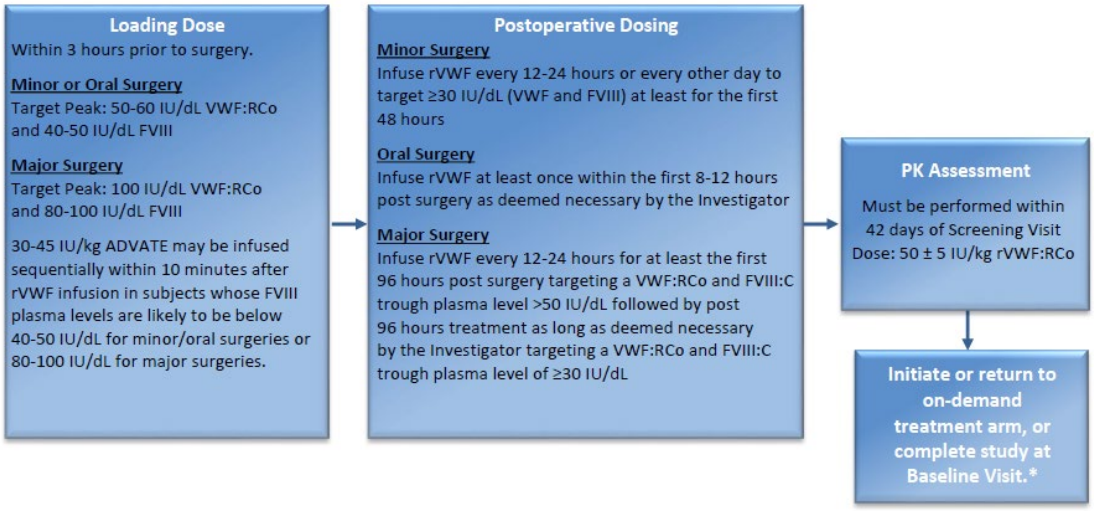
*Source: 071102 protocol page 96

Figure 6 Study Design for Takeda Clinical Study 071102; Elective Surgery Arm:



*Source: 071102 protocol page 97

Figure 7 Study Design for Takeda Clinical Study 071102; Emergency Surgery Arm:



*Source: 071102 protocol page 98

Study SHP 677-304:

For the purposes of the pediatric indication expansion, we focused on 18 patients in cohorts 3, 4, and 5:

- Cohort 3: Adolescent patients (aged 12 to <18 years) transitioning from 071102 switched from OD to once or twice weekly prophylaxis.
- Cohort 4: Newly enrolled adolescent (aged 12 to <18 years) patients switching from OD with VWF products to once or twice weekly prophylaxis.
- Cohort 5: Pediatric patients of all ages from Study 071102 who continue OD.

Reviewer's Comment:

- *1 patient from Cohort 3 and 1 patient from Cohort 4 are included in the surgery analysis as they underwent surgery while receiving prophylaxis in SHP 677-304.*
- *OD patients underwent initial PK assessment after 50 IU/kg of Vonvendi within 42 days of screening with at least 168-hour washout period. A pre-infusion blood draw within 30 minutes prior to the infusion followed by 3 post-infusion PK blood draws were performed over a 96-hour period.*
- *Patients were randomized to 3 different post-infusion blood drawing sequences:*
    - *sequence 1: 60 ±5 minutes, 24 ±2 hours, and 72 ±2 hours*
    - *sequence 2: 15 ±2 minutes, 12 ±2 hours, and 48 ±2 hours*
    - *sequence 3: 6 ±2 hours, 30 ±2 hours, and 96 ±2 hours*
- *If BE and treatment occurred during PK assessment, PK repeated after washout of at least 168 hours.*
- *Emergency surgery patients without prior PK underwent PK assessment within 42 days post screening after a washout of at least 168 hours.*

Definition of surgeries for 071102, SHP 677-304, and RWE Study CCR-2024-200475:
Major surgeries:
1. Major orthopedic surgery (joint replacement, synovectomy, arthrodesis, hardware removals such as plates or intramedullary nails, etc.).
2. Major abdominal surgery (hernioplasty, cholecystectomy, colon or small bowel resection, etc.).
3. Major gynecological surgery (myomectomy, hysterectomy, removal of endometriosis, polyps, cysts, adhesiolysis, etc.).
4. Major head and neck surgery (tonsillectomy, adenoidectomy, rhinoplasty, lymphadenectomy, thyroidectomy, parotidectomy, etc.).
5. Any intracranial, cardiovascular, or spinal surgery.
6. Any other surgery which has a significant risk of large volume blood loss or blood loss into a confined anatomical space.
7. Extraction of impacted 3rd molars is generally considered a major surgery due to the expected difficulty of surgery and expected blood loss.

Minor surgeries/surgical procedures: placement of IV access devices, removal of small skin lesions, arthroscopy, gastroscopy, colonoscopy, conization, myringotomy, etc.

Oral surgeries include extractions of fewer than 3 teeth, and teeth are non-molars without bony involvement.

Duration of Treatment:

Study 071102 OD Arm up to 20 months with extension of up to 6 months if the continuation study isn't available past 12 months. Surgery Arm up to 4 months with the opportunity to transition into the posttrial access program.

An electronic patient diary was provided to each patient at the screening visit to record the following information:
• Vonvendi infusions: date, start and stop times of infusion, number of vials used, and infusion volume for prophylaxis and treatment of BE's.
• Details of BE (site, type, severity and date/time of bleeding and response to treatment).
• Patientive hemostatic efficacy assessments.
• Untoward events/unwanted experiences.
• Concomitant medications (including immunizations) and non-drug therapies.
• Patient Reported Outcomes (PROs).

RWE Study CCR-2024-200475 was a retrospective study that collected data one year prior to procedure through 14 days post-operative period.

6.2.3 Population

Key Inclusion Criteria (071102/SHP 677-304):
1. Diagnosis of severe VWD (defined as VWF:RCo <20%).
2. Age 0 to <18 years at the time of screening.
3. For PTP's as well as for patients undergoing surgery:
- Unable to tolerate, are inadequately responsive to, or not good candidates for DDAVP (type 2B or type 3).
- ≥ 1 documented bleed requiring VWF replacement therapy during previous 12 months.
- ≥ 3 or EDs to VWF replacement therapy.

For PUP's: the patient has not received prior VWF coagulation factor replacement therapy.

Key Exclusion Criteria (071102/SHP 677-304):
1. Diagnosis of pseudo-VWD or another hereditary or acquired coagulation disorder other than VWD.
2. History or presence of a VWF inhibitor at Screening.
3. History or presence of a FVIII inhibitor with a titer ≥0.4 Bethesda units (BU) (by Nijmegen assay) or ≥0.6 BU (by Bethesda assay).
4. Documented history of a VWF:RCo half-life <6 hours.
5. Known hypersensitivity to any of the components of the study drug, such as mouse or hamster proteins.
6. Medical history of immunological disorders, excluding seasonal allergic rhinitis/ conjunctivitis/ asthma, food allergies, or animal allergies.
7. Medical history of a thromboembolic event.
8. Human immunodeficiency virus positive, with an absolute CD4 count < 200/mm3.
10. Diagnosis of significant liver disease.
11. Diagnosis of renal disease, with a serum creatinine level ≥2.5 mg/dL.
12. Immunomodulatory drug treatment other than anti-retroviral chemotherapy within 30 days prior.
13. Pregnant or lactating at the time informed consent (or assent, if appropriate) is obtained.

Key Inclusion Criteria (CCR-2024-200475):
• Age < 18 years at time of surgical procedure.
• Confirmed diagnosis of congenital hereditary von Willebrand Disease (VWD).
• Enrollment in the ATHNdataset.
• Treatment with Vonvendi to prevent or treat a surgical bleed (Vonvendi either within 48 hrs. of procedure or indicated as preprocedural dose).
• Minimum of 6 months of clinical data/visit prior to the date of surgery.
• Minimum of 14 days of clinical data/visit following the date of surgery.

Key Exclusion Criteria (CCR-2024-200475):
• Diagnosed with any other bleeding disorder or factor deficiency in addition to VWD.
• Known neutralizing antibodies to VWF.

Reviewer's Comment:
This review includes only patients with the pre-specified criteria of severe vWD in 071102 and SHP 677-304.

6.2.4 Study Treatments or Agents Mandated by the Protocol

OD BE dosage (071102 and SHP 677-304):

The initial OD dose of Vonvendi was 40 to 80 IU/kg, with 30 to 45 IU/kg Advate if the patient didn't have a hemostatically effective baseline FVIII (≥ 30%).

Subsequent BE's were treated with Vonvendi 40 to 60 IU/kg (up to 80 IU/kg for a major BE), with 30 to 45 IU/kg Advate if FVIII levels fall < 30 IU/dL.

Subsequent dosing was given every 8 to 24 hours to maintain VWF:RCo and FVIII levels for as long as deemed necessary by the Investigator.

Surgery dosage (071102 and SHP 677-304):

Elective surgery: a priming dose of Vonvendi was given 12 to 24 hours prior to surgery to raise FVIII levels to ≥ 30 IU/dL for minor/oral surgery and ≥ 60 IU/dL for major surgery.

Elective and emergency surgery: a loading dose of 40 to 60 IU/kg Vonvendi was given within 3 hours prior to surgery. 30 to 45 IU/kg Advate was administered to raise FVIII levels to recommended levels, preferably within 10 minutes after the Vonvendi infusion if FVIII was less than 40 to 50 IU/dL for minor/oral surgery or 80 to 100 IU/dL for major surgery. The Advate dose could be increased in patients requiring emergency surgery who did not receive a preoperative priming dose. The peri- and postoperative substitution regimen was individualized according to PK results, intensity, duration of the hemostatic challenge, and the institution's standard of care.

Reviewer's Comment:
When reviewing the data, it was unclear the criteria in which patients were to receive Advate as well as assessment of hemostatic efficacy when Advate was given, an IR was sent to clarify with the applicant's responses below:

- *"The dosing recommendations for OD treatment in the protocols were for 30 to 45 IU/kg Advate to be administered along with Vonvendi, unless the subject had a hemostatically effective baseline FVIII level. In another words, Advate was only to be administered if plasma FVIII levels fell below 30 IU/dL."*
- *"For surgery management, Advate, at a dose of 30 to 45 IU/kg, could be infused as part of the pre-operative priming and loading dose if Vonvendi infusion would not be (or would be highly unlikely to be) sufficient to raise the plasma FVIII levels to the recommended target levels (40 to 50 IU/dL for minor/oral surgery or 80 to 100 IU/dL for major surgery) before the initiation of the surgery. Similarly, the postoperative additional Advate infusion depended on whether FVIII trough levels could be maintained =30 IU/dL with Vonvendi."*
- *"The primary efficacy assessment of Vonvendi for OD treatment was the investigator-assessed hemostatic efficacy rating of BE treatment, based on comparing the estimated to the actual number of infusions of Vonvendi required to resolve the bleed. The efficacy assessments were directed to be performed in the same way whether or not Advate was administered, but Advate infusions (or no infusion) were to be taken into consideration in the estimation of the required number of Vonvendi infusions, and, therefore, did not impact the assessment of Vonvendi. The efficacy of managing surgical bleeding was based on a comparison between hemostasis achieved with Vonvendi (with or without Advate) and the hemostasis outcome expected for the type of surgical procedure performed in a hemostatically normal subject, so Advate use was also considered when performing the assessment."*
- *"Additionally, FVIII supports the broader coagulation cascade, but does not interfere with Vonvendi's primary role in addressing VWF deficiency (to restore VWF levels, enabling platelet adhesion and aggregation). VWF levels reached with Vonvendi infusion were not affected by the administration of Advate, but a single infusion of Vonvendi leads to an increase in FVIII after least 6 hours and a peak at about 24 hours. Prior clinical trials assessing Vonvendi have successfully demonstrated its efficacy in adults, without Advate, or when co-administered with Advate, establishing that the 2 therapies work synergistically, and the approaches of efficacy assessment minimize the confounding effects of Advate. By focusing on these distinct contributions, it is evident that co-administration of Advate does not hinder the accurate assessment of Vonvendi efficacy. The design of the protocols further ensures that the presence of exogenous FVIII does not confound Vonvendi efficacy evaluation by defining clear endpoints specific to*

VWF activity and endpoints of both Vonvendi and Advate consumption. For example, PK/PD analyses can measure VWF plasma levels and its effect on stabilizing FVIII over time, and bleeding cessation can be studied in relation to Vonvendi and Advate infusion consumption without bias."

RWE study CCR-2024-200475 was retrospective. All treatment was at the discretion of the investigator.

6.2.5 Directions for Use

Vonvendi is provided as lyophilized powder in single use vials containing nominally 650-1300 international units for intravenous use.

Advate is provided as lyophilized powder in single use vials containing nominally 250, 500, 1000, 1500, 2000, 3000 or 4000 IU for intravenous use.

6.2.6 Sites and Centers

071102 was conducted at 45 sites in 13 countries including US (15 sites), France (8 sites), Italy (4 sites), Germany, Russia, and Turkey (3 sites each), Austria and Spain (2 sites each), Belgium, Czech Republic, Netherlands, Ukraine, and the UK (1 site each).

SHP 677-304's subset included in this analysis was conducted at 9 sites in 6 countries including US, France, Austria, Netherlands, Spain, and Turkey.

RWE Study CCR 2024-200475 was a retrospective study collecting data from sites across the US. The subsets of patients with severe VWD included in this review came from 4 sites within the US.

6.2.7 Surveillance/Monitoring

Table 29 Study Procedures and Assessments for OD Patients 071102

Procedures / Assessments	Screening Visit[a]	Baseline Visit[b] (PK Assessment ≤42 Days Post-Screening Visit)			On-Demand Bleeding Episode Treatment				Optional Follow-Up Clinic Visit	Quarterly Study Visits (3, 6, 9 Months ± 2 Weeks After Baseline Visit Infusion)	Completion Visit (12 to 18[k] Months ± 3 Weeks After Baseline Visit Infusion)
					1st Bleeding Episode		Subsequent Bleeding Episodes				
		Pre-Infusion	Infusion	Post-Infusion	Initial Infusion (In Clinic)	Follow-Up Telephone Call[j] (Within 24 Hours of Bleed Onset)	Infusion (In Clinic or Home)	Follow-Up Telephone Call[j] (Within 24 Hours of Bleed Onset)			
Informed Consent[c]	X										
Eligibility Criteria	X										
Medical History	X										
Physical Examination	X	X[l]		X	X	*		*	X	X	X
Vital Signs[d]	X	X[m]		X[m]	X	*		*	X	X	X
Concomitant Medications and Non-drug Therapies	X[e]	X	X	X	X	X	X	X	X	X	X
Laboratories[f]	X	X		X	X	*	X	*	X	X	X
ECG	X	X[g]		X[h]					X		X
rVWF Infusion			X		X		X				
ADVATE Infusion[n]					X		X				
Investigator Assessment of Bleeding Episode Severity[i]					X	*	X	*			
Investigator Assessment of Hemostatic Efficacy						X		X	X		
HRQoL Questionnaires	X										X
Subject Electronic Diary	X	X	X	X	X	X	X	X	X	X	X
Untoward Medical Occurrences	X	X	X								
Adverse Events				X	X	X	X	X	X	X	X

*Source: 071102 Protocol Pages 99-100

Table 30 Study Procedures and Assessments for Elective Surgery Patients 071102

Procedures / Assessments	Screening Visit[a,b]	Baseline Visit[b] (PK Assessment ≤42 Days post-Screening Visit)			Surgery				Day 7 Post-Operative Visit (±1 Day)	Day 14 Post-Operative Visit (±2 Days)
					Priming Dose	Loading Dose	Intra-operative	Post-operative		
		Pre-Infusion	Infusion	Post-Infusion	12-24 Hours Prior to Surgery	≤3 Hours Prior to Surgery				
Informed Consent[c]	X									
Eligibility Criteria	X									
Medical History	X									
Physical Examination	X	X[d]		X	X[a]	X[a]		X[a]	X	X
Vital Signs[e]	X	X[f]		X[f]	X[f]	X[f]	X[f]	X[f]	X[f]	X[f]
Concomitant Medications and Non-drug Therapies	X[k]	X	X	X	X	X	X	X	X	X
Laboratories[g]	X	X		X	X	X	X	X	X	X
ECG	X	X[l]		X[m]						
rVWF Infusion			X		X	X	X	X	X[o]	X[o]
ADVATE Infusion[n]					X	X	X	X	X	X

Procedures / Assessments	Screening Visit[a,b]	Baseline Visit[b] (PK Assessment ≤42 Days post-Screening Visit)			Surgery				Day 7 Post-Operative Visit (±1 Day)	Day 14 Post-Operative Visit (±2 Days)
					Priming Dose	Loading Dose	Intra-operative	Post-operative		
		Pre-Infusion	Infu-sion	Post-Infusion	12-24 Hours Prior to Surgery	≤3 Hours Prior to Surgery				
Untoward Medical Occurrences	X	X	X							
Adverse Events	X	X	X	X	X	X	X	X	X	X

*Source: 071102 Protocol pages 102-103

Table 31 Study Procedures and Assessments for Emergency Surgery Patients 071102

Procedures / Assessments	Abbreviated Screening	Surgery			Day 7 Post-Operative Visit (±1 Day)	Day 14 Post-Operative Visit (±2 Days)	Screening Visit[a]	Baseline Visit (PK Assessment ≤42 Days Post-Screening Visit)		
		Loading Dose ≤3 Hours Prior to Surgery	Intra-Operative	Post-Operative				Pre-Infusion	Infusion	Post-Infusion
Informed Consent[b]	X						X			
Confirmation of Severe VWD Diagnosis	X									
Eligibility Criteria							X			
Medical History							X			
Physical Examination		X[c]		X[c]	X	X	X	X[c]		X
Vital Signs[d]		X[e]	X[e]	X[e]	X[e]	X[e]	X	X[e]		X[e]
Concomitant Medications and Non-drug Therapies		X	X	X	X	X	X[f]	X	X	X
Laboratories[g]		X	X	X	X	X	X	X		X
ECG							X	X[h]		X[i]
rVWF Infusion		X	X	X	X	X			X	
ADVATE Infusion[a]		X	X	X	X	X				
Assessment of Hemostatic Efficacy[j]				X						
Blood Loss		X (estimated)	X (actual)	X	X[k]	X[k]				

Procedures / Assessments	Abbreviated Screening	Surgery			Day 7 Post-Operative Visit (±1 Day)	Day 14 Post-Operative Visit (±2 Days)	Screening Visit[a]	Baseline Visit (PK Assessment ≤42 Days Post-Screening Visit)		
		Loading Dose ≤3 Hours Prior to Surgery	Intra-Operative	Post-Operative				Pre-Infusion	Infusion	Post-Infusion
Treatment Days (estimated)		X								
Adverse Events		X	X	X	X	X	X	X	X	X

*Source: 071102 Protocol pages 105-106

Table 32 Study Procedures/Assessments for Prophylaxis and Surgery Patients in SHP 677-304 transitioning from Study 071102 (Cohort 3)

Procedures/ Assessments	Screening Visit [a]	Prophylaxis Initiation Visit [a]	Follow-Up Study Visits							End of Study Visit
			1 month (±1) week	2 months (±1) week	3 months (±2) weeks	6 months (±2) weeks	9 months (±2) weeks	12 months (±2) weeks	Every 3 months (±2) weeks	
Informed Consent [b]	X									See Table 9
Eligibility Criteria	X									
Medical History	*									
Physical Exam	*	X	X	X	X	X	X	X	X	
Vital Signs [c]	*	X	X	X	X	X	X	X	X	
IP Treatment [d]		X	X	X	X	X	X	X	X	
Concomitant Medications and Nondrug Therapies [e]	*	X	X	X	X	X	X	X	X	
Adverse Events [e]	*	X	X	X	X	X	X	X	X	
Bleeding Episodes and Treatment [e]	*	X	X	X	X	X	X	X	X	
Investigator Assessment of Hemostatic Efficacy [e]	*	X	X	X	X	X	X	X		
IR Determination [d]		X	X	X	X	X	X	X		
Laboratories (See Table 6)	*	X	X	X	X	X	X	X	X	
ECG	*					X		X		
Subject Diary [f]	X	X	X	X	X	X	X	X	X	
PROs (HRQoL, TSQM-9 etc.)		X				X		X		

*Source: SHP 677-304 Protocol Page 32

Table 33 Study Procedures and Assessments for newly enrolled Prophylaxis and Surgery Patients in SHP 677-304 (Cohort 4)

Procedures/ Assessments	Screening Visit	PK Assessment [h]			Prophylaxis Initiation Visit[i]	Follow-Up Study Visits							End of Study Visit
		Pre-infusion [g]	Infusion	Post-infusion [g]		1 month (±1) week	2 months (±1) week	3 months (±2) weeks	6 months (±2) weeks	9 months (±2) weeks	12 months (±2) weeks	Every 3 months (±2) weeks	
Informed Consent [a]	X												See Table 10
Eligibility Criteria	X												
Medical History [b]	X												
Physical Exam	X	X			X	X	X	X	X	X	X	X	
Vital Signs [c]	X	X		X	X	X	X	X	X	X	X	X	
IP Treatment [d]			X		X	X	X	X	X	X	X	X	
Concomitant Medications and Non-drug Therapies [e]	X	X	X	X	X	X	X	X	X	X	X	X	
Adverse Events [e]		X	X	X	X	X	X	X	X	X	X	X	
Bleeding Episodes and Treatment [e]	X	X	X	X	X	X	X	X	X	X	X	X	
Investigator Assessment of Hemostatic Efficacy [e]	X	X	X	X	X	X	X	X	X	X	X		
Laboratories (See Table 7)	X	X		X		X	X	X	X	X	X	X	
IR Determination					X	X	X	X	X	X	X		
ECG	X								X		X		
Subject Diary [f]	X				X	X	X	X	X	X	X	X	
PROs (HRQoL, TSQM-9, etc.)					X[j]				X		X		

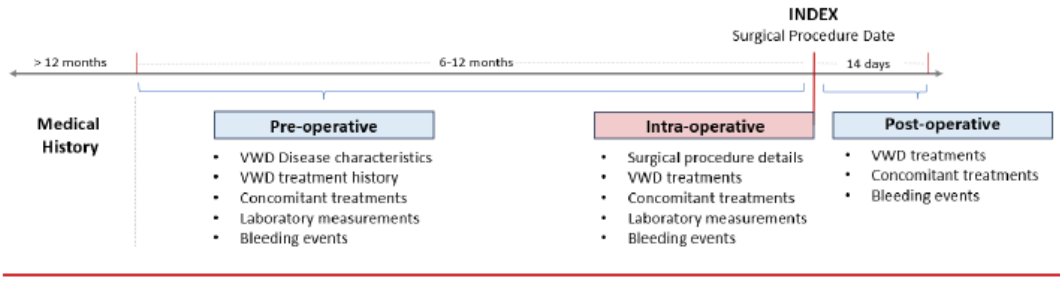
*Source: SHP 677-304 Protocol Page 34

Table 34 Study Procedures and Assessments for OD and Surgery Patients in SHP 677-304 transitioning from Study 071102 (Cohort 5)

Procedures/Assessments	Screening Visit [a]	Follow-Up Study Visits					End of Study Visit
		3 months (±2) weeks	6 months (±2) weeks	9 months (±2) weeks	12 months (±2) weeks	Every 3 months (±2) weeks	
Informed Consent [b]	X						
Eligibility Criteria	X						
Medical History	*						
Physical Exam	*	X	X	X	X	X	X
Vital Signs [c]	*	X	X	X	X	X	X
Concomitant Medications and Non-drug Therapies [d]	*	X	X	X	X	X	X
Adverse Events [d]	*	X	X	X	X	X	X
Bleeding Episodes and On-demand Treatment [d]	*	X	X	X	X	X	X
Investigator Assessment of Hemostatic Efficacy [d]	*	X	X	X	X	X	X
Laboratories (See Table 5)	*	X	X	X	X	X	X
ECG	*		X		X		X
Subject Diary [e]	X	X	X	X	X	X	X
PROs (HRQoL, TSQM-9, etc.)	X		X		X		X

*Source: SHP 677-304 Protocol Page 30

Figure 8 Study Design for RWE Study CCR-2024-200475



*Source: CCR-2024-200475 protocol page 7

6.2.8 Endpoints and Criteria for Study Success

Primary Endpoint:

Primary Endpoint (071102):
The primary endpoint was hemostatic efficacy defined by the number and percentage of pediatric patients with treatment success for treated nonsurgical BEs (4-point scale). A treatment success was defined as a mean efficacy rating score of <2.5 for a patient's IP-treated BEs during a treatment period.

Table 35 Definitions of 4-Point Hemostatic Efficacy Rating Scales in 071102/SHP 677-304

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

*Source: 071102 (page 56) and SHP 677-304 (page 97) Protocols

Reviewer's Comment:
Hemostatic efficacy assessment of bleeding assessments was based on comparing estimated to actual number of infusions of Vonvendi required to treat bleed for OD.

Primary Endpoint (CCR-2024-200475) pertinent to indication:
- Assessment of safety of Vonvendi in perioperative setting.
- Assessment of effectiveness of Vonvendi in perioperative setting.

Safety assessment based on TEAE's and side effects occurring peri-operatively including (CCR-2024-200475):

- Hypersensitivity/Allergic reactions
- Thrombotic Events
- VWF inhibitor development
- Transfusion-transmitted infections
- Malignancy
- Cardiovascular events
- Neurological events
- Death

Efficacy assessment based on clinical outcomes perioperatively including:

- Surgical procedure details (Type, Severity, Category).
- Average dose of Vonvendi and FVIII (IU/kg) of the initial and subsequent infusions and number of infusions (pre-, intra- and post-operative).
- Average number of post-operative bleeds.
- Type, severity, location.
- Average dose of Vonvendi (IU/kg) per infusion & number of infusions administered.
- Average time to bleed resolution.
- Average treatment duration.

Secondary Endpoint:

Secondary Efficacy Endpoint (071102):

- Number of treated nonsurgical BEs, with an efficacy rating of "excellent" or "good".
- Number of infusions, Vonvendi units, and ADVATE units (if needed), per BE.
- For elective or emergency surgery: an overall assessment of hemostatic efficacy 24 hours after the last perioperative infusion of Vonvendi, or on Day 14, whichever is earlier, based on a 4-point scale.
- Overall hemostatic efficacy rating at the resolution of bleed for the initial 12 months on study treatment.
- Number of infusions of Vonvendi and Advate utilized to treat BEs while enrolled in the study.
- Weight-adjusted consumption of Vonvendi and Advate per BE while enrolled in the study.

Table 36 Definitions of 4-Point Hemostatic Efficacy Rating Scales in the perioperative setting in 071102/SHP 677-304

RATING	Overall Assessment of Hemostatic Efficacy 24 Hours After the Last Perioperative rVWF Infusion
Excellent (1)	Intra- and post-operative hemostasis achieved with vonicog alfa with or without ADVATE was as good or better than that expected for the type of surgical procedure performed in a hemostatically normal subject
Good (2)	Intra- and post-operative hemostasis achieved with vonicog alfa with or without ADVATE was probably as good as that expected for the type of surgical procedure performed in a hemostatically normal subject
Moderate (3)	Intra- and post-operative hemostasis with vonicog alfa with or without ADVATE was clearly less than optimal for the type of procedure performed but was maintained without the need to change the vonicog alfa concentrate
None (4)	Subject experienced uncontrolled bleeding that was the result of inadequate therapeutic response despite proper dosing, necessitating a change of vonicog alfa concentrate

*Source: 071102 (page 57) and SHP 677-304 (page 98) Protocols

Reviewer's Comment:
Surgery hemostatic efficacy assessment was based on comparison between hemostasis achieved with Vonvendi and hemostatic outcome expected based on type of procedure in a hemostatically normal patient.

Secondary Safety Endpoints (077102):

- Incidence and severity of adverse events (AEs) by system organ class and preferred term.
- Incidence of thrombotic events.
- Incidence of severe hypersensitivity reactions.
- Development of neutralizing antibodies to VWF and Factor VIII (FVIII).
- Development of total binding antibodies to VWF.
- Development of antibodies to CHO proteins, murine immunoglobulin G (IgG), and rFurin.

Secondary Endpoints (CCR-2024-200475):
Describe the hemostatic control with Vonvendi in the peri-operative and post-operative setting.

Exploratory Endpoints:
Exploratory Endpoints (071102):
Health-related Quality of Life variables for patients aged 2 to 18 years at Screening:

- Generic: Pediatric Quality of Life InventoryTM (PedsQLTM), Parent proxy version:

- PedsQLTM Child report for children (ages 8 to 12) (23 items)
- PedsQLTM Parent report for young children (ages 5 to 7) (23 items)
- PedsQLTM Parent report for toddlers (ages 2 to 4) (21 items)
    - Health utility: EuroQoL five-dimension questionnaire (EQ-5D): the youth version EQ-5D-Y for patients ≥7 years (parent-proxy version for ages 4 to <7 years)
    - Pain: Visual analog scale
- HRU (hospitalizations, emergency room visits, doctor office visits, days missed from school, etc.)

Reviewer's Comment:
The endpoints for continuation study SHP 677-304 aligned with 071102 with differences including:

- *The primary endpoint for SHP 677-304 was not pertinent to the pediatric indication.*
- *Surgery assessment was a secondary endpoint in 071102 vs. exploratory in SHP 677-304.*
- *There were no exploratory endpoints for RWE Study CCR-2024-200475.*

6.2.9 Statistical Considerations & Statistical Analysis Plan

Please see statistical review memo.

6.2.10 Study Population and Disposition:

6.2.10.1 Populations Enrolled/Analyzed (071102 and SHP 677-304):
The full analysis set for efficacy (FAS) included all patients who were enrolled and met all inclusion/exclusion criteria, received any amount of the study drug, and provided at least one hemostatic assessment within 24 hours of a study drug infusion.

The safety analysis set (SAF) included all patients in the enrolled set who received Vonvendi, including PK.

Populations Enrolled/Analyzed (CCR 2024-200475):
All patients included in both efficacy and safety analyses.

6.2.10.1.1 Demographics

Please see section 1.1.

6.2.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

All patients had multimer analysis and/or genetic testing confirming their severe VWD diagnosis and type.

6.2.10.1.3 Patient Disposition

In 071102, a planned total of at least 21 pediatric OD patients divided into 3 age cohorts (8 each in cohorts 1 and 2 and 5 in cohort 3). At least 4 PTP's were enrolled across all age groups prior to enrollment of PUP's.

At least 10 evaluable pediatric patients with severe VWD undergoing at least 12 surgeries divided into 3 age cohorts were planned. These 10 patients could include any eligible patients already enrolled in the OD arm.

Cohort 1: ≥12 to <18 years of age: at least 3 patients and at least 1 major surgery in patient with type 3 VWD.
Cohort 2: ≥6 to <12 years of age: at least 3 patients and at least 1 major surgery in patient with type 3 VWD.
Cohort 3: <6 years of age: at least 3 patients (minimum 1 patient with type 3 VWD) with at least 1 major surgery. At least 1 patient <2 years of age.

In SHP 677-304, a planned total of up to 34 pediatric/adolescent patients transitioning from study 071102 and at least 7 and up to 15 newly enrolled adult and pediatric/adolescent patients on prior OD VWF products.

In RWE Study CCR 2024-200475, target enrollment was at 3-6 patients; each with at least 1 surgery.

Table 3720 Patient Disposition of patients supporting pediatric indication expansions

Study	Indication	FAS	SAF	Disposition
071102	On-Demand Treatment in Children	18	25	24 completed, 1 discontinued
SHP 677-304	On-Demand Treatment in Children	16	16	16 completed
071102	Perioperative Management in Children	4	4	4 Completed
SHP 677-304	Perioperative Management in Children	4	4	3 completed, 1 discontinued
CCR-2024-200475	Perioperative Management in Children	2	2	2 Completed

*Source: 071102 and Integrated 90-day safety update ADSL datasets. CCR 2024-200475 CSR and ADSL dataset

Reviewer's Comment:

- *In 071102, 29 patients were included in the SAF (25 OD and 4 surgery patients). One OD patient had emergency surgery and is included in both arms. 25 in the OD arm completed the study (including the emergency surgery patient). All 4 surgery patients completed the study. In FAS, there were 18 patients in OD and 4 in surgery. All but 1 patient in the OD arm completed the study with 1 patient discontinuing from the study due to physician decision to start prophylaxis 319 days after PK dosing.*
- *In SHP 677-304, 18 patients were included in the safety set (16 rolled over from 071102 and continued OD, 1 rolled over from 071102 and switched from OD to prophylaxis, and 1 newly enrolled prophylaxis patient). 17 completed the study, and 1 discontinued due to physician decision secondary to new diagnosis of juvenile idiopathic arthritis in the patient. 4 of these patients underwent surgeries.*
- *CCR-2024-200474 had 2 patients with qualifying surgeries and reportable outcomes with safety and efficacy data.*

6.2.11 Efficacy Analyses

6.2.11.1 Analyses of Primary Endpoint(s)

Primary Endpoint (071102):

The primary endpoint was hemostatic efficacy defined by the number and percentage of pediatric patients with treatment success for treated nonsurgical BEs. Treatment success defined as a mean efficacy rating score of <2.5 with excellent = 1, good, = 2, moderate = 3, and none = 4.

Treatment success was achieved for all BE's with reported outcomes. All 18 patients experienced BE's with a total of 104 BE's and mean of 5.8 (median 4; range 1, 22) BE's per patient. There were 57 treated BEs in ages ≥12 to <18 years with a mean of 9.5 (median 7.5; range 3, 22) per patient, 37 treated BE's in ages ≥6 to <12 years with a mean of 4.1 (median 3; range 1, 9) per patient, and 10 treated BE's in age <6 years with a mean of 3.3 per patient (median 3; range 3, 4).

98 BE's had outcomes reported, all with excellent or good efficacy achieved: 97 excellent and 1 good. 6 BE ratings were missing with missing adjudicated as excellent. The majority of BE's resolved with 1 infusion (80/104 or 81.6%) with a mean total dose of 64 IU/kg (median 51; range 18-366) and mean dose per infusion of 48 IU/kg (median 49; range 18-63).

Table 3821 Hemostatic Efficacy (FAS) for treated Nonsurgical bleeds in 071102

Parameter	OD Patients N = 18	≥ 12 To < 18 years N =7	≥ 6 To < 12 years N = 9	< 6 years N = 5
Hemostatic Efficacy Rating (N, %)				
Excellent	97 (93)	52 (91)	35 (94)	10 (100)
Good	1 (1)	0	1 (3)	0
Moderate	0	0	0	0
None	0	0	0	0
Missing	6 (6)	5 (9)	1 (3)	0
Episodes per patient, mean	5.8	9.5	4.1	3.3
Treatment Success	18 (100)	6 (100)	9 (100)	3 (100)

*Source: 071102 CSR and ADBE dataset

Reviewer's Comment:

- *Efficacy results were consistent amongst age, VWD type, severity, and bleed location.*
- *BE's with hemostatic efficacy by bleed severity include: 48 minor, 29 moderate, and 2 major. Efficacy rating was not reported for 1 moderate BE. 18 BE's with unknown severity had excellent hemostatic efficacy and 5 with unknown severity had missing outcomes.*
- *All spontaneous BE's with reported outcomes had an efficacy of excellent or good. One spontaneous BE did not have a reported outcome. All traumatic and menstrual BE's had reported excellent efficacy. BE's with unknown causes had 3 rated as excellent and 5 with outcomes not reported.*
- *When broken down by location, all BE's with reported outcomes in mucosa (nose and mouth), skin, muscle, soft tissue, joint, and multiple/other all had excellent efficacy. Gum mucosa had one BE reported as good with all others being excellent. 1 BE with unknown location didn't have reported outcome.*
- *When broken down by VWD type:*
    - *12 BE's in 2 patients with Type 1; all with excellent hemostatic efficacy.*

  - *37 BE's in 3 patients with Type 2A; 32 with excellent hemostatic efficacy and 5 unknown.*
  - *5 BE's in 2 patients with Type 2B; all with excellent hemostatic efficacy.*
  - *50 BE's in 11 patients with Type 3 VWD; 48 with excellent hemostatic efficacy, 1 with good and 1 missing.*
- *The primary endpoint for SHP 677-304 was not pertinent to this pediatric indication.*

Primary Endpoint (CCR-2024-200475) pertinent to indication:
- Assessment of safety of Vonvendi in perioperative setting
- Assessment of effectiveness of Vonvendi in perioperative setting

No TEAE's were reported. Two qualifying procedures in 2 patients had outcomes reported: both successful.

Reviewer's Comment:
- *TEAE's were evaluated 6 to 12 months pre-op and from 1 day pre-op up to 14 days post-op.*
- *2 "allergic reactions" in patient reported during baseline prior to Vonvendi administration and related to pd-VWF per investigator. Reviewer agrees that these reactions were not related to Vonvendi as they were prior to Vonvendi administration.*
- *Both patients were on OD prior to procedures.*
- *One procedure was a minor IUD placement in 17-year-old. 1 infusion of Vonvendi (22 IU/kg) given the day prior to surgery and no other infusions given.*
- *One procedure was a major hypospadias repair in 12-year-old with one infusion of Vonvendi given pre-operatively on the day of surgery followed by two post-operative infusions on post-operative days 1 and 2. All infusions were 56 IU/kg. This patient also received post-op pd-VWF.*
- *No reported treatment with Factor VIII, tranexamic acid, DDAVP, or blood products reported peri-op.*
- *No reported post-operative bleeding.*
- *Overall, this study has limitations including small sample size and the retrospective, observational nature of the study that can lead to potential missing data. The RWE team was consulted (Whitney Steele, Tainya Clarke, and Stephen Chang) with response: "The results of the real-world data (RWD)/ RWE studies support the findings of the clinical studies that Vonvendi [von Willebrand factor (recombinant)] is safe and effective for the proposed indication(s). For these RWE studies to be used alone as evidence of safety and effectiveness, they would have required a more robust methodological approach that addressed the potential biases and confounders that are inherent in RWD. These limitations as well as the small sample sizes, absence of control groups, limited to no confirmatory statistics, and misalignments with the pivotal clinical trial population, prevent the use of the RWE studies on the label. Given these limitations, the RWE review team concludes that as stand-alone studies, they do not demonstrate the safety or effectiveness of Vonvendi [von Willebrand factor (recombinant) and therefore should not be cited on the label. We support the removal of the text with specific references to the RWD/RWE studies from lines 510-522, 600-623 of the current labeling document (with markup)."*

6.2.11.2 Analyses of Secondary Endpoints

Secondary Endpoints (071102):

An overall assessment of hemostatic efficacy 24 hours after the last perioperative infusion of Vonvendi, or on Day 14, whichever is earlier:
There was 1 emergency surgery in a patient enrolled in the OD arm of 071102 and 3 additional elective surgeries in newly enrolled patients. All were minor surgeries and had reported excellent intra-operative and overall hemostatic efficacy without post-operative bleeding. Two patients were 6 to < 12 years and 2 were 12 to < 17 years. No patients < 6 years had surgery. 1 had Type 1 VWD and 3 had Type 3 VWD. The mean dose of Vonvendi pre-op was 94 IU/kg with a mean of 1.8 pre-op infusions. The mean post-op dose was 117 IU/kg with a mean of 2.3 infusions. One surgery required Advate with 1 dose pre-op and 4 doses post-op.

Reviewer's Comment (071102):

- *There was one major surgery in a patient who also had minor surgery. The major surgery was treated with commercial Vonvendi and not included in the analysis.*
- *A 6-year-old in Cohort 2 underwent an emergent surgery of a tunneled subcutaneous port removal. The patient received 5 peri-op infusions of Vonvendi (2 pre-op on day of surgery and 3 post-op, 2 on post-op day 1 and 1 on post-op day 2). All peri-op Vonvendi doses were 62 IU/kg. This patient also received 5 periop infusions of Advate at same timepoints as the Vonvendi infusions. All peri-op Advate doses were 47 IU/kg. This patient's baseline Factor VIII activity was 1 IU/dL.*
- *A 12-year-old in Cohort 1 underwent an elective surgery of second stage buccal mucosa hypospadias reconstruction. The patient received 4 infusions of Vonvendi peri-op (2 pre-op, one day prior to surgery and on the day of surgery, and 2 post-op on same day of surgery and on post-op day 1). The two pre-op infusions were 49 IU/kg one day prior and 50 IU/kg same day prior to surgery. The post-op infusion the same day of surgery was 28 IU/kg and 27 IU/kg on post-op day 1. No Advate given with baseline Factor VIII activity of 87 IU/dL.*
- *A 6-year-old in Cohort 2 underwent an elective surgery of circumcision. The patient received 16 infusions of Vonvendi peri-op with 2 pre-op (one day prior to surgery on the day of surgery), and 14 post-op doses through post-op day 15 (twice daily through post-op day 4 then, daily through day 7, then every other day through day 15). All doses 57-58 IU/kg. No Advate given with baseline Factor VIII activity of 1 IU/dL.*
- *A 12-year-old in Cohort 1 underwent an elective surgery of circumcision. The patient received 15 infusions of Vonvendi peri-op with 2 pre-op (one day prior to surgery and on the day of surgery) and 13 post-op through post-op day 15 (twice daily through post-op day 3 then, daily through day 7, then every other day through day 15). All doses 49-53 IU/kg. No Advate given with baseline Factor VIII activity of 1 IU/dL.*

Reviewer's Comment (SHP 677-304):

Surgery endpoints were exploratory in SHP 677-304 and also included intraoperative hemostatic efficacy, actual vs. predicted blood loss through postop day 14. Additional surgery endpoint in SHP 677-304 was and Vonvendi and Advate perioperative usage:

- *Four patients underwent 5 surgeries, 4 minor and 1 oral. Four had overall hemostatic efficacy ratings of "excellent". One missing overall hemostatic efficacy had an intraop efficacy rating of "excellent" with reviewer adjudication of excellent for overall hemostatic efficacy. Four had intraop hemostatic efficacy and blood loss ratings of "excellent". One missing intraop hemostatic efficacy and blood loss ratings had an overall hemostatic efficacy rating of "excellent." There was no post-op blood loss in any surgery with overall blood loss 58 % less than predicted with a mean of 1.9 ml. actual blood loss vs. 3.2 ml predicted blood loss. No intraoperative doses of Vonvendi were given.*
- *A 13-year-old in Cohort 3 underwent an upper intestinal endoscopy. The patient received 3 peri-op infusions of Vonvendi: 1 infusion one day prior to surgery (53 IU/kg), 1 infusion pre-op on day of surgery (26 IU/kg) and 1 on post-op day 1 (53 IU/kg). No Advate given with baseline Factor VIII activity of 2 IU/dL.*
- *A 12-year-old in Cohort 4 underwent two surgeries:*
    - *Arthroscopy with partial meniscectomy medial. The patient received 4 peri-op infusions of Vonvendi with 1 pre-op on day of surgery, and 3 post-op on post-op days 1, 2, and 3. All doses 59 IU/kg.*
    - *Left knee arthroscopic partial lateral meniscectomy. The patient received 4 peri-op infusions of Vonvendi with 1 pre-op on day of surgery, and 3 post-op on post-op days 1, 2, and 3. All 55 IU/kg.*
    - *No Advate given for either surgery. The patient's baseline Factor VIII activity was 32 IU/dL.*
- *An 11-year-old in Cohort 5 underwent an oral surgery of primary tooth removal. The patient received 2 pre-op doses of Vonvendi; one on day prior to surgery and one on day of surgery. No post-op doses given. All doses were 50 IU/kg. No Advate given. The patient's baseline Factor VIII activity was 65 IU/dL.*
- *An 11-year-old in Cohort 5 underwent a submucosal glubran injection for recurrent epistaxis. The patient received 3 peri-op doses of Vonvendi with one infusion pre-op on day of surgery and two post-op doses on post-op days 1 and 2. All doses were 48 IU/kg. The patient received one dose of Advate (37 IU/kg) pre-op on day of surgery. The patient's baseline Factor VIII activity was 11 IU/dL.*

Table 3922 Vonvendi and Advate weight-adjusted doses in SHP 677-304 pediatric surgery patients (IU/kg)

Drug	Pre-Op Priming Dose	Pre-Op Loading Dose	Total Post-Op Dose	Average Daily Post-Op Dose	Total Peri-Op Dose	Average Daily Peri-Op Dose
Vonvendi	51	48	123	54	167	51
Advate	NA	37	37	NA	NA	NA

Source: SHP 677-304 CSR and ADEX datasets

Overall hemostatic efficacy rating at the resolution of BE for the initial 12 months on study treatment.
98 of 104 treated BE''s had efficacy ratings of excellent or good; 97 excellent, 1 good, and 6 missing with missing responses adjudicated as excellent.

Reviewer's Comment:
In SHP 677-304, treatment success was achieved for all 164 treated BE's with reported outcomes; 160 with excellent rating, 2 good, and 2 missing. All 16 patients experienced BE's with treatment success with a mean of 10.3 BE's per patient: 83 treated BEs in ages ≥12 to <18 years with a mean of 10.4 per patient, 46 treated BE's in age ≥6 to <12 years with a mean of 9.2 per patient, and 35 treated BE's in ages <6 years with a mean of 11.7 per patient. The majority resolved with 1 infusion with a mean dose per infusion of 49.7 IU/kg.

Number of infusions of Vonvendi and Advate utilized to treat BEs while enrolled in the study.

In 071102, the majority (80) of BE's required 1 infusion of Vonvendi treatment at 81.6%, 12 BE's (12%) required 2 infusions, 4 (4%) required 3 infusions, and 2 (2%) required > 5 infusions. 28 BE's in 7 patients required 1 infusion of Advate; none required > 1 infusion of Advate. These patients had a baseline Factor VIII activity between 1-13 IU/dL.

Reviewer's Comment:
- *Patient* (b) (6) *had two left ankle BEs requiring 8 and 9 infusions.*
- *In SHP 677-304, the majority of BE's required only one infusion of Vonvendi treatment with a mean of 1.1. 43 BE's in 7 patients were treated with Advate in addition to Vonvendi with a mean of 1 Advate infusion per BE. These patients had a baseline Factor VIII activity between 2-15 IU/dL.*

Weight-adjusted consumption of Vonvendi and Advate per BE:
In 071102, the mean Vonvendi dose per BE was 64 IU/kg (average dose per infusion was 48 IU/kg) and the mean Advate dose per BE was 31 IU/kg.

A total of 28 BEs in 7 patients were treated with an initial dose of Vonvendi with Advate. The per-protocol dose of Vonvendi was 40 to 60 IU/kg. The median dose given was 48 IU/kg with a range 18 to 63 IU/kg. The per-protocol dose of Advate was 30 to 45 IU/kg. The median dose given was 33 IU/kg with a range 9 to 45 IU/kg. A total of 76 BEs in 15 patients received an initial dose of Vonvendi without Advate due to baseline FVIII level of at least 30%. The median dose of Vonvendi given without Advate was 49 IU/kg with a range 18 to 86 IU/kg. In 8 patients, at least one additional dose of Vonvendi without Advate was administered in 18 BEs every 8 to 24 hours to maintain VWF:RCo and FVIII levels. Of BE's that received Advate, all required only 1 infusion.

Reviewer's Comment (071102):
- *There were 16 BE's with initial Vonvendi treatment dose of < 40 IU/kg with 12 doses being between 36-39 IU/kg, which is reasonable dosing based on vial size, ensuring the dose is +/- 10% of vial size, which is acceptable in clinical practice. The 4 doses that were < 36 IU/kg ranged from 18–27 IU/KG. All 4 were mild BE's that required 1 Vonvendi infusion with excellent hemostatic efficacy:*

- *Patient* (b) (6) *had a mild spontaneous mucosal (nose) BE and received Vonvendi 18 IU/kg. The infusion was interrupted due to "blocked tubing" and not resumed and therefore, the patient did not receive the planned full dose of 50 IU/kg.*
- *Patient* (b) (6) *had 2 mild muscle BE's secondary to injury and received Vonvendi for each BE at a dose of 25 IU/kg and 27 IU/kg. The dose of 25 IU/kg had a planned dose of 65 IU/kg. The dose of 27 IU/kg had a planned dose of 27 IU/kg.*
- *Patient* (b) (6) *had a mild muscle bleed secondary to injury and received Vonvendi I8 IU/kg with a planned dose of 20 IU/kg.*

• *There were 4 BE's with initial Vonvendi treatment dose of > 60 IU/kg with 3 ranging from 62-63 IU/kg, which is reasonable dosing based on vial size, ensuring the dose is +/- 10% of vial size, which is acceptable in clinical practice.*

- *Patient* (b) (6) *had a major BE in which the initial infusion of Vonvendi was 86 IU/kg. It required 3 infusions total with 2 subsequent doses being 42 IU/kg with excellent hemostatic efficacy. The planned initial dose was 80 IU/kg secondary to a major BE.*

• *No BE's were treated with > 45 IU/kg of Advate. 11 BE's were treated with < 30 IU/kg of Advate ranging from 9-29 IU/kg. 2 doses ranged from 27-29 IU/kg, which is reasonable dosing based on vial size, ensuring the dose is +/- 10% of vial size, which is acceptable in clinical practice. 9 doses ranged from 9-26 IU/kg all with excellent hemostatic efficacy.*

- *Patient* (b) (6) *had a mild "other" BE secondary to injury and a moderate spontaneous right ankle bleed both treated with 18 IU/kg (1 planned dose of 18 IU/kg and 1 of 20 IU/kg).*
- *Patient* (b) (6) *had 2 mild muscle bleeds secondary to injury treated with 19 and 20 IU/kg (both with planned dose of 19 IU/kg).*
- *Patient* (b) (6) *had 5 mild BE's treated with 9-26 IU/kg; 1 mucosal (nose) treated with 9 IU/kg with planned dose 25 IU/kg with full dose not received due to "blocked tubing." This patient also had 3 spontaneous mucosal (nose) BE's and 1 right knee BE secondary to injury treated with 24-26 IU/kg. All were mild BE's with a planned dose of 25 IU/kg.*

Reviewer's Comment (SHP 677-304):

- *In SHP 677-304, the mean Vonvendi dose per BE was 56 IU/kg and mean Advate dose was 39 IU/kg.*
- *A total of 46 BE's in 7 patients were treated with an initial dose of Vonvendi with Advate. The per-protocol dose of Vonvendi was 40 to 60 IU/kg. The median dose given was 51 IU/kg with a range 29 to 63 IU/kg. The per-protocol dose of Advate was 30 to 45 IU/kg. The median dose given was 37 IU/kg with a range of 21 to 48 IU/kg. A total of 121 BEs in 13 patients received an initial dose of Vonvendi without Advate due to baseline FVIII level of at least 30%. The median dose was 49 IU/kg with a range 36 to 99 IU/kg without Advate. In 4 patients, at least one additional dose of Vonvendi without Advate was administered in 6 BEs and in 2 patients at least one additional dose of Vonvendi with Advate in 3 BEs was administered every 8 to 24 hours to maintain VWF:RCo and FVIII levels. Of BE's that received Advate, all required 1-2 infusions with 43 BE's (93%) requiring 1 and 3 BE's requiring 2 (7%).*

• *There were 4 BE's treated with initial dose of Vonvendi < 40 IU/kg. 3 patients received doses between 36-39 IU/kg, which is reasonable dosing based on vial size, ensuring the dose is +/- 10% of vial size.*

- *Patient* (b) (6) *received 1 dose of 29 IU/kg for a mild soft tissue bleed secondary to injury (planned dose 25 IU/kg) with excellent hemostatic efficacy.*

• *There were 9 BE's treated with initial dose of Vonvendi > 60 IU/kg, all with excellent or good hemostatic efficacy. 2 patients received doses of 61-63 IU/kg for 4 BE's, which is reasonable dosing based on vial size, ensuring the dose is +/- 10% of vial size.*

- *Patient* (b) (6) *received 1 dose of 67 IU/kg for a spontaneous moderate mucosal (gum) bleed (planned dose 50 IU/kg).*
- *Patient* (b) (6) *received 2 doses of 80 IU/kg for 2 spontaneous mild mucosal (oral) bleeds (planned dose 50 IU/kg).*

- *Patient* (b) (6) *received 1 dose of 88 IU/kg for a mild multiple (joint, skin) bleed secondary to injury (planned dose 50 IU/kg). This patient also received 2 doses of 99 IU/kg for 2 mild "other" bleeds secondary to injury (planned dose 50 IU/kg).*

• *There were 2 BE's treated with Advate outside of per protocol range of 30 to 45 IU/kg. One patient received a dose of 48 IU/kg, which is reasonable dosing based on vial size, ensuring the dose is +/- 10% of vial size.*

- *Patient* (b) (6) *received 1 dose of 21 IU/kg for a mild soft tissue bleed secondary to injury (planned dose 20 IU/kg).*

Secondary Safety Endpoints (071102/SHP 677-304):

- Incidence and severity of adverse events (AEs) by system organ class and preferred term
- Incidence of thrombotic events
- Incidence of severe hypersensitivity reactions
- Development of neutralizing antibodies to VWF and Factor VIII (FVIII)
- Development of total binding antibodies to VWF
- Development of antibodies to Chinese Hamster Ovary (CHO) proteins, murine immunoglobulin G (IgG), and rFurin

There were no thrombotic events, severe hypersensitivity reactions, or antibodies in either 071102 or SHP 677-304. Please see section 8 for integrated adverse event table.

Reviewer's Comment:
Safety analysis was a primary endpoint for RWE Study CCR 2024-200475 and included in that section.

6.2.11.3 Subpopulation Analyses

NA

6.2.11.4 Dropouts and/or Discontinuations

Table 40 Patient Disposition 071102

Study 071102	OD	Surgery	Total
SAF	25	4	29
FAS	18	4	22
Completed Study	24	4	28
Discontinued	1	0	1

*Source: 071102 and integrated 90-day safety update ADSL datasets

Reviewer's Comment:

One patient discontinued 319 days after PK dosing due to physician decision to start prophylaxis. The last dose of OD Vonvendi was given day 313.

Table 41 Patient Disposition SHP 677-304

Study SHP 677-304	OD	Surgery	Total
SAF	16	4	20
FAS	16	4	20
Completed Study	14	2	16
Still on Study	2	1	3
Discontinued	0	1	1

*Source: SHP 677-304 and integrated 90-day safety update ADSL datasets

Reviewer's Comment:

- *1 patient discontinued due to physician decision.*
- *2 patients who underwent surgery were in OD arm (Cohort 5) and 2 in prophylaxis arm (Cohorts 3, 4).*
- *2 subjects analyzed in CCR 2024-200475 completed the study with no dropouts.*

6.2.11.5 Exploratory and Post Hoc Analyses

Exploratory Endpoints (071102 and SHP 677-304):

- Health-related Quality of Life variables for patients aged 2 to 18 years at Screening:
  - Generic: Pediatric Quality of Life InventoryTM (PedsQLTM), Parent proxy version:
- PedsQLTM Child report for children (ages 8 to 12) (23 items).
- PedsQLTM Parent report for young children (ages 5 to 7) (23 items).
- PedsQLTM Parent report for toddlers (ages 2 to 4) (21 items):
  - Health utility: EuroQoL five-dimension questionnaire (EQ-5D): the youth version EQ-5D-Y for patients ≥7 years (parent-proxy version for ages 4 to <7 years).
  - Pain: Visual analog scale.
- HRU (hospitalizations, emergency room visits, doctor office visits, days missed from school, etc.).

In 071102, the PedsQL in the older age groups of 8-18 years, showed improvement in physical, emotional, and social functioning. EQ-5D in patients > 12 showed no change or improvement in all areas besides pain which was "slight" at completion visit (N=4) vs. none at baseline (n=6). In patients 7 to ≤ 12, 1 patient responded at both baseline and completion with no change. In patients 4 to < 7, 1 patient responded at baseline and 2 at completion with no change. The VAS scores were similar at baseline and completion visits across all ages. Finally, HRU was low across all patients.

Reviewer's Comment:

- *In SHP 677-304, in PedsQL showed overall improvements from baseline to 12-month visit. EQ-5D showed no major differences from baseline to 12 months. VAS scores were also similar to slightly decreased from baseline to end of visit. Finally, HRU was low across all patients.*
- *Overall, the number of respondents was low in both studies and not all patients responded at each timepoint. The patient-reported, QOL data were evaluated as part of the application review but given the limitations of QOL assessments in uncontrolled, open-label trials, interpretation of patient-reported outcomes is challenging in uncontrolled clinical trials, because it is unclear to what extent the outcomes can be ascribed to the treatment effect of studied regimen versus to underlying disease and patient characteristics. Therefore, it is difficult to draw conclusions and not included in the label.*
- *There were no exploratory endpoints for RWE Study CCR-2024-200475.*

6.2.12 Safety Analyses

Safety was secondary endpoints for 071102 and SHP 677-304. See section 6.2.11.2 for secondary endpoints and Section 8 for integrated analysis.

CCR 2024-200475 primary endpoint was safety. See section 6.2.11.1 for primary endpoint analysis.

6.2.12.1 Methods

29 patients were included in the SAF from 071102 and SHP 677-304 with 25 in the OD group and 8 in the surgery group. Safety was assessed through TEAEs; development of antibodies to VWF, FVIII, and trace proteins in Vonvendi; and clinical laboratory assessments, vital signs, and electrocardiograms (ECGs). All adverse events were either observed by the investigator or reported by the patient.

2 patients were included in the SAF for this review from RWE study CCR 2024-200475. Safety was assessed through reported TEAE's defined by the EUHASS program and other TEAE's including hypersensitivity/allergic reactions, thrombotic events, VWF inhibitor development, treatment-emergent side effects of therapy, transfusion-transmitted infections, malignancy, cardiovascular events, neurological events, and death.

6.2.12.2 Overview of Adverse Events

In 071102, there were 125 TEAE's in 24 patients; 24 OD patients had 122 TEAE's and 2 surgery patients had 3 TEAE's. Most were mild (84 in 21 (75%) of patients) with 38 in 16 (57%) patients being moderate and 3 severe in 2 (1%) patients. 6 SAE's were reported in 5 (18%) patients. No severe TEAE's or SAE's were related to study drug. There was 1 moderate TEAE of nausea in 1 patient related to study drug. No thromboembolic, serious hypersensitivity, or anaphylactic TEAE's reported. No immunogenicity concerns.

Reviewer's Comment:
The 1 moderate TEAE of nausea is added to the adverse reactions table in the label.

SHP 677-304 had similar safety profile with 116 AE's in 15 patients in OD patients and 1 AE in 1 patient in the surgery patients. Overall, the majority of TEAE's were mild in severity with 1 TEAE in 1 patient considered severe. 5 SAE's were reported in 3 (19%) patients. No severe TEAE or SAE related to study drug. There were 2 TEAEs of potential hypersensitivity of conjunctivitis allergic (mild) and dermatitis (moderate) in 2 (8%) OD patients. Both not related to study drug based on timing of event and resolution without intervention. No thromboembolic, serious hypersensitivity, or anaphylactic TEAE's reported. No immunogenicity concerns

See section 8 for the integrated safety analysis.

Reviewer's Comment:
1 pediatric patient in SHP 677-304 had a binding IgG antibody to FVIII intermittently, both before and after exposure to Vonvendi.

6.2.12.3 Deaths

No deaths in 071102, SHP 677-304, and CCR 2024-200475.

6.2.12.4 Nonfatal Serious Adverse Events

There were 6 SAE's in 5 patients in 071102 and 5 in 3 patients in SHP 677-304. None related to study drug.

6.2.12.5 Adverse Events of Special Interest (AESI)

In 071102, 1 mild AE of pruritis in 1 patient was identified as potential hypersensitivity reaction.

In SHP 677-304, 2 events of mild allergic conjunctivitis and moderate dermatitis were reported in 2 patients. Both not related to study drug based on timing of event and resolution without intervention.

Reviewer Comment:
- *The AE of mild pruritis resolved in and was reported by the investigator as "skin sensitivity to mediport dressing" and occurring prior to study treatment and was not related.*
- *The AE of dermatitis occurred > 24 hours following Vonvendi and considered not related.*

6.2.12.6 Clinical Test Results

The clinical laboratory testing in in 071102, SHP 677-304, and RWE Study CCR-2024-200475 did not identify any clinically important results.

6.2.12.7 Dropouts and/or Discontinuations

No TEAE's resulting in discontinuation from treatment or study.

6.2.13 Study Summary and Conclusions

Study 071102:

- Treatment success of hemostatic efficacy was achieved for all nonsurgical BE's in the OD arm.
- There was 1 emergency surgery in a patient enrolled in the OD arm of 071102 and 3 additional elective surgeries in newly enrolled patients. All were minor surgeries with excellent intra-operative and overall hemostatic efficacy without post-operative bleeding.

Study SHP 677-304:

Similar results as 071102 with treatment success of hemostatic efficacy achieved for all nonsurgical BE's with reported outcomes in the OD arm. Four patients underwent 5 surgeries, 4 minor and 1 oral. Four procedures had overall hemostatic efficacy ratings; all 4 were "excellent". The one missing overall hemostatic efficacy had an intraoperative efficacy rating of "excellent" and adjudicated overall hemostatic efficacy of excellent. Four procedures had intraoperative hemostatic efficacy and blood loss ratings; all 4 were "excellent". The one missing intraoperative hemostatic efficacy and blood loss rating had an overall hemostatic efficacy rating of "excellent." There was no post-operative blood loss in any surgery.

CCR-2024-200475:

Two qualifying surgeries with both outcomes reported as successful. No AE's reported.

7. INTEGRATED OVERVIEW OF EFFICACY

7.1 Indication #1

To expand the current approved adult prophylaxis indication for type 3 VWD to include adults with type 1 and type 2 VWD

Results include data from studies 071301, SHP 677-304, and RWE Study ATHN 9

7.1.1 Methods of Integration

Integrated datasets and study reports were utilized.

7.1.2 Demographics and Baseline Characteristics

See section 1.1

7.1.3 Patient Disposition

Table 4223 Patient disposition for adult prophylaxis indication expansion in studies 071301, SHP 677-304, and RWE Study ATHN 9 (FAS)

Disposition	Prior OD Patients	Prior Prophylaxis Patients
Completed	4	7
Ongoing	0	2
Discontinued	1	3

*Source: 071301, SHP 677-304, and ATHN9 ADSL datasets

Reviewer's Comment:

- *One patient from 071301 excluded from efficacy analysis as patient only received 2 days of prophylaxis treatment prior to discontinuing.*

- *Two patients in 071301 discontinued early due to the need for prohibited medications (steroids).*
- *The mean duration of prophylactic treatment during the study 071301 for FAS (N=4) was 8.6 months with a median duration of 9.2 months.*
- *All patients in SHP 677-304 completed the study.*
- *In ATHN 9, 6 patients completed the study, 2 remain on study, 1 lost to follow up, and 1 discontinued with mean follow up time of 1.6 years.*
- *In Study 071301, two patients from OD group and 1 patient from Switch group received a prophylaxis regimen of Vonvendi 50 units/kg twice weekly throughout the study. One patient in the Switch group with Type 2A VWD received a prophylaxis regimen of 80 units/kg once weekly.*
- *In Study SHP 677-304, all patients started at once weekly prophylaxis at a mean dose of 59 units/kg. Weekly prophylactic dosing was evaluated based on experience with pd-VWF and mean residence time (MRT) of Vonvendi to evaluate a wider dosing range.*
    - *2 switched to twice weekly after 12 months.*
    - *1 switched to every 4 days at about 10 months and then back to weekly at 12 months.*
- *Mean compliance of 94% for both 071301 and SHP 677-304 at data cutoff date January 3, 2025.*
- *In RWE Study ATHN 9, the mean prophylaxis dose was consistent with the label of 50 IU/kg twice weekly at 52 to 53.7 IU/kg, 1.8 to 2.3 times weekly depending on the timepoint assessed of 6 months (N=8), 12 months (N=8), 18 months (N=6), and 24 months (N=6). 8 patients were on prophylaxis with Vonvendi at enrollment with two starting Vonvendi prophylaxis at some point during the study. The data collected for this study doesn't include treatment history prior to enrollment so unknown length of time on Vonvendi prophylaxis, dose/regimen prior to enrollment, and if any history of pd-VWF prior to enrollment. Also, bleeding history prior to enrollment is unknown.*

7.1.4 Analysis of Primary Endpoint(s)

Primary endpoint:
Prospectively recorded ABR for spontaneous (not related to trauma) BEs during prophylactic treatment with Vonvendi and the patients' historical ABR for spontaneous BEs during on-demand treatment.

Reviewer's Comment:
While primary endpoint was spontaneous ABR, this review also assessed total ABR (treated and untreated) and can be found in section 6.1.11.1 Analyses of Primary Endpoint(s).

Table 43 Treated and Untreated sABR in 071301 and SHP 677-304 FAS (N=7)

	071301 OD N = 2	**071301 Switch N = 2**	**SHP 677-304 OD N = 3**	**SHP 677-304 Switch N = 1**	**Total OD N = 5**	**Total Switch N = 2**	**Total N = 7**
Historic							
Mean	3.5	0	10	0	7.4	0	5.3
Median	3.5	0	7	0	4	0	3
Min, Max	3, 4	0, 0	3, 20	0, 0	3, 20	0, 0	0, 20
On study 12 month							
Mean	0	0	2.4	0	1.4	0	1
Median	0	0	3	0	1	0	0
Min, Max	0, 0	0, 0	1, 3.1	0, 0	0, 3.1	0, 0	0, 3.1

*Source: Integrated 071301/SHP 677-304 ADBE dataset and table 2.1.6.1.A in integrated CSR

Table 44 Treated sABR in 071301 and SHP 677-304 FAS (N=7)

	071301 OD N = 2	071301 Switch N = 2	SHP 677-304 OD N = 3	SHP 677-304 Switch N = 1	Total OD N = 5	Total Switch N = 2	Total N = 7
Historic							
Mean	3	0	9.3	0	6.8	0	4.8
Median	3	0	7	0	3	0	3
Min, Max	3, 3	0, 0	3, 18	0, 0	3, 18	0, 0	0, 18
On study 12 month							
Mean	0	0	2.4	0	1.4	0	1
Median	0	0	3	0	1	0	0
Min, Max	0, 0	0, 0	1, 3.1	0, 0	0, 3.1	0, 0	0, 3.1

*Source: Integrated 071301/SHP 677-304 ADBE dataset and table 2.1.6.1.A in integrated CSR

Reviewer's Comment:

- *Four patients in each study but total N = 7 as one patient was a rollover from 071301 onto SHP 677-304*
- *All OD patients met success with at least 25 % decrease in sABR. All switch patients maintained an sABR of 0 historically and on study.*

Clinical outcomes of prophylaxis in patients over 6-month time periods were a secondary outcome for RWE Study ATHN 9:

- 40% of total bleeds and 40% of treated bleeds were spontaneous.
- Mean total ABR was 1 at 6 months (N=9), 1.3 at 12 months (N=9), 1 at 18 months (N=7), and 4.5 at 24 months (N=7).
- Mean total treated ABR was 0.4 at 6 months (N=9), 0.2 at 12 months (N=9), 1 at 18 months (N=7), and 4.1 at 24 months (N=7).

Reviewer's Comment:

- *While not a historical comparison, ATHN 9 supports the claim of low sABR and total ABR while on Vonvendi prophylaxis.*
- *Mean ABR values for the 24-month follow-up visit were higher than the previous timepoints due to one patient experiencing a high number of bleeds during that time.*

7.1.5 Analysis of Secondary Endpoint(s):

Secondary endpoints for 071301 and SHP 677-304 included sABR defined as number of episodes during prophylactic treatment (0, 1-2, 3-5, or >5), number of infusions and consumption of Vonvendi per week and total, and sABR by bleeding location.

Table 45 Number of patients with spontaneous treated BE's during prophylaxis on 071301 and SHP 677-304 (OD = 5 patients and switch = 2 patients)

# of BEs	Historical		12 months		Entire study	
	OD	Switch	OD	Switch	OD	Switch
0	0	2	2	2	2	2
1-2	0	0	1	0	2	0
3-5	3	0	2	0	1	0
>5	2	0	0	0	0	0

*Source: Integrated ADBE dataset

Reviewer's Comment:
All patients in study 071301 and the switch patient in Cohort 1 of SHP 677-304 had 0 sABR. In the OD patients, sABR decreased from historical, at 12 months, and throughout the entire study.

The integrated number of infusions and consumption for prophylaxis was consistent with the label at a mean dose of 55.5 IU/kg per infusion and mean of 1.4 infusions per week. In SHP 677-304, the patients received weekly prophylaxis for the majority of the study with one patient receiving a higher dose of 80 IU/kg weekly. Therefore, the average dose was higher than 071301 at 12 months at 62.2 IU/kg but comparable at data cut off at 58.7 IU/kg with less frequent infusions with a mean of 1.03 infusions per week at 12 months and 1.1 at data cutoff compared to 1.5 in 071301.

Reviewer's Comment:

- *No Advate used in study 071301. Two patients with Advate use for BE's in SHP 677-304:*
    - (b) (6) *required Advate for 4 BEs, all moderate and major, 2 spontaneous and 2 secondary to injury. One BE required 2 Advate infusions with all others requiring 1. All had excellent/good outcome. The baseline Factor VIII was 31%.*
    - (b) (6) *required 1 Advate infusion 1 skin/soft tissue BE secondary to injury with excellent outcome. It was mild per investigator and moderate per the patient. The baseline Factor VIII was 19%.*

Spontaneous ABR by bleeding location while on prophylaxis was similar in 071301 and SHP 677-304. There was 0 sABR in 071301 and in SHP 677-304, treated sABR for mucosal, muscle, joint, GI, menstrual/heavy menstrual was < 1 and 0 for CNS, skin, soft tissue, and body cavity.

7.1.6 Other Endpoints

NA

7.1.7 Subpopulations

The entirety of this review for the adult prophylaxis indication expansion includes only adult patients with severe Type 1 and Type 2 VWD.

7.1.8 Persistence of Efficacy

Patients in 071301 were followed up to 12 months with two completing the 12 months including one that continued onto SHP 677-304. Patients in SHP 677-304 had a maximum duration of participation of 3 years. Overall, across both studies, Vonvendi exposure was 964 days with 969 total infusions with mean duration of prophylaxis of 35.8 months.

7.1.9 Product-Product Interactions

Per the CSR, no studies were done to assess drug-drug interactions with Vonvendi.

7.1.10 Additional Efficacy Issues/Analyses

NA

7.1.11 Efficacy Conclusions

The integrated efficacy data supports the use of prophylaxis with Vonvendi in adults with all types of VWD as it is safe and effective.

7. INTEGRATED OVERVIEW OF EFFICACY

7.2 Indication #2

To expand the use of Vonvendi to children (0 to <18 years of age) with VWD for on demand treatment and control of BEs and perioperative management of bleeding
Results include data from studies 071102, SHP 677-304, and RWE Study CCR-2024-200475

7.2.1 Methods of Integration

Integrated datasets and study reports were utilized.

7.2.2 Demographics and Baseline Characteristics

See section 1.1

7.2.3 Patient Disposition

Table 4624 Patient disposition for pediatric indication expansion (SAF): studies 071102, SHP 677-304, and RWE Study CCR-2024-200475

Disposition	OD Patients	Surgery Patients
Completed	25	10
Ongoing	0	0
Discontinued	1	1

*Source: CCR 2024-200475 ADSL dataset, 90-day safety update dataset for 071102 and SHP 677-304

Reviewer's Comment:

- *Within the clinical trials 071102 and SHP 677-304, there were 29 patients total between OD (25 patients) and surgery (8 patients) patients in the safety analysis and 23 in FAS (21 OD patients and 8 surgery patients). 1 surgery patient discontinued at day 497 but was included in surgery FAS.*
- *18 OD patients and 1 surgery patient transitioned into SHP 677-304. 5 subjects were not dosed for OD BE's during SHP 677-304 and included only in FAS for 071102. 3 subjects were not dosed for OD BE's during 071102 but dosed during SHP 677-304 and included only in FAS for SHP 677-304.*
- *CCR-2024-200474 had 2 patients with qualifying surgeries and reportable outcomes with safety and efficacy data. The severity of VWD in these patients were consistent with the clinical trials as was the follow up postoperative period. The inclusion criteria included "Treatment with Vonvendi to prevent or treat a surgical bleed (defined as Vonvendi treatment either recorded as within 48 hours of index surgical procedure or indicated as preprocedural dose)" and "Minimum of 14 days of clinical data/visit following the date of procedure." Both surgeries had reported treatment success without safety concerns supporting Vonvendi is safe and effective for pediatric surgeries. However, this was a retrospective study with perioperative management at the treating physician's discretion and therefore, may not be consistent with the clinical trials. Therefore, these may not be an accurate comparator to the patients who underwent surgery in the clinical trials.*

7.2.4 Analysis of Primary Endpoint(s)

Primary Endpoint:
The primary endpoint was hemostatic efficacy defined by the number and percentage of pediatric patients with treatment success for treated nonsurgical BEs (4-point scale). A treatment success will be defined as a mean efficacy rating score of <2.5 for treated BE's with excellent = 1, good = 2, moderate = 3, and none = 4.

Table 25 Hemostatic Efficacy (FAS) for treated Nonsurgical bleeds in 071102 and SHP 677-304 (FAS)

Parameter	OD Patients N = 21	≥ 12 To < 18 years N =7	≥ 6 To < 12 years N = 9	< 6 years N = 5
Hemostatic Efficacy Rating (N, %)				
Excellent	256 (96)	83 (93)	127 (96)	46 (98)
Good	4 (1)	0	3 (2)	1 (2)
Moderate	0	0	0	0
None	0	0	0	0
Missing	8 (3.0)	6 (7)	2 (2)	0
Episodes per patient, mean	12.8	12.7	14.7	9.4
Treatment Success	21 (100)	7 (100)	9 (100)	5 (100)

* Source:071102 and SHP 677-304 ADBE datasets

Reviewer's Comment:

- *The primary endpoint for SHP 677-304 was not pertinent to the pediatric indication. However, hemostatic efficacy of BEs was assessed within the secondary endpoint and included with the primary endpoint of hemostatic efficacy for study 071102 for this integrated review.*
- *The endpoints for CCR 2024-200475 were pertinent only to the pediatric surgery indication and are discussed with secondary endpoints for 071102 and SHP 677-304, which included surgery outcomes.*

7.2.5 Analysis of Secondary Endpoint(s)

Number of treated nonsurgical BEs, with an efficacy rating of "excellent" or "good":

Overall hemostatic efficacy rating at the resolution of bleed with respect to the treatment of BEs for the initial 12 months on study treatment (071102 and SHP 677-304).

There was a total of 268 treated nonsurgical BEs between the two studies with 260 having an efficacy rating of good or excellent: 256 with excellent rating, 4 with good rating, and 8 with missing ratings.

Number of infusions and weight- adjusted consumption of Vonvendi and ADVATE (if needed), per BE:
The majority of BE's resolved with one infusion (88%) with a mean dose per infusion of 50 IU/kg and mean dose per BE of 50. 18 (7%) were treated with 2 infusions, 4 (1.5%) were treated with 3 infusions, 1 (0.4%) required 5 infusions, and 2 (0.7%) required > 5 infusions.

Advate was administered for 71 BE's with all but 3 requiring 1 infusion. These 3 BE's required 2 infusions of Advate. The mean dose of Advate across both studies was 35 IU/kg.

Reviewer's Comment:

- *Patient* (b) (6) *in 071102 had two nonsurgical BEs requiring 8 and 9 infusions of Vonvendi. Both were left ankle BE's. Both with excellent outcome.*
- *Patient* (b) (6) *in SHP 677-304 had a moderate spontaneous left hip bleed requiring 2 Advate infusions with excellent outcome.*
- *Patient* (b) (6) *in SHP 677-304 had a moderate multiple site BE (left ankle, left knee, muscle) secondary to injury requiring 2 Advate infusions with good outcome and a moderate muscle bleed secondary to injury requiring 2 Advate infusions with missing outcome.*

For elective or emergency surgery: an overall assessment of hemostatic efficacy 24 hours after the last perioperative infusion of Vonvendi, or on Day 14, whichever is earlier, assessed by the Investigator (hematologist) on a 4-point scale:

There were 9 surgeries in 8 patients between the two studies, 4 in ages 12 to < 18 years, 4 in ages 6 to < 12 years, and 0 in ages < 6 years. Three patients with Type 1 VWD, 1 with Type 2 B, and 4 Type 3 underwent surgeries. There were 8 minor surgeries and 1 oral surgery. Eight surgeries had excellent overall perioperative hemostatic efficacy with 1 missing rating with reviewer adjudication of excellent overall hemostatic efficacy. Eight surgeries had excellent intraoperative hemostatic efficacy with 1 missing rating. Eight surgeries had excellent blood loss rating (actual vs. predicted) of excellent with 1 missing rating. The surgery with a missing overall efficacy was a minor surgery with intraoperative efficacy rating of excellent.

Vonvendi was given pre-op in all 9 surgeries with a mean of 1.6 infusions prior to surgery and mean total dose of 80 IU/kg. None required intra-op infusions, and 8 surgeries received post-op Vonvendi with a mean of 2.3 infusions and mean total dose of 120 IU/kg. Advate was given pre-op in 2 surgeries with a mean of 1 infusion prior to surgery and mean total dose of 42 IU/kg and 1 post-op in 1 surgery with 4 infusions given with a mean total dose of 186 IU/kg. No intraop Advate was required.

Reviewer's Comment:

- *Surgery outcome was an exploratory endpoint in SHP 677-304 but included with secondary endpoint analysis of surgery outcomes in 071102 for this integrated review.*
- *While there were no major surgeries in pediatric patients, there were 10 major and 5 minor surgeries in adult patients included in the label. Overall hemostatic efficacy was excellent in 60% and good in 40%. Intraoperative hemostatic efficacy was excellent in 73.3% and good in 26.7%. In the 10 major surgeries, overall hemostatic efficacy was excellent in 5 and good in 5. In the 5 minor surgeries, overall hemostatic efficacy was excellent in 4 and good in 1.*
- *2 surgeries utilized Advate and were minor surgeries with baseline Factor VIII levels of 1 and 11 IU/dL.*

In CCR-2024-200475, there were two patients with qualifying procedures and outcomes reported. There were no reports of other medications to control hemostasis that were given peri-operatively.

7.2.6 Other Endpoints

Other endpoints included QOL assessments and health resource use. See section 6.2.11.5 Exploratory and Post Hoc Analyses.

Reviewer's Comment:

- *Overall, the number of respondents was low. Also, not all patients responded at each timepoint. Therefore, it is difficult to draw any conclusions from the QOL and HRU data. Given the limitations of QOL assessments in uncontrolled, open-label trials with time-to-event endpoints, interpretation of patient-reported outcomes is challenging as it is unclear to what extent the outcomes can be ascribed to the treatment effect of studied regimen versus to underlying disease and patient characteristics and therefore will not be included in the label.*

7.2.7 Subpopulations

NA

7.2.8 Persistence of Efficacy

24 patients in 071102 were followed 12 to 17 months. Two additional surgery patients were enrolled with 12 months of follow up occurring August 2025. 16 patients from 071102 continued into study SHP 677-304 for on-demand therapy. Two additional patients were included in the surgery arm. SHP 677-304 had a maximum duration of participation of 3 years with all completing the study besides 1.

7.2.9 Product-Product Interactions

Per the CSR, no studies were done to assess drug-drug interactions with Vonvendi.

7.2.10 Additional Efficacy Issues/Analyses

NA

7.2.11 Efficacy Conclusions

The integrated efficacy data supports the use of Vonvendi for on-demand BEs and perioperative management in pediatric patients.

8. INTEGRATED OVERVIEW OF SAFETY

8.1 Safety Assessment Methods

Indication #1

To expand the current approved adult prophylaxis indication for type 3 VWD to include adults with type 1 and type 2 VWD

Integrated datasets and study reports were utilized.

8.2 Safety Database

8.2.1 Studies/Clinical Trials Used to Evaluate Safety

Safety data for 071301 and SHP 677-304 through January 3, 2025, and through August 31, 2024, for ATHN 9.

8.2.2 Overall Exposure, Demographics of Pooled Safety Populations

Table 26 Demographics of clinical trials (071301 and SHP 677-304) and RWE study (ATHN 9) supporting adult prophylaxis indication expansion (SAF)

	Study 071301 N = 5	Study SHP 677-304 N = 4	Total clinical trials N = 8*	ATHN 9 N = 10	Total Including RWE data N = 18*
Age (years)					
Mean	52.2	50	48.1	57.5	53.3
Min, Max	20, 77	30, 76	20, 77	19, 89	19, 89
Sex, n (%)					
Male	4 (80)	3 (75)	6 (75)	3 (30)	9 (50)
Female	1 (20)	1 (25)	2 (25)	7 (70)	9 (50)
Race, n (%)					
White	5 (100)	4 (100)	8 (100)	8 (80)	16 (89)
Asian	0	0	0	1 (10)	1 (5.5)
Black	0	0	0	1 (10)	1 (5.5)
Hispanic/Latino	2 (40)	1 (25)	2 (25)	0	2 (11)
Not Hispanic/Latino	3 (60)	3 (75)	6 (75)	10 (100)	16 (89)
BMI (kg/m2)					
Mean	24.6	30.9	27.3	31.4	29.6
Min, Max	20, 29	21, 39	20, 39	19, 48.6	19, 48.6
VWD Type (%)					
Type 1	3 (60)	0	3 (37.5)	1 (10)	4 (22)
Type 2A	1 (20)	4 (100)	4 (50)	8 (80)	12 (67)
Type 2 B	1 (20)	0	1 (12.5)	1 (10)	2 (11)
Prior Treatment (%)					
OD	3 (60)	3 (75)	6 (75)	2 (20)	8 (44)
Prophylaxis	2 (40)	1 (25)	2 (25)	8 (80)	10 (56)
Geographic Region (%)					
Europe	5 (100)	3 (75)	7 (87.5)	0	7 (39)
US and Canada	0	1 (25)	1 (12.5)	10 (100)	11 (61)

* Source: Integrated CSR and ADSL datasets for 071301 and SHP 677-304; CSR and ADSL and ADVS dataset for ATHN 9
*1 patient participated in both studies 071301 and SHP 677-304

8 patients were included in SAF from studies 071301 and SHP 677-304 with 969 infusions over 964 days administered in these patients with 885 days and doses being prophylaxis infusions and 11 days and doses for PK infusions. The mean duration of prophylaxis was 22.2 months with mean number of prophylaxis infusions per patient of 127 and 1.4 per week.

Ten patients were included in the safety analysis for RWE Study ATHN 9.

8.2.3 Categorization of Adverse Events

For studies 071301 and SHP 677-304, treatment-emergent AEs (TEAEs) are defined as AEs with start dates on or after the first exposure to IP. They were categorized according to MedDra dictionary and summarized by system organ class and preferred terms.

For RWE Study ATHN 9, events defined by the European Union Hemophilia Safety Surveillance System (EUHASS) 2018 were captured and reported prospectively via the ATHN Adverse Event Module. Reportable events are described in section 6.1.11.1.

8.3 Caveats Introduced by Pooling of Data Across Studies/Clinical Trials

Studies 071301 and SHP 677-304 have integrated analyses including datasets and study reports. RWE Study ATHN 9 were captured prospectively with datasets submitted for analysis. While ATHN 9 is adequate to support the data from the clinical trials 071301 and SHP 677-304, different reporting systems, categorization of TEAE's, etc. provides limitations for direct comparative analyses.

8.4 Safety Results

Treatment-emergent AEs (TEAEs) are defined as AEs with start dates on or after the first exposure to investigational product (IP).

A total of 61 TEAE's were reported in 5 patients in 071301 and SHP 677-304 (7 in 3 patients in 071301 and 54 in 3 patients in SHP 677-304). Overall, the majority of TEAE's were mild in severity with 3 TEAE's in 2 patients considered severe: 5 SAE's in 3 patients. None related to study drug. There was 1 TEAE of rash pruritic (local) identified as a potential hypersensitivity reaction in 1 patient which was nonserious, mild in severity, and considered not related to study drug. No thromboembolic, serious hypersensitivity, or anaphylactic TEAE's reported. No deaths or TEAE's resulting in discontinuation of study or study drug. None considered related to study drug.

Table 27 TEAE's in studies 071301 and SHP 677-304 (SAF):

Causality	Mild	Moderate	Severe
Not related	42	15	2
Unlikely related	1	0	1
Related	0	0	0

*Source: Integrated ADAE Dataset

Table 5028 TEAE's in 071301 and SHP 677-304 (SAF) via MedDRA SOC and PT:

System Organ Class (SOC)	Adverse Event	Total (N = 8) N (%)
Blood and lymphatic system disorders	Anemia	2 (25)
	IDA	1 (12)
General disorders and administration site conditions	Pyrexia	2 (25)
Infections and infestations	COVID - 19	2 (25)
	Gastroenteritis	1 (12)
	Pharyngitis	1 (12)
	Pneumonia	1 (12)
Vascular disorders	Hypertension	2 (25)
	Varicose Vein	1 (12)
Congenital, familial, and genetic disorders	Lymphatic malformation	1 (12)
Eye disorders	Cataract	1 (12)
Gastrointestinal disorders	Abdominal pain	1 (12)
	Constipation	1 (12)
	Diarrhea	1 (12)
	Enteritis	1 (12)
	Abnormal stool color	1 (12)
	GERD	1 (12)
	Toothache	1 (12)
	Vomiting	1 (12)
Hepatobiliary	Bile duct stone	1 (12)
	Cholecystitis	1 (12)
	Cholelithiasis	1 (12)
	Hemobilia	1 (12)
Injury, poisoning, and procedural complications	Bone contusion	1 (12)
	Chest injury	1 (12)
	Contusion	1 (12)
	Epicondylitis	1 (12)
	Fibula fracture	1 (12)
	Fracture displacement	1 (12)
	Head injury	1 (12)
	Limb injury	1 (12)
	Post procedural hemorrhage	1 (12)
	Tibia fracture	1 (12)
	Traumatic haematoma	1 (12)
Investigations	ALT increase	1 (12)
	AST increase	1 (12)
	Triglycerides increased	1 (12)
Metabolism and nutrition disorders	Hypogmagnesemia	1 (12)
Musculoskeletal and connective tissue disorders	Back Pain	1 (12)
	Muscle spasms	1 (12)
	Muscular weakness	1 (12)
	Rheumatoid arthritis	1 (12)
	Seronegative arthritis	1 (12)
Psychiatric disorders Respiratory, thoracic and mediastinal disorders	Anxiety	1 (12)
	Asthma	1 (12)
	Catarrh	1 (12)
	Pleural Effusion	1 (12)
Skin and subcutaneous tissue disorders	Ecchymosis	1 (12)
	Pruritic Rash	1 (12)

*Source: Integrated and 90-day safety update ADAE Datasets

In RWE Study ATHN 9, there was one patient who had 9 AE's including 1 event of thrombosis and 8 other included 2 events of acute respiratory failure, 2 events of metabolic encephalopathy, and 1 event of acute

exacerbation of COPD, anemia, closed fracture of humerus, and GI hemorrhage. The patient had multiple co-morbidities. The thrombosis was reported during a hospitalization with multiple complications and risk factors with last dose of Vonvendi received 9 days prior to the hospitalization. Reviewer agrees with assessment of thrombosis not related to Vonvendi. No other AE's reported.

8.4.1 Deaths

No deaths in 071301, SHP 677-304, and RWE Study ATHN 9.

8.4.2 Nonfatal Serious Adverse Events

In 071301 and SHP 677-304, there were 5 nonfatal severe TEAE's in 3 patients, all non-related. The SAE's were rheumatoid arthritis, post-procedural hemorrhage, pneumonia, fibula fracture, and tibia fracture.

8.4.3 Study Dropouts/Discontinuations

No dropouts or continuations secondary to TEAE's in 071301, SHP 677-304, and RWE Study ATHN 9.

8.4.4 Common Adverse Events

See section 8.4.

8.4.5 Clinical Test Results

There were no clinically meaningful changes observed during studies 071301, SHP 677-304, or ATHN 9.

8.4.6 Systemic Adverse Events

See Section 8.4

8.4.7 Local Reactogenicity

One patient in 071301 had 1 nonserious, mild TEAE of rash, reported as potential hypersensitivity reaction, not related to study drug. No other local reactions reported.

None reported in RWE Study ATHN 9.

8.4.8 Adverse Events of Special Interest

In 071301 and SHP 677-304, thromboembolic events, hypersensitivity, and anaphylaxis were considered AESI's. One local rash was reported as potential hypersensitivity reaction, not related to study drug. No other AESI's reported.

There were no AESI's in RWE Study ATHN 9. One thrombosis was reported in 1 patient during a hospitalization with multiple complications and risk factors with last dose of Vonvendi received 9 days prior to the hospitalization. No other AESI's from 071301/SHP 677-304 reported in ATHN 9.

8.5 Additional Safety Evaluations

NA

8.5.1 Dose Dependency for Adverse Events

NA

8.5.2 Time Dependency for Adverse Events

NA

8.5.3 Product-Demographic Interactions

No studies conducted.

8.5.4 Product-Disease Interactions

No studies conducted.

8.5.5 Product-Product Interactions

No studies conducted.

8.5.6 Human Carcinogenicity

None reported.

8.5.7 Overdose, Drug Abuse Potential, Withdrawal, and Rebound

No information on the dependence potential of Vonvendi.

8.5.8 Immunogenicity (Safety)

None of the patients developed binding antibodies to VWF, FVIII, murine immunoglobulin, CHO protein, and/or rFurin, and no confirmed neutralizing antibodies against human VWF or FVIII were reported in all three studies.

8.5.9 Person-to-Person Transmission, Shedding
NA

8.6 Safety Conclusions

Based on the mechanism of action, the main safety concerns for VWF products including Vonvendi are thrombosis, hypersensitivity, anaphylaxis, and immunogenicity. During this review of clinical studies 071301 and SHP 677-304 and RWE Study ATHN 9, there were no concerns for thrombosis, anaphylaxis, or immunogenicity. Therefore, there are no additional safety concerns that changed the favorable safety profile of Vonvendi within the label.

8. INTEGRATED OVERVIEW OF SAFETY

8.2.1 Safety Assessment Methods

Indication #2

To expand the use of Vonvendi to children (0 to <18 years of age) with VWD for on demand treatment and control of BEs and perioperative management of bleeding.

Integrated datasets and study reports were utilized.

8.2.2 Safety Database

8.2.2.1 Studies/Clinical Trials Used to Evaluate Safety

Safety data cutoff date for 071102 and SHP 677-304was January 3, 2025, and January 24, 2025, for CCR 2024-200475.

8.2.2.2 Overall Exposure, Demographics of Pooled Safety Populations

Table 29 Demographics of clinical trials (071102 and SHP 677-304) supporting pediatric on-demand (OD) indication expansion (SAF)

	Study 071102 N = 25	**Study SHP 677-304 N = 16**	**Total N = 25**
Age (years)			
Mean	10	10	10
Min, Max	1, 17	2, 18	1, 17
Age category, n (%)			
≥12 to <18 years	9 (36)	8 (50)	9 (36)
≥6 to <12 years	11 (44)	5 (31)	11 (44)
<6 years	5 (20)	3 (19)	5 (20)
Sex, n (%)			
Male	10 (40)	7 (44)	10 (40)
Female	15 (60)	9 (56)	15 (60)
Race, n (%)			
White	21 (91)	14 (88)	21 (84)
Asian	1 (4)	0	1 (4)
Multiple	1 (4)	1 (6)	1 (4)
Not reported	2	1 (6)	2 (8)
Hispanic/Latino	3 (13)	1 (6)	3 (12)
Not Hispanic/Latino	21 (87)	14 (88)	21 (84)
Not reported	1	1	1
BMI (kg/m2)			
Mean	20	22	20
Min, Max	13, 41	13, 41	13, 41
VWD Type (%)			
Type 1	5 (20)	4 (25)	5 (20)
Type 2A	6 (24)	1 (6)	6 (24)
Type 2 B	3 (12)	3 (19)	3 (12)
Type 3	11 (44)	8 (50)	11 (44)
Geographic Region (%)			
Europe	10 (40)	7 (44)	10 (40)
US	15 (60)	9 (56)	15 (60)

* Source: CSR and ADSL datasets (integrated and 90-day update) for 071102 and SHP 677-304

Table 30 Demographics of clinical trials (071102 and SHP 677-304) and RWE study (CCR-2024-200475) supporting pediatric surgery indication expansion (FAS) and (SAF)

	Study 071102 N = 4	Study SHP 677-304 N = 4	Total in clinical trials N = 8	CCR-2024-200475 N = 2	Total including RWE data N = 10
Age (years)					
Mean	9	13	10	15	11
Min, Max	6, 12	12, 15	6, 13	12, 17	6, 17
Age category, n (%)					
≥12 to <18 years	2 (50)	4 (100)	4 (50)	2 (100)	6 (60)
≥6 to <12 years	2 (50)	0	4 (50)	0	4 (40)
<6 years	0	0	0	0	
Sex, n (%)					
Male	3 (75)	4 (100)	7 (88)	1 (50)	8 (80)
Female	1 (25)	0	1 (12)	1 (50)	2 (20)
Race, n (%)					
White	4 (100)	4 (100)	8 (100)	2 (100)	10 (100)
Not Hispanic/Latino	4 (100)	4 (100)	8 (100)	2 (100)	10 (100)
BMI (kg/m2)					
Mean	17	22	20		20
Min, Max	14, 23	16, 34	14, 33		14, 33
Not reported	0	0	0	2	2
VWD Type, n (%)					
Type 1	1 (25)	2 (50)	3 (38)	1 (50)	4 (40)
Type 2A	0	0	0	1 (50)	1 (10)
Type 2 B	0	1 (25)	1 (12)	0	1 (10)
Type 3	3 (75)	1 (25)	4 (50)	0	4 (40)
Geographic Region, n (%)					
Europe	2 (50)	3 (75)	5 (63)	0	5 (50)
US	2 (50)	1 (25)	3 (37)	2 (100)	5 (50)
Surgery Category, n (%)					
Major	0	0	0	1 (50)	1 (10)
Minor	4 (100)	4 (90)	7 (88)	1 (50)	8 (80)
Oral	0	1 (10)	1 (12)	0	1 (10)

* Source: CSR and ADSL datasets (integrated and 90-day update) for 071102 and SHP 677-304, CSR and ADSL dataset for CCR 2024-200475.

29 patients were included in SAF from 071102 and SHP 677-304. 447 infusions were administered with 385 infusions in 25 patients in the OD arm: 300 to treat BE's, 58 to maintain hemostasis, 25 for PK infusions, and 2 had missing reasons. The 8 surgery patients received a total of 62 infusions peri-operatively.

2 patients were included in SAF for CCR-2024-200475 with 4 infusions given periop (2 pre-op and 2 post-op).

8.2.2.3 Categorization of Adverse Events

For studies 071102 and SHP 677-304, treatment-emergent AEs (TEAEs) are defined as AEs with start dates on or after the first exposure to IP. They were categorized according to MedDra dictionary and summarized by system organ class and preferred terms.

For RWE Study CCR 2024-200475, events defined by the European Union Hemophilia Safety Surveillance System (EUHASS) 2018 were captured and reported prospectively via the ATHN Adverse Event Module.

8.2.3 Caveats Introduced by Pooling of Data Across Studies/Clinical Trials

Studies 071102 and SHP 677-304 have integrated analyses including datasets and study reports. RWE Study CCR 2024-200475 were captured retrospectively with datasets submitted for analysis. While CCR 2024-200475 is adequate to support the data from the clinical trials 071102 and SHP 677-304, different reporting systems, categorization of TEAE's, etc. provides limitations for direct comparative analyses.

8.2.4 Safety Results

A total of 237 TEAE's were reported in 25 patients in 071102 and SHP 677-304 (125 in 24 patients in 071102 and 117 in 16 patients in SHP 677-304). In 071102, 24 OD patients had 122 TEAE's and 2 patients had 3 AE's in the surgery arm. In SHP 677-304, there were 116 AE's in 15 patients in OD patients and 1 AE in 1 patient in the surgery patients. Overall, the majority of TEAE's were mild in severity with 4 TEAE's in 3 patients considered severe and 11 SAE's in 6 patients. None related to study drug. There was 1 moderate TEAE of nausea in 1 patient considered related to study drug. There were 2 TEAEs of conjunctivitis allergic (mild) and dermatitis (moderate) in 2 (8%) OD patients identified as potential hypersensitivity not related to study drug. No thromboembolic, serious hypersensitivity, or anaphylactic TEAE's reported. No immunogenicity concerns. No deaths or TEAE's resulting in discontinuation of study or study drug.

No TEAE's reported in CCR 2024-200475.

Reviewer's Comment:

- *The adverse reaction of nausea in the pediatric patient was included with adults' adverse reactions within the label.*

Table 313 TEAE's in 071102 and SHP 677-304 (SAF) via MedDRA SOC and PT:

System Organ Class (SOC)	Adverse Event	OD (N=25) n (%)	Surgery (n=8) n (%)	Total (N = 29) n (%)
Infections and infestations	COVID -19	8 (32)	0	8 (28)
	URI	7 (28)	0	7 (24)
	Coronavirus	3 (12)	0	3 (10)
	Influenza	3 (12)	0	3 (10)
	Otitis media	2 (8)	1 (12)	3 (10)
	Gastroentiritis	2 (8.0)	0	2 (7)
	Nasopharyngitis	2 (8.0)	0	2 (7)
	Pharyngitis	2 (8.0)	0	2 (7)
	Sinusitis	2 (8.0)	0	2 (7)
	Viral infection	2 (8.0)	0	2 (7)
Gastrointestinal disorders	Vomiting	5 (20.0)	0	5 (17)
	Abdominal Pain	4 (16.0)	0	4 (14)
	Constipation	3 (12.0)	0	3 (10)
	Diarrhea	3 (12.0)	0	3 (10)
	Nausea	3 (12.0)	0	3 (10)
Injury, poisoning, and procedural complications	Fall	2 (8.0)	0	2 (7)
	Ligament sprain	2 (8.0)	0	2 (7)
	Limb injury	2 (8.0)	0	2 (7)
	Sunburn	2 (8.0)	0	2 (7)
	Traumatic hematoma	2 (8.0)	0	2 (7)
Respiratory, thoracic, and mediastinal disorders	Cough	7 (28)	0	7 (24)
	Oropharyngeal pain	5 (20.0)	0	5 (17)
	Nasal congestion	3 (12.0)	0	3 (10)
Bloody and lymphatic system disorders	Iron deficiency anemia	5 (20.0)	0	5 (17)
	Anemia	2 (8.0)	0	2 (7)
	Microcytic Anemia	2 (8.0)	0	2 (7)
	Iron deficiency	2 (8.0)	0	2 (7)
Musculoskeletal and connective tissue disorders	Pain in extremity	3 (12.0)	0	3 (10)
	Arthralgia	2 (8.0)	0	2 (7)
General disorders and administration site conditions	Pyrexia	4 (16.0)	0	4 (14)
Nervous system disorders	Headaches	3 (12.0)	0	3 (10)
Skin and subcutaneous disorders	Rash	3 (12.0)	0	3 (10)
Investigations	ALT increased	2 (8.0)	0	2 (7)

*Source: Integrated and 90-day safety update ADAE Datasets

8.2.4.1 Deaths

There were no deaths in studies 071102, SHP 677-304, or RWE Study CCR 2024-200475.

8.2.4.2 Nonfatal Serious Adverse Events

In 071102 and SHP 677-304 OD patients, there were 4 nonfatal severe TEAE's in 3 patients, all non-related, including were pyrexia, respiratory tract congestion, urinary tract infection, and traumatic hematoma. There were no severe TEAE's in the surgery arm. 11 SAE's in 6 patients, all non-related, including coronavirus, UTI, vascular device infection, Yersinia infection, fall, spinal compression fracture, traumatic hematoma, medical devise extravasation, pyrexia, OCD, and hypotension.

8.2.4.3 Study Dropouts/Discontinuations

No dropouts or continuations secondary to TEAE's in 071102, SHP 677-304, and RWE Study CCR 2024-200475.

8.2.4.3 Common Adverse Events

See Section 8.2.4.

8.2.4.5 Clinical Test Results

In 071102 and SHP 677-304, there were no clinically meaningful changes observed during the studies.

8.2.4.6 Systemic Adverse Events

See Section 8.2.4.

8.2.4.7 Local Reactogenicity

In 071102 and SHP 677-304, there were 2 TEAE's of conjunctivitis allergic and dermatitis in 2 OD patients identified as potential hypersensitivity.

8.2.4.8 Adverse Events of Special Interest

In 071301 and SHP 677-304, thromboembolic events, hypersensitivity, and anaphylaxis were considered AESI's. Two TEAE's of conjunctivitis allergic and dermatitis identified as potential hypersensitivity reactions in 2 OD patients. No other AESI's reported.

8.2.5 Additional Safety Evaluations

NA

8.2.5.1 Dose Dependency for Adverse Events

NA

8.2.5.2 Time Dependency for Adverse Events

NA

8.2.5.3 Product-Demographic Interactions

No studies conducted.

8.2.5.4 Product-Disease Interactions

No studies conducted.

8.2.5.5 Product-Product Interactions

No studies conducted.

8.2.5.6 Human Carcinogenicity

None reported.

8.2.5.7 Overdose, Drug Abuse Potential, Withdrawal, and Rebound

No information on the dependence potential of Vonvendi.

8.2.5.8 Immunogenicity (Safety)

No immunogenicity concerns.

Reviewer's Comment:

- *1 pediatric patient in SHP 677-304 had a binding IgG antibody to FVIII intermittently, both before and after exposure to Vonvendi.*
- *No neutralizing antibodies against VWF or FVIII reported. No other antibodies reported including VWF, murine IgG, CHO protein, or rFurin.*

8.2.5.9 Person-to-Person Transmission, Shedding
NA

8.2.6 Safety Conclusions

Based on the mechanism of action, the main safety concerns for VWF products including Vonvendi are thrombosis, hypersensitivity, anaphylaxis, and immunogenicity. During this review of clinical studies 071102 and SHP 677-304 and RWE Study CCR 2024-200475, there were no concerns for thrombosis, anaphylaxis, or immunogenicity. Therefore, there are no additional safety concerns that changed the favorable safety profile of Vonvendi within the label.

9. ADDITIONAL CLINICAL ISSUES

9.1 Special Populations

9.1.1 Human Reproduction and Pregnancy Data

No pregnancies were reported during this study. Vonvendi has not been evaluated in pregnant women. Animal developmental and reproductive toxicity studies have not been conducted with Vonvendi. It is not known if Vonvendi can cause fetal harm when administered to pregnant women or whether it can affect reproductive abilities.

9.1.2 Use During Lactation

Vonvendi has not been evaluated in lactating women. There is no information regarding the presence of Vonvendi in human milk, its effect on breastfed infant or its effect on milk production.

9.1.3 Pediatric Use and PREA Considerations

As an orphan designated product, Vonvendi is not patient to PREA. This review includes the indication for on demand treatment and control of BEs and perioperative management of bleeding in the pediatric population (0 to <18 years of age).

9.1.4 Immunocompromised Patients

This product has not been specifically evaluated in immunocompromised patients. However, it is not an immunomodulatory agent and there is no reason to expect a different outcome in efficacy or safety in immunocompromised patients.

9.1.5 Geriatric Use

Within this review, there were only 3 patients above the age of 65. Due to the small number, a safety and efficacy comparison of the geriatric population vs. younger populations was not done.

9.2 Aspect(s) of the Clinical Evaluation Not Previously Covered

NA

10. CONCLUSIONS

Data from 5 studies was reviewed in support of the two indication expansions.

Indication 1: To expand the current approved adult prophylaxis indication for type 3 VWD to include adults with type 1 and type 2 VWD:
Integrated data from studies 071301 and SHP 677-304 and RWE Study ATHN 9. Studies 071301 and SHP 677-304 demonstrated that prophylaxis with Vonvendi with Type 1 and 2 is safe and effective. Patients on prior OD therapy had decreased spontaneous and total ABR compared to historical ABR. Patients on prior prophylaxis with pd-VWF that switched to Vonvendi maintained 0 sABR. Treatment success was defined as ≥ 25% reduction in sABR, which was achieved in all patients in both studies.

RWE Study ATHN 9 supported the clinical trials with 10 patients meeting the same pre-specified inclusion criterion including the definition of severe Type 1 and Type 2 VWD. There are limitations with this trial as it is an observational study requiring patients to submit responses at each timepoint for data and not all patients submitted responses at each timepoint. The limited data is supportive that Vonvendi prophylaxis is safe and effective.

Indication 2: To expand the use of Vonvendi to children (0 to <18 years of age) with VWD for on demand treatment and control of bleeding episodes and perioperative management of bleeding:
Integrated data from studies 071102 and SHP 677-304 and RWE Study CCR 2024-200475. Studies 071102 and SHP 677-304 demonstrated that Vonvendi for on-demand BEs and perioperative management is safe and effective in the pediatric population with all on-demand BEs and perioperative management that had reported outcomes achieving hemostatic efficacy.

RWE Study CCR 2024-200475 supported the clinical trials for the pediatric surgery indication with 2 patients meeting the same pre-specified inclusion criterion including the definition of severe VWD. There are limitations as it is a retrospective, observational study with potential for missing data. Although a small sample size, the data is supportive that Vonvendi is safe and effective in the perioperative management in the pediatric population.

11. RISK-BENEFIT CONSIDERATIONS AND RECOMMENDATIONS

11.1 Risk-Benefit Considerations

Table 54 Risk-Benefit Considerations

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• VWD is the most common inherited bleeding disorder affecting about 1% of general population with symptomatic VWD prevalence estimated at 1 in 10,000. Symptoms include serious and sometimes life-threatening bleeding complications. These BEs can be spontaneous or secondary to injury/trauma. • Long-term complications of bleeding can include joint arthropathy secondary to recurrent bleeding potentially leading to need for orthopedic surgery, iron deficiency anemia, surgical procedures to stop bleeding including nasal cauterization, endometrial ablation/hysterectomy, and GI endoscopy/colonoscopy. • Prophylaxis to prevent or reduce the frequency of BEs would improve patient outcomes and help reduce economic burden to the US healthcare system. Access to recombinant VWF in the pediatric population for OD BEs and perioperative management would decrease the risk of blood-borne viral transmission and the burden of testing for these viruses in this patient population.	• Severe forms of VWD are associated with acute and long-term clinical manifestations and complications, which can't result in negative effects on patient QOL and a high level of HRU.
Unmet Medical Need	• There are currently no available recombinant VWF products approved in the US for prophylaxis for all types of VWD in adult patients. Currently, Vonvendi is approved for prophylaxis in Type 3 VWD. Available VWF products for Types 1 and 2 include pd-VWF. There are currently no available recombinant VWF products approved in the US for pediatric patients with VWD. Only pd-VWF is currently approved in the pediatric population.	• Routine prophylaxis of VWD is needed for subjects with recurrent BEs to prevent life-threatening bleeding and long-term complications. • On demand treatment for BEs and perioperative management is needed in the pediatric population to treat potentially life-threatening bleeding or those that can cause long-term complications.
Clinical Benefit	• The key benefits of prophylaxis with Vonvendi in adult patients with VWD investigated in the pivotal prophylaxis and continuation studies include: • Prophylaxis prevents and/or reduces the frequency of spontaneous BEs. • Prophylaxis may reduce or avoid serious complications and sequelae associated with recurrent BEs. • The key benefits of treatment with Vonvendi for on-demand BEs and perioperative management in pediatric patients include: • On-demand treatment BEs achieved hemostatic efficacy • Perioperative management achieved hemostatic efficacy	• Routine prophylaxis with Vonvendi prevents or reduces the frequency of BE's in adults with VWD. • In pediatric patients, Vonvendi was successful in treating BEs and in perioperative management. • Overall, recombinant would decrease the risk of blood-borne viral transmission and the burden of testing for these viruses in this patient population.
Risk	• The key risks are based on the safety results in the pivotal trials and continuation studies as well as use in the approved indications. • Potential concerns based on its mechanism of action and other VWF products include thrombosis, hypersensitivity/anaphylactic reactions, and immunogenicity. • There was no new safety concerns identified in this review.	• No new risks were identified in review of the pivotal trials and continuation studies and the risk management activities described in the current risk management plan continue to appear adequate for ongoing Vonvendi risk evaluation
Risk Management	• Limitations include small sample sizes for this rare disease	• Small sample sizes are usual for clinical research in rare diseases. • Routine pharmacovigilance will monitor risks for this product.

11.2 Risk-Benefit Summary and Assessment
Indication 1: To expand the current approved adult prophylaxis indication for type 3 VWD to include adults with type 1 and type 2 VWD

The benefits of prophylaxis with Vonvendi in Type 1 and Type 2 VWD, observed as a reduction in sABR in patients who switched from on-demand and maintenance of sABR in patients who switched from prophylaxis with pd-VWF support meeting an unmet medical need in these patients. The safety profile remains favorable in this patient population. Overall, the risks appear to be minimal, transient and treatable or self-resolving supporting a favorable benefit-risk profile.

Indication 2: To expand the use of Vonvendi to children (0 to <18 years of age) with VWD for on demand treatment and control of bleeding episodes and perioperative management of bleeding

The benefits of treatment with Vonvendi in the pediatric population for on-demand BE's and perioperative management, observed as successful hemostatic efficacy support meeting an unmet medical need in pediatric patients with VWD. The safety profile remains favorable in this patient population. Overall, the risks appear to be minimal, transient and treatable or self-resolving supporting a favorable benefit-risk profile for the use of Vonvendi.

11.3 Recommendations on Regulatory Actions
The clinical review team recommends approval of both indication expansions including:
1. To expand the current approved adult prophylaxis indication for type 3 VWD to include adults with type 1 and type 2 VWD.
2. To expand the use of Vonvendi to children (0 to <18 years of age) with VWD for on demand treatment and control of BEs and perioperative management of bleeding.

11.4 Labeling Review and Recommendations
In section 6.1, the adverse reactions table is a pooled analysis of both adult and pediatric patients. There was only 1 additional adverse reaction of nausea within pediatrics and no additional adverse reactions in adults.

RWE studies were not included in the label and is supportive evidence only for the indication expansions. Prior communication with the applicant stated that the RWE would be reviewed as supportive and only patients that met the pre-specified criterion of the definition of severe VWD within the clinical trials would be included in the review:

- RWE study TAK -507-4007 did not include datasets, and we are unable to confirm that the patients included met the definition of severe VWD that were within the clinical trials and therefore, this study was not included in the review of this s-BLA.
- RWE study CCR 2024-200475 was a retrospective study. While CCR 2024-200475 did include datasets and confirmation that the patients did meet the definition of severe VWD included within the clinical trials, retrospective does have limitations including the potential for missing data and therefore was not included in the label.
    - RWE Study ATHN 9 was a longitudinal, observational, prospective study that did include datasets as well confirmation that patients did meet the definition of severe VWD included within the clinical trials. However, there are

limitations with this trial as it is an observational study requiring patients to submit responses at each timepoint for data allowing for missing data and therefore should not be included in the label.

Reviewer's Comment:
The RWE team was consulted for this review with recommendations included in sections 6.1.13 and 6.2.11.1.

11.5 Recommendations on Postmarketing Actions

The pharmacovigilance plan proposed by the sponsor is adequate. The available data do not indicate a safety concern that would necessitate a Risk Evaluation and Mitigation Strategy (REMS), a post marketing commitment (PMC) or a required post marketing (PMR) study specifically designed to evaluate a safety concern. The continuation Study SHP677-304 ending January 30, 2025, collected additional safety data for adults and children up to 3 years and added to the overall clinical safety dataset for Vonvendi. Safety data from this trial and routine pharmacovigilance will provide additional safety information about Vonvendi. Therefore, the review team does not recommend a post-marketing safety study.

Addendum:
The final CSR for the continuation study SHP 677-304 was submitted July 29, 2025, with data cutoff date January 30, 2025. The final CSR data was not included in this review. This review reflects safety analysis for both pediatric OD and surgery patients as well as adult prophylaxis patients and efficacy analysis only for pediatric surgery patients through January 3, 2025, in SHP 677-304. The efficacy analysis cutoff date for OD pediatric patients and adult prophylaxis patients with Type 1 and Type 2 VWD remains January 26, 2024. While not included in this memo, a brief review of the final CSR for SHP 677-304 demonstrates that it aligns with the key safety and efficacy findings discussed in this memo.