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Application Type	Supplemental Biologic License Application (sBLA)
STN	125577/691
CBER Received Date	03/12/25
PDUFA Goal Date	09/11/25
Division / Office	DCEH/OCE/OTP
Committee Chair	Christine Knoll, M.D.
Clinical Reviewer(s)	Christine Knoll, M.D.
Project Manager	Nevitt Morris
Priority Review	Yes
Reviewer Name(s)	Jiyeon Song, Ph.D. Visiting Associate, TEB2/DB/OBPV
Supervisory Concurrence	Lin Huo, Ph.D. Team Lead, TEB2/DB/OBPV
	Lihan Yan, Ph.D. Branch Chief, TEB2/DB/OBPV
Applicant	Takeda Pharmaceuticals USA, Inc.
Established Name	von Willebrand Factor (recombinant)
(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 dehydrates, stabilizer
Dosage Form(s) and Route(s) of Administration	rVWF: Lyophilized powder and solvent to prepare solution for injection
Dosing Regimen	The initial infusion of rVWF:RCo will be at a dose of 40 to 80 IU/kg, along with 30 to 45 IU/kg ADVATE
Indication(s) and Intended Population(s)	• To expand the current approved adult routine prophylaxis indication for type 3 VWD to include adults with type 1 and type 2 VWD • 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

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GLOSSARY

Abbreviation	Definition
ABR	Annualized Bleeding Rate
AE	Adverse Event
AESI	Adverse Event of Special Interest
BE	Bleeding Episodes
BLA	Biologics License Application
CBER	Center for Biologics Evaluation and Research
CI	Confidence Interval
EU	European Union
FAS	Full Analysis Set
FDA	Food and Drug Administration
FVIII	Factor VIII
FVIII:C	Factor VIII Clotting Activity
IP	Investigational Product
IR	Information Request
ISE	Integrated Summary of Efficacy
ISS	Integrated Summary of Safety
MedDRA	Medical Dictionary for Regulatory Activities
MHLW	Ministry of Health, Labour and Welfare
OD	On-demand
PD	Pharmacodynamic
pdVWF	Plasma Derived von Willebrand Factor Product
PeRC	Pediatric Review Committee
PK	Pharmacokinetic
PP	Per-protocol
rFVIII	Recombinant Factor VIII
rVWF	Recombinant von Willebrand Factor
RWE	Real World Evidence
sABR	Spontaneous Annualized Bleeding Rate
SAE	Serious Adverse Event
SAER	Serious Adverse Event Report
SAF	Safety Analysis Set
SAP	Statistical analysis plan
sBLA	Biologics License Application Supplement
SD	Standard Deviation
SUSAR	Suspected Unexpected Serious Adverse Reaction
TEAE	Treatment-Emergent Adverse Event
UK	United Kingdom
US	United States
VWD	von Willebrand Disease

VWF	von Willebrand Factor
VWF:RCo	von Willebrand Factor: Ristocetin cofactor activity

1. EXECUTIVE SUMMARY

The applicant (Takeda Inc.) submitted on a supplemental biologics license application (sBLA, STN**:** 125577/691) for VONVENDI (recombinant von Willebrand Factor [rVWF]) to 1) expand the currently approved routine prophylaxis indication in adult patients with type 3 von Willebrand disease (VWD) to include adult patients with type 1 and type 2 VWD, and 2) to expand the use of VONVENDI to pediatric patients (0 to <18 years of age) with VWD for on demand treatment and control of bleeding episodes, and perioperative management of bleeding.

The safety and efficacy evidence supporting this supplement for VONVENDI is based on three Phase 3 clinical studies: Study 071102, Study 071301 (from STN**:** 125577/616), and the continuation study SHP 677-304.

Efficacy

For the pediatric on-demand treatment and control of bleeding episode indication, Study 071102 demonstrated 100% treatment success in 104 evaluable non-surgical bleeding episodes among all 18 pediatric patients (95% CI: 81.5–100%), with 94% (98 out of 104) of the episodes rated as "excellent" (97) or "good" (1). In Study SHP677-304, 16 patients experienced 164 bleeding episodes, of which 160 were rated "excellent" and 2 "good" with 2 missing ratings. For the pediatric perioperative management of bleeding indication, Study 071102 reported "excellent" hemostatic efficacy in two minor surgeries across two patients, and four were rated "excellent" with one rating missing across five elective procedures in four patients in Study SPH677-304.

For the Type 3 VWD adult routine prophylaxis indication, Study 071301 showed substantial benefit in patients transitioning from on-demand therapy (n=12 including 2 Types 1 and 2 patients), with median annualized bleeding rates (ABRs) for treated spontaneous and traumatic bleeds decreasing from 4.0 to 0.0, all spontaneous and traumatic bleeds from 4.5 to 0.5, and joint bleeds from 1.5 to 0.0. Patients switching from other prophylaxis regimens (n=10 including 2 Types 1 and 2 patients) maintained low treated bleed rates at 0.0, though all spontaneous and traumatic bleeds (including untreated bleeds) increased from 1.0 to 3.6, with joint bleeds remaining at 0.0. Integrated data from Studies 071301 and SPH 677-304 confirmed these findings in seven adult patients with Type 1 and Type 2 VWD. Five patients (one Type 1 and four Type 2) previously received on-demand treatment experienced a reduction in median spontaneous annualized bleeding rate (sABR) from 3.0 to 1.0 after 12 months of rVWF prophylaxis. Two patients (one Type 1 and one Type 2) switching to rVWF prophylaxis maintained a sABR of 0.

Safety

For safety evaluation, 5 (19.2%) pediatric patients in Study 071102 experienced 6 serious treatment-emergent adverse events (TEAEs). In Study SHP677-304, 4 serious TEAEs were reported by 2 (11%) pediatric patients, and 4 serious TEAEs occurred in 2

(50%) adult patients. The applicant determined that all these serious TEAEs were unrelated to the investigational products. Further evaluation of safety data is deferred to the clinical team.

Conclusion and Recommendation

No major statistical issues were identified in the review of this submission. The efficacy results were confirmed by independent analyses and support the proposed indication expansions. No major safety concerns were identified. I defer to the clinical team on the acceptance of overall safety profile of VONVENDI.

2. CLINICAL AND REGULATORY BACKGROUND

2.1 Disease or Health-Related Condition(s) Studied

von Willebrand Disease (VWD) is the most frequently inherited bleeding disorder, affecting approximately 1% of the general population, although the incidence of clinically manifested or diagnosed cases is lower: about 100 cases per million (Gill 2007; Goodeve et al. 2010; Mannucci 2004). Von Willebrand Disease is classified into three main types (1, 2, and 3) with peculiar phenotype and genotype (Gill 2007).

VWD patients, especially those with type 2 or 3 disease, face increased risk for life-threatening bleeding requiring immediate or prophylactic treatment to correct VWF (mucosal bleeding) or FVIII deficiencies (soft tissue and post-operative bleeding). Treatment aims to correct both abnormal coagulation (low FVIII levels) and impaired platelet adhesion (prolonged bleeding time). Desmopressin acetate (DDAVP) is first-line therapy for type 1 VWD, as it releases endogenous VWF from cellular stores, correcting FVIII/VWF levels and bleeding time in most cases (Castaman et al. 2003). For type 3 and severe forms of types 1 and 2 VWD where DDAVP is ineffective, FVIII/VWF replacement therapy is required for bleeding episodes, surgery, and long-term prophylaxis (Mannucci 2004).

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

Please refer to the clinical review.

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

VONVENDI (recombinant von Willebrand Factor [rVWF]) received its initial approval in the United States on December 8, 2015, for the treatment and control of bleeding episodes in adults with VWD. On April 13, 2018, its indication was expanded to include

perioperative management in adult patients with VWD, and on January 28, 2022, it was further approved for prophylaxis in adults with type 3 VWD. In the United States (US), Canada, and Japan, the product is marketed under the trade name VONVENDI, whereas in the European Union (EU), Switzerland, and Australia, it is marketed as VEYVONDI.

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

In January 2022, VONVENDI gained U.S. approval for prophylaxis in adults with type 3 VWD. In November 2023, a Type C meeting reviewed evidence on VONVENDI's effectiveness and safety for on-demand (OD) treatment, perioperative management, and prophylaxis in pediatric patients with VWD, with feedback and follow-up on real-world evidence (RWE) studies for a planned supplemental Biologics License Application (sBLA). In March 2025, an sBLA was submitted to extend adult prophylaxis to types 1 and 2 VWD and to extend pediatric indications (0 <18 years) for OD treatment, perioperative management, and prophylaxis. Priority review was granted.

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

5.1 Review Strategy

In STN 125577/691, the applicant submitted efficacy and safety data from two Phase 3 clinical studies 071102 and SHP677-304 to support a labeling expansion for pediatric patients and adult patients with VWD. Study 071102 was a phase 3, prospective, uncontrolled, open label study to determine the efficacy, safety, tolerability of VOVENDI with or without ADVATE in the treatment and control of bleeding episode. Study SHP677-304 was a phase 3b prospective, open-label, uncontrolled, unrandomized study evaluating long-term safety and efficacy of VONVENDI for prophylaxis and OD treatment of bleeding episodes.

Only interim prophylaxis data for adult patients with type 1 and type 2 VWD from Study SHP677-304 was used to support the labeling expansion regarding the prophylaxis indication in adults, based on January 26, 2024 data cutoff prior to study completion. These two studies were reviewed individually in Section 6 of this memo. Furthermore, to provide the integrated evaluation for the indication of routine prophylaxis to reduce the frequency of bleeding episodes in adults with VWD Types 1, 2 and 3, data from Study 071301 submitted under BLA 125577/616 and Study SPH677-304 were reviewed in Section 7.1.

The sponsor provided the completed study report for Study SPH677-304 (STN 125577/767) on July 29, 2025, as an amendment of this efficacy supplement submission. This report was presented to provide final safety analysis updates and was

reviewed in this memo. The comprehensive evaluation of the safety has been deferred to the clinical review team for further analysis.

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

- Application Orientation Meeting (AOM) slides, presented by the applicant on April 23, 2025.
- STN 125772/691 Module 1.14 Labeling.
- STN 125772/691 Module 1.2 Reviewer's Guide.
- STN 125772/691 Module 2.5 Clinical Overview.
- STN 125772/691 Module 2.7.3 Summary of Clinical Efficacy.
- STN 125772/691 Module 2.7.4 Summary of Clinical Safety.
- STN 125772/691 Module 2.7.6 Synopses of Individual Studies.
- STN 125772/691 Module 5.2 Tabular Listing of all Clinical Studies.
- STN 125772/691 Module 5.3.5.2 Study 071102 Protocol, Statistical Analysis Plan (SAP), Clinical Study Report (CSR) and supporting documents and datasets.
- STN 125772/691 Module 5.3.5.2 Study SHP677-304 Protocol, SAP, CSR and supporting documents and datasets.
- STN 125772/616 Module 5.3.5.2 Study 071301 Protocol, SAP, CSR and supporting documents and datasets.
- STN 125772/691 Module 5.3.5.3 Integrated Summary of Safety for Adult Patients.
- STN 125772/691 Module 5.3.5.3 Integrated Summary of Safety for Pediatric Patients.
- STN 125772/691 Response to Statistical Information Request #1 submitted on June 23, 2025.
- STN 125772/538 FDA Information Request dated November 30, 2021.

5.3 Table of Studies/Clinical Trials

Table 1 summarizes the overview of individual studies in the clinical program.

Table 1. Overview of Individual Studies

Protocol (Phase)	Key Objective	Design	Treatment/ Treatment Duration	Endpoint	Sample Size	Status
071102 (PHASE 3)	Determine the efficacy, safety, and tolerability of VONVENDI: 1) with or without ADVATE in the treatment and control of bleeding Episodes, 2) in elective and emergency surgeries in *pediatric* patients with severe VWD.	Prospective, multicenter, uncontrolled, open label	• OD treatment of nonsurgical bleeding • Surgical procedures: Elective Surgery / Emergency surgery. • Up to 20 months.	Hemostatic efficacy (as the number of pediatric patients with treatment success for VONVENDI - treated nonsurgical bleeding episodes.	Planned: 24 patients Actual: 26 (by 12/01/2023) - OD = 25 - Surgery = 2 (1 patient enrolled in both OD and surgery arm)	Complete
SHP677-304 (PHASE 3B)	Evaluate long-term safety and efficacy, of VONVENDI for prophylaxis and on-demand (OD) treatment of bleeding episodes in *adult and pediatric* patients with severe VWD.	Prospective, open-label, uncontrolled, non-randomized, multicenter	• Prophylactic treatment • On-demand treatment • At least 12 months	1) Spontaneous annualized bleeding rate. 2) hemostatic efficacy.	Planned: Up to 71 patients Actual: - Adult = 4 - Ped = 18 (by 01/26/2024)	Complete
071301 (PHASE 3)	Investigate the efficacy and safety of prophylactic treatment with VONVENDI in *adult* patients with severe VWD.	Prospective, open label, international multicenter	• The Prior OD: previously received OD treatment. • The Switch: previously taking prophylactic pdVWF treatment prior to study. • At least 12 months up to 15 months.	Annualized bleeding rate (ABR) for treated spontaneous bleeding episodes.	Planned: 22 patients Actual: 23 - OD = 13 - Switch = 10	Complete

Abbreviations: VWD- von Willebrand disease; OD – On demand; pdVWF - plasma derived von Willebrand factor product.
Source: Adapted from sBLA 125577/691; Clinical Overview, Table 1.a.

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 Study 071102

Study 071102 is titled as "Phase 3, prospective, multicenter, uncontrolled, open-label clinical study to determine the efficacy, safety, and tolerability of rVWF with or without ADVATE in the treatment and control of bleeding episodes, the efficacy and safety of rVWF in elective and emergency surgeries, and the pharmacokinetics (PK) of VONVENDI in rVWF diagnosed with severe von Willebrand Disease."

6.1.1 Objectives (Primary, Secondary, etc)

6.1.1.1 Primary Objectives

The primary objective was 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.

6.1.1.2 Secondary Objectives

- To evaluate the hemostatic efficacy following the last perioperative VONVENDI in patients undergoing elective or emergency surgery.
- To evaluate the safety of VONVENDI.
- To evaluate the PK of VONVENDI.

6.1.2 Design Overview

Study 071102 was a prospective, multicenter, open-label, uncontrolled Phase 3 trial that evaluated the on-demand treatment of nonsurgical bleeding episodes and the perioperative management of bleeding in pediatric patients with severe, hereditary VWD.

The study consists of 3 treatment arms: On-demand, elective surgery, and emergency surgery. The study planned to enroll approximately 34 pediatric patients, including at least 24 in the on-demand treatment arm and at least 10 who underwent surgical or invasive procedures, with a minimum of 12 procedures in total (including at least 3 major and up to 9 minor across age cohorts). The on-demand arm had a planned 12-month treatment period, which was extended to 18 months in certain cases due to delays in initiating the continuation study. Some surgical patients also transitioned to the on-demand arm post-operatively when eligibility criteria were met.

The study population was stratified into three age cohorts, each with at least 8 evaluable patients: Cohort 1 (≥12 to <18 years), Cohort 2 (6 to <12 years), and Cohort 3 (<6 years, including at least 3 children with Type 3 VWD). This structured approach allows for stepwise safety, PK, and efficacy evaluation while building comprehensive evidence for VONVENDI use across bleeding and surgical settings in pediatric VWD.

6.1.3 Population

This study enrolled pediatric patients (<18 years of age) with severe, hereditary VWD defined as von Willebrand factor: ristocetin cofactor activity (VWF:RCo) < 20%.

6.1.4 Study Treatments or Agents Mandated by the Protocol

The initial on-demand dose of VONVENDI is 40-80 IU/kg with 30-45 IU/kg ADVATE, unless the patient maintains hemostatically effective baseline FVIII levels. Subsequent bleeding episodes are treated with VONVENDI 40-60 IU/kg, with ADVATE 30-45 IU/kg administered only when plasma FVIII levels fall below 30 IU/L during treatment.

For surgical procedures, VONVENDI loading dose of 40-60 IU/kg should be administered within 3 hours prior to surgery. ADVATE 30-45 IU/kg may be infused sequentially within 10 minutes after VONVENDI in patients whose FVIII plasma levels are below 40-50 IU/dL for minor/oral surgery or 80-100 IU/dL for major surgery.

6.1.6 Sites and Centers

The study 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).

6.1.7 Surveillance/Monitoring

Please refer to the clinical review for more details on study surveillance and monitoring.

6.1.8 Endpoints and Criteria for Study Success

Primary

Hemostatic efficacy, defined as the number of pediatric patients with treatment success for VONVENDI-treated nonsurgical bleeding episodes (using a 4-point scale; Excellent = 1/Good=2/Moderate=3/None=4).

Secondary

- Number of treated nonsurgical bleeding episodes with an efficacy rating of ‘excellent’ or ‘good’.
- Number of infusions, VONVENDI units, and ADVATE units (if needed), per bleeding episode.
- For elective/emergency surgery: an overall assessment of hemostatic efficacy 24 hours after the last perioperative infusion of VONVENDI, assessed by the Investigator (hematologist) on a 4-point scale.

Safety

- Incidence and severity of adverse events (AEs) by system organ class (SOC) and preferred term.
- Incidence of thrombotic events.
- Incidence of severe hypersensitivity reactions.

- Development of neutralizing antibodies to VWF and FVIII.
- Development of total binding antibodies to VWF.
- Development of antibodies to CHO proteins, murine IgG, and rFurin.

Success Criterion
Bleeding episode treatment success was proposed as a mean efficacy rating score of <2.5.

6.1.9 Statistical Considerations & Statistical Analysis Plan
Sample Size
At least 24 pediatric patients with severe VWD were planned, which was not based on a power calculation for a significance test.

Statistical Hypotheses
No formal statistical tests were considered in the study.

Analysis population/sets
Analyses sets are given as follows:

- The full analysis set (FAS): all patients who received any amount of study drug and provided at least on hemostasis assessment withing 24 hours of a study drug infusion with or without ADVATE.
- The per protocol analysis set (PPAS): all patients with available overall assessment of hemostatic efficacy assessed by the Investigator 24 hours after last infusion of study drug or at Completion Visit.
- The safety analysis set (SAF): all patients who received the IP with or without ADVATE.

Analysis for Primary/Secondary Endpoints
Descriptive summaries were to be presented for the primary, and secondary outcome measures.

For primary endpoint analysis, point estimates and corresponding 2-sided exact 95% confidence intervals (CI) were to be calculated for the rate of patients with a treatment success.

The secondary efficacy outcome measures of the number of treatment bleeding episodes with an efficacy rating of 'excellent' or 'good' and hemostatic efficacy in the case of elective surgery were to be analyzed by presenting point estimates of counts and proportions.

Supplementary Analysis

- Subgroup Analysis: Both primary and secondary endpoint analyses presented efficacy results stratified by treatment arms (on-demand/elective surgery/emergent

surgery), age cohorts (<6 years/6 to 12 years/12 to 18 years), surgical procedure types (minor, major, oral), and VWD subtypes (type 1/type 2A/type 2B/type 2M/type 2N/type 3) for all patients. Additionally, bleeding location and severity of bleeding episodes were utilized for subgroup stratification in the analyses.

Missing Data Analysis

Unless otherwise specified, missing data were not to be imputed.

6.1.10 Study Population and Disposition

6.1.10.1 Populations Enrolled/Analyzed

Forty-one patients were enrolled in the study. Following exclusion of 12 screen failures and 3 untreated patients, the SAF included 26 patients (See Table 2). The FAS consisted of 19 patients; 7 patients from the OD treatment arm were excluded from the FAS because these patients did not have any bleeding episodes (BE) that required treatment with the study drug (these 7 patients only received PK infusion at baseline). The PPAS included 18 patients; 1 additional patient from the OD treatment arm was excluded due to major protocol deviations of lack of source documentation and high volume of missing efficacy data that could have impacted the efficacy analysis.

Table 2. Analysis Populations: Study 071102

	On-Demand N=28	Elective Surgery N=1	Emergency Surgery N=1	Total N=41
Safety Analysis Set	25	1	1	26
Full Analysis Set	18	1	1	19
Per-Protocol Analysis Set	17	1	1	18
Pharmacokinetic Analysis Set	21	1	1	22

Source: Adapted from sBLA 125577/691; 071102 Clinical Study Report, Table 15.1.1.1.

6.1.10.1.1 Demographics

Twenty-six patients comprised the SAF across treatment arms: 25 in the OD treatment arm, 1 in the elective surgery arm, and 1 in the emergent surgery arm (See Table 3). The patient enrolled in the emergency surgery arm was also enrolled in the OD arm. The SAF population had a mean age of 10.3 years (standard deviation 5.1 years), distributed across 3 age categories: 5 patients (19.2%) were under 6 years old, 11 patients (42.3%) were 6 to <12 years old, and 10 patients (38.5%) were 12 to <18 years old.

Table 3. Demographics of Patients: Study 071102 (Safety Analysis Set)

Characteristic	On-Demand N=25	Elective Surgery N=1	Emergency Surgery N=1	Total N=26
Age				
Mean (SD)	10.2 (5.2)	12.0 (NA)	6.0 (NA)	10.3 (5.1)
Median (Min, Max)	11.0 (1.0, 17.0)	12.0 (12.0, 12.0)	6.0 (6.0, 6.0)	11.0 (1.0, 17.0)
Age Category				
< 6 years	5 (20.0%)	0 (0.0%)	0 (0.0%)	5 (19.2%)
>= 6 to < 12 years	11 (44.0%)	0 (0.0%)	1 (100.0%)	11 (42.3%)
>= 12 to < 18 years	9 (36.0%)	1 (100.0%)	0 (0.0%)	10 (38.5%)
Sex				
Female	15(60.0%)	0 (0.0%)	1 (100.0%)	15 (57.7%)
Male	10 (40.0%)	1 (100.0%)	0 (0.0%)	11 (42.3%)
BMI				
Mean (SD)	20.2 (6.3)	22.7(NA)	15.3 (NA)	20.3 (6.2)
Median (Min, Max)	18.6 (12.8, 40.7)	22.7 (22.7, 22.7)	15.3 (15.3, 15.3)	18.7 (12.8, 40.7)
Race				
White	21 (84.0%)	1 (100.0%)	1 (100.0%)	22 (84.6%)
Asian	1 (4.0%)	0 (0.0%)	0 (0.0%)	1 (3.8%)
Multiple	1 (4.0%)	0 (0.0%)	0 (0.0%)	1 (3.8%)
Not Reported	2 (8.0%)	0 (0.0%)	0 (0.0%)	2 (7.7%)
Ethnicity				
Hispanic or Latino	3 (12.0%)	0 (0.0%)	0 (0.0%)	3 (11.5%)
Not Hispanic or Latino	21 (84.0%)	1 (100.0%)	1 (100.0%)	22 (84.6%)
Not Reported	1 (4.0%)	0 (0.0%)	0 (0.0%)	1 (3.8%)
Region				
Europe	15 (60.0%)	0 (0.0%)	0 (0.0%)	15 (57.7%)
United States	10 (40.0%)	1 (100.0%)	1 (100.0%)	11 (42.3%)
VWD Type				
Type 1	5 (20.0%)	1 (100.0%)	0 (0.0%)	6 (23.1%)
Type 2A	6 (24.0%)	0 (0.0%)	0 (0.0%)	6 (23.1%)
Type 2B	3 (12.0%)	0 (0.0%)	0 (0.0%)	3 (11.5%)
Type 3	11 (44.0%)	0 (0.0%)	1 (100.0%)	11 (42.3%)

Source: Original sBLA 125577/691; 071102 Clinical Study Report, Table 15.1.4.1.4.

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population.

Disease type for patients in the SAF can be found in Table 3. Of the 26 patients in SAF, 21 (80.8%) were previously treated for VWD. Among those treated:

- 19 (73.1%) patients received OD treatment: FVIII (antihemophilic factor)/VWF (16 [61.5%] patients), VWF (2 [7.7%] patients), octogog alfa, and VONVENDI (1 [3.8%] patient each).
- 6 (23.1%) patients received prophylactic treatment: FVIII (antihemophilic factor)/VWF (5 [19.2%] patients), and VWF (1 [3.8%] patient).

6.1.10.1.3 Subject Disposition

Of the 41 patients enrolled, 12 were screening failures and 3 were not treated, resulting in 26 patients who received at least one dose of VONVENDI (See Table 4). Additionally, 7 patients received at least one dose of ADVATE. Twenty-five patients (96.2%) completed the study, with one patient discontinuing due to physician decision.

Table 4 Subject Disposition: Study 071102 (All Enrolled Set)

	On-Demand N = 28[1]	Elective Surgery N = 1[1]	Emergency Surgery N = 1[1]	Total N = 41[1]
All Subjects Enrolled	28	1	1	41
Screening Failures	0	0	0	12
Not Treated	3	0	0	3
Safety Analysis Set	25 (100%)	1 (100%)	1 (100%)	26 (100%)
Received at Least 1 Dose of VONVENDI	25 (100%)	1 (100%)	1 (100%)	26 (100%)
Received at Least 1 Dose of ADVATE	7 (28%)	0	1 (100%)	7 (27%)
End of Study Status				
Completed	24 (96%)	1 (100%)	1 (100%)	25 (96%)
Ongoing	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Discontinued	1 (4.0%)	0 (0%)	0 (0%)	1 (4.0%)
Discontinuation Reason				
Adverse Event	0	0	0	0
Physician Decision	1 (100%)	0	0	1 (100%)
Withdrawal by Subjects	0	0	0	0
Study Terminated by Sponsor	0	0	0	0
Other	0	0	0	0

[1] n(%); % = Percentage of subjects relative to the number of subjects in the Safety Analysis Set.
Source: Adapted from sBLA 125577/691; 071102 Clinical Study Report, Table 15.1.1.1.

6.1.11 Efficacy Analyses

6.1.11.1 Analyses of Primary Endpoint(s)

On-Demand

All 18 pediatric patients in the OD treatment arm achieved 100% treatment success across a total of 104 non-surgical bleeding episodes with 95% CI from 81.5% to 100.0% (See Table 5). Treatment success remained consistently 100% across all age subgroups (<6 years: 3 patients, 10 episodes; 6-12 years: 9 patients, 37 episodes; 12-18 years: 3 patients, 57 episodes) and all VWD types (Type 1: 2 patients, 12 episodes; Type 2A: 3 patients, 37 episodes; Type 2B: 2 patients, 5 episodes; Type 3: 11 patients, 50 episodes). Similarly, 100% efficacy was observed across all bleeding severity categories, ranging from mild (48 episodes) to severe (2 episodes) bleeding events.

Table 5. Efficacy of Treatment in Pediatric On-Demand Patients (Full Analysis Set)

Characteristic	No. of Patients with Treatment Success	No. of Treated non-surgical BEs
Overall	18 (100%) [81.5%, 100.0%]	104
By Age		
<6	3 (100%) [29.2%, 100.0%]	10
6 to 12	9 (100%) [66.4%, 100.0%]	37
12 to 18	3 (100%) [54.1%, 100.0%]	57
By Type		
Type 1	2 (100%) [15.8%, 100.0%]	12
Type 2A	3 (100%) [29.2%, 100.0%]	37
Type 2B	2 (100%) [15.8%, 100.0%]	5
Type 3	11 (100%) [71.5%, 100.0%]	50
By Severity		
Mild	13 (100%) [85.2%, 100.0%]	48
Moderate	13 (100%) [92.6%, 100.0%]	31
Severe	2 (100%) [88.8%, 100.0%]	2
Unknown	3 (100%) [15.8%, 100.0%]	23

Source: Adapted from sBLA 125577/691; 071102 Clinical Study Report, Table 15.2.1.1.

Perioperative management

In the surgical treatment arm, a total of 2 surgeries were managed with VONVENDI. All hemostatic outcomes were rated as "Excellent," with treatment effectively controlling blood loss during surgical interventions (See Table 6).

Table 6. Efficacy of Treatment in Pediatric Surgical Patients (Full Analysis Set)

Characteristic	Elective Surgery N=1	Emergency Surgery N=1
Age	12	6
VWD Type	Type 1	Type 3
Intraoperative Hemostatic Efficacy	Excellent	Excellent
Actual vs. Predictive blood loss rating	Excellent	Excellent
Overall Hemostatic Efficacy	Excellent	Excellent

Source: Original sBLA 125577/691; 071102 Clinical Study Report, Table 15.2.2.4.

6.1.11.2 Analyses of Secondary Endpoints

On-Demand

Among a total of 104 non-surgical BEs treated with the study drug, 48 (46%) events were mild, 31 (30%) events were moderate, and 2 (2%) events were severe (See Table 7). Hemostatic efficacy rating of “excellence” were 97 (99%) events in the total non-surgical BEs, with only 1 event (1.0%) rated as "Good". The majority of bleeding events (82%) required only a single VONVENDI infusion, with a median total dose of 51.0 IU/kg per bleed, though severe bleeds required higher doses than mild bleeds (median 108.4 IU/kg vs. 50.6 IU/kg). Additionally, 28 of 104 bleeding events (27%) treated with ADVATE at a mean dose of 30.8 IU/kg per episode, receiving only a single infusion.

Table 7. Efficacy by Severity of Bleeding Episodes in Pediatric On-Demand Patients (Full Analysis Set)

Characteristic	Mild N=13	Moderate N=13	Severe N=2	Unknown N=3	Total N=18
No. of Treated non-surgical BEs	48 (46%)	31 (30%)	2 (2%)	23 (22%)	104 (100%)
Hemostatic Efficacy Rating[1]					
Excellent	48 (100%)	29 (97%)	2 (100%)	18 (100%)	97 (99%)
Good	0 (0%)	1 (3%)	0 (0%)	0 (0%)	1 (1%)
Unknown	0	0	0	0	6
Number of Actual VONVENDI Infusions per BE[2]					
1	37(84%)	23 (77%)	1 (50%)	19 (86%)	80 (82%)
2	6 (14%)	4 (13%)	0 (0%)	2 (9%)	12 (12%)
3	1 (2%)	1 (3%)	1 (50%)	1 (5%)	4 (4%)
>5	0 (0%)	2 (7%)	0 (0%)	0 (0%)	2 (2%)
Unknown	4	1	0	1	6
Total Dose per Bleed for VONVENDI (IU/kg)					
Mean (SD)	55.1 (24.8)	79.4 (75.4)	108.0 (86.8)	58.6 (24.5)	64.4 (48.3)
Median (Min, Max)	50.6 (17.6, 156.7)	53.0 (42.7, 365.9)	108.4 (47.0, 169.8)	48.5 (46.9, 145.5)	51.0 (17.6, 365.9)
Average Dose per Infusion per Bleed for VONVENDI (IU/kg)					
Mean (SD)	46.4 (10.4)	50.0 (6.2)	51.8 (6.7)	49.7 (3.3)	48.4 (8.1)
Median (Min, Max)	47.1 (17.6, 59.7)	51.3 (37.9, 62.4)	51.8 (47.0, 56.6)	48.5 (46.9, 63.0)	48.5 (17.6, 63.0)
Number of ADVATE Infusions per BE					
1	15 (31%)	12 (39%)	0 (0%)	1 (4%)	28 (27%)
Average ADVATE Dose per BE (IU/kg)					
Mean (SD)	27.6 (9.4)	34.2 (6.2)	0 (NA)	36.3 (NA)	30.8 (8.6)
Median (Min, Max)	26.1 (9.1, 42.7)	34.6 (18.0, 45.0)	0 (NA)	36.3 (36.3, 36.3)	32.9 (9.1, 45.0)

[1] Percentages are based on bleeding episodes with known hemostatic efficacy ratings.
[2] Percentages are based on bleeding episodes with known number of actual VONVENDI infusions.
Source: Adapted from sBLA 125577/691; 071102 Clinical Study Report, Table 15.2.2.3.

Perioperative management

No treated bleeding episodes occurred among patients in either the elective surgery group (See Table 8). The elective surgery used higher pre-operative VONVENDI (99 IU/kg Elective vs. 62 IU/kg Emergency) doses while the emergency surgeries required higher post-operative VONVENDI doses (248 IU/kg Emergency vs. 55 IU/kg Elective).

Table 8. Number of Infusion and Actual Dose for Surgical Management in Pediatric Surgical Patients (Full Analysis Set)

	Elective Surgery N = 1[1]	Emergency Surgery N = 1[1]
Number of Treated Surgical Bleeding Episodes	0	0
Number of VONVENDI Infusions per Surgery Bleeding	0	0
Amount of VONVENDI (IU/kg) Administered Pre-operatively	99; 99 (NA)	62; 62 (NA)
Amount of VONVENDI (IU/kg) Administered Post-operatively	55; 55 (NA)	248; 248 (NA)
Number of ADVATE Infusions per Surgery Bleeding	0	0
Amount of ADVATE (IU/kg) Administered Pre-operatively	-	47; 47 (NA)
Amount of ADVATE (IU/kg) Administered Post-operatively	-	186; 186 (NA)

[1] Mean; Median (SD)

Source: Adapted from sBLA 125577/691; 071102 Clinical Study Report, Table 15.2.2.3.1.

6.1.11.3 Subpopulation Analyses

Given that hemostatic efficacy was achieved in all bleeding events (100% overall), all subgroups—by age, sex, and race—also demonstrated 100% efficacy accordingly. Please see Table 5 for subgroup analyses by age, disease type, bleeding severity. Furthermore, subgroup analyses by bleeding location and cause on pediatric on-demand patients, pertinent to the prescribing information and efficacy results, are presented below.

Bleeding Location

The subgroup analysis by bleeding location is presented in Table 9. Hemostatic efficacy by bleeding location demonstrated excellent or good treatment outcomes across all categories. Most episodes required only a single infusion, with joint bleeds showing most frequent multiple infusions (37% required ≥2 infusions). VONVENDI dosing was relatively consistent across sites, with mean doses ranging from 44.74 to 50.88 IU/kg. ADVATE was mostly used for joint bleeds treatment (53%) and least for mouth and oral cavity bleeding (0%), with consistent dosing across bleeding locations with mean doses ranging from 26.15 to 36.79IU/kg when utilized.

Table 9. Secondary Efficacy by Bleeding Location in Pediatric On-Demand Patients (Full Analysis Set)

Characteristic	Joint N = 17[1]	Mucosal: Nasopharyngeal N = 25[1]	Mucosal: Mouth and Oral Cavity N = 14[1]	Mucosal: Menstrual Bleeding N = 11[1]	Muscle/ Skin/ Soft Tissue N = 14[1]	Multiple/ Other N = 22[1]
Hemostatic Efficacy Rating[2]						
Excellent	17 (100%)	20 (100%)	13 (93%)	11 (100%)	14 (100%)	22 (100%)
Good	0 (0%)	0 (0%)	1 (7.1%)	0 (0%)	0 (0%)	0 (0%)
Unknown	0	5	0	0	0	0
Number of Actual VONVENDI Infusions per BE[3]						
1	10 (63%)	21 (88%)	10 (77%)	10 (100%)	12 (86%)	16 (80%)
2	3 (19%)	2 (8.3%)	2 (15%)	0 (0%)	1 (7.1%)	4 (20%)
3	1 (6.3%)	1 (4.2%)	1 (7.7%)	0 (0%)	1 (7.1%)	0 (0%)
>5	2 (13%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Unknown	1	1	1	1	0	2
Average Dose of VONVENDI (IU/kg)	48.89; 47.99 (6.36)	48.72; 49.64 (7.97)	44.74; 43.00 (7.40)	49.65; 47.52 (4.32)	45.69; 50.78 (13.02)	50.88; 50.39 (6.47)
Number of ADVATE Infusions per BE						
1	9 (53%)	8 (32%)	0 (0%)	3 (27%)	3 (21%)	5 (23%)
Average Dose Infusion of ADVATE (IU/kg)	32.40; 32.94 (7.73)	26.15; 26.57 (7.73)	NA; NA (NA)	36.79; 37.32 (2.26)	26.81; 20.38 (12.10)	33.91; 35.41 (9.83)

[1] n (%); Mean; Median (SD)
[2] Percentages are based on bleeding episodes with known hemostatic efficacy ratings.
[3] Percentages are based on bleeding episodes with known number of actual VONVENDI infusions.
Source: Adapted from sBLA 125577/691; 071102 Clinical Study Report, Table 15.2.2.1.

Bleeding Cause

Analysis by bleeding cause showed that traumatic bleeds achieved 100% excellent efficacy compared to 97% for spontaneous bleeds, with both requiring similar VONVENDI dosing (mean 48 IU/kg) and mainly single infusions (80% traumatic and 75% spontaneous) (See Table 10).

Table 10. Secondary Efficacy by Bleeding Cause in Pediatric On-Demand Patients (Full Analysis Set)

Characteristic	Spontaneous N = 33[1]	Traumatic N = 52[1]	Other N = 11[1]	Unknown N = 8[1]
Hemostatic Efficacy Rating[2]				
Excellent	31 (97%)	52 (100%)	11 (100%)	3 (100%)
Good	1 (3.1%)	0 (0%)	0 (0%)	0 (0%)
Unknown	1	0	0	5
Number of Actual VONVENDI Infusions per BE[3]				
1	24 (75%)	39 (80%)	10 (100%)	7 (100%)
2	6 (19%)	6 (12%)	0 (0%)	0 (0%)
3	1 (3.1%)	3 (6.1%)	0 (0%)	0 (0%)
>5	1 (3.1%)	1 (2.0%)	0 (0%)	0 (0%)
Unknown	1	3	1	1
Average Dose of VONVENDI (IU/kg)	48; 50 (8)	48; 49 (9)	50; 48 (4)	50; 49 (7)
Number of ADVATE Infusions per BE				
1	14 (42%)	10 (19%)	3 (27%)	1 (13%)
Average Dose Infusion of ADVATE (IU/kg)	29; 30 (8)	31; 34 (10)	37; 37 (2)	36; 36 (NA)

[1] n (%); Mean; Median (SD)
[2] Percentages are based on bleeding episodes with known hemostatic efficacy ratings.
[3] Percentages are based on bleeding episodes with known number of actual VONVENDI infusions.
Source: Adapted from sBLA 125577/691; 071102 Clinical Study Report, Table 15.2.2.2.

6.1.11.4 Dropouts and/or Discontinuations

There was one discontinuation due to physician decision, but this patient was not included in the FAS; therefore, there was no impact on the robustness of the efficacy analysis (See Table 4).

6.1.12 Safety Analyses

6.1.12.1 Methods

The safety analysis was performed with safety analysis set. Descriptive statistics were used to summarize adverse events in SAF.

6.1.12.3 Deaths

No deaths occurred during the study.

6.1.12.4 Nonfatal Serious Adverse Events

Among 26 patients across on-demand and surgery treatment groups, a total of 125 adverse events (AEs) were reported in 24 patients (92.3%) during the study, including 6 severe AEs in 5 patients, all from the on-demand treatment group. Although one AE from one patient was related to VONVENDI, it was not severe.

6.2 SHP677-304

Study SPH677-304 is titled as "A Phase 3b, prospective, open-label, uncontrolled, multicenter study on longer safety and efficacy of rVWF in pediatric and adult subjects with sever Von Willebrand disease (VWD)." The adult patients with type 1 and type 2 VWD prophylaxis data from the interim clinical study report were used in combination of those in patients with type 3 VWD to support the labeling expansion of the currently approved adult prophylaxis indication for type 3 VWD to include type 1 and type 2 VWD. Other results in the study are also included for completeness.

6.2.1 Objectives

6.2.1.1 Primary

The primary objective was to evaluate the efficacy of VONVENDI prophylaxis based on the annualized bleeding rate (ABR) of spontaneous (not related to trauma) bleeding episodes in adult (aged ≥18 years) and pediatric/adolescent (aged 12 to <18 years) patients during the first 12 months on study treatment.

6.2.1.2 Secondary

- To evaluate the long-term safety of VONVENDI in adult and pediatric patients as assessed by AEs including thrombogenicity, hypersensitivity, and immunogenicity, as well as by vital signs and clinical laboratory parameters.
- To evaluate the efficacy of VONVENDI prophylaxis in adult and pediatric/adolescent patients while enrolled in the study.
- To evaluate the efficacy of different dose regimens for prophylactic treatment in adult and pediatric/adolescent patients.
- To assess the efficacy of VONVENDI for OD treatment of bleeding episodes (spontaneous and traumatic) in adult and pediatric patients.

6.2.2 Design Overview

Study SPH677-304 was a phase 3b, prospective, open-label, uncontrolled, non-randomized, multicenter study evaluating long-term safety and efficacy of VONVENDI for prophylaxis and OD treatment of bleeding episodes in pediatric and adult patients with severe VWD.

The study has prophylactic treatment arm cohorts and OD treatment arm cohorts. The study planned to include up to 71 pediatric/adolescent and adult patients with severe VWD (including at least 5 newly enrolled patients with type 3 VWD on prophylaxis regimen), composed of: a) up to 22 adult patients transitioning from Study 071301; b) up to 34 pediatric/adolescent patients transitioning from Study 071102; and c) at least 7 and up to 15 newly enrolled adult and pediatric/adolescent (aged 12 to <18 years) patients who had been receiving VWF products for on-demand treatment.

During the entire study period, bleeding episodes requiring substitution therapy with VWF concentrate was treated with VONVENDI with or without ADVATE. If surgery was needed patients would receive VONVENDI, with or without ADVATE, for management of perioperative bleeding. Patients were observed for a minimum of 12 months.

6.2.3 Population

Patients enrolled include adults and pediatric/adolescent (aged 12 to <18 years) with severe VWD with the option of once weekly dosing, and further assess the safety and efficacy of VONVENDI in OD treatment of bleeding episodes, and in perioperative management of surgical bleeding.

6.2.4 Study Treatments or Agents Mandated by the Protocol

The study comprised two major cohorts: prophylactic treatment cohorts and on-demand cohorts.

Prophylactic treatment Cohorts:

- **Cohort 1:** Adult patients continued the same prophylactic regimen from Study 071301, which was expected to be 50 (±10) IU/kg VONVENDI.
- **Cohort 2:** Adult patients from Study 071301 who had experienced no clinically significant bleeding episode over the past 6 months and elected to start prophylactic treatment with reduced dosing frequency and/or change of dose per infusion.
- **Cohort 3**: Pediatric/adolescent patients who transitioned from Study 071102 with at least 3 bleeding episodes (excluding menorrhagia) requiring VWF in the past 12 months and were considered eligible for prophylactic treatment. Dosing was either twice weekly or once weekly at 50 (±10) IU/kg VONVENDI based on investigator assessment.
- **Cohort 4**: New adult and pediatric/adolescent patients who had at least 3 bleeding episodes (excluding menorrhagia) requiring on-demand VWF treatment in the past 12 months and were considered eligible for prophylactic treatment. These patients received VONVENDI at 50 (±10) IU/kg once weekly.

OD Treatment Cohorts:

- **Cohort 5:** Pediatric patients of all ages (aged <18 years) from Study 071102 who were considered ineligible for prophylactic treatment or elected not to transition to prophylaxis per investigator recommendation.
- **Cohort 6**: Adult patients from Study 071301 medically more suitable for OD treatment or who prefer to switch back to OD treatment regimen per investigator recommendation.

For Cohort 5 and 6, dosage and frequency were individualized based on the patient's weight, VWD type and severity of bleeding episode with an initial dose of 40 to 60 IU/kg VONVENDI.

6.2.6 Sites and Centers

Forty-six study sites in the US, Canada, UK, Turkey, Russian, Federation, Ukraine, and the EU.

6.2.7 Surveillance/Monitoring

Please refer to the clinical review for more details on study surveillance and monitoring.

6.2.8 Endpoints and Criteria for Study Success

Primary

Spontaneous ABR (sABR) during prophylaxis treatment with VONVENDI based on the data collected during the first 12 months on study would be used for the primary endpoint. The ABR for treated spontaneous BEs was derived as

$$Treated\ Sponaenous\ ABR = \frac{No.of\ Treated\ Spontaenous\ Bleeding\ Episode}{Observational\ Period\ (yr)},$$

where $Obeservaiotional\ Period = \frac{12\ Month\ End\ Date - Date\ of\ First\ Infusion + 1}{365.2425}$.

Secondary

- Efficacy of Prophylaxis
  - sABR under prophylactic treatment with VONVENDI while enrolled in the study.
  - Time to first bleeding event under each prophylaxis regimen.
  - sABR by location of bleeding (gastrointestinal [GI], epistaxis, joint bleeding, menorrhagia, oral, muscle and soft tissue, etc.) while on prophylactic treatment with VONVENDI.
  - Total number of infusions and the average number of infusions per week during prophylactic treatment with VONVENDI.
  - Total weight adjusted consumption of VONVENDI during prophylactic treatment.
  - Transfusion free maintenance of hemoglobin and plasma ferritin levels over time.
- Efficacy of the Treatment of Bleeding Episodes
  - Overall hemostatic efficacy rating at the resolution of bleed with respect to the treatment of bleeding episodes for the initial 12 months on study treatment.
  - Number of infusions of VONVENDI and ADVATE (recombinant factor eight [rFVIII], octocog alfa) utilized to treat bleeding episodes while enrolled in the study.
  - Weight-adjusted consumption of VONVENDI and ADVATE (rFVIII, octocog alfa) per bleeding episode while enrolled in the study.

Safety

- AEs/serious adverse events (SAEs): incidence, severity, causality.
- Occurrence of thromboembolic events.
- Occurrence of hypersensitivity reactions.

6.2.9 Statistical Considerations & Statistical Analysis Plan

Treatment assignments

For the efficacy analysis, patients were categorized into different treatment arms within pediatric and adult groups based on their clinical management (See Section 6.2.4 Study Treatments or Agents Mandated by the Protocol for detailed cohort descriptions):

- **Pediatric:**
  - Arm 1: OD treatment (Cohort 5).
  - Arm 2: Surgery (Cohorts 3, 4, 5).
- **Adult:**
  - Arm 1: Prior OD treatment; patients previously received on-demand treatment (Cohort 4 - newly enrolled treatment-naïve patients).
  - Arm 2: Switch; patients switching from previous prophylactic pdVWF treatment (Cohort 1 - patients transitioning from Study 071301).

Sample Size

Up to 71 pediatric/adolescent and adult patients with severe VWD (including at least 5 newly enrolled patients with type 3 VWD on prophylactic regimen) were planned to be included, composed of:

- Up to 22 adult patients transitioning from Study 071301.
- Up to 34 pediatric/adolescent patients transitioning from Study 071102.
- At least 7 up to 15 newly enrolled adult and pediatric/adolescent (aged 12 to <18 years) patients who have been receiving VWF products for OD treatment.

The sample size was derived not based on the power calculation for a significance test.

Statistical Hypotheses

No formal statistical tests were planned in the study.

Analysis population/sets

Analyses sets are given as follows:

- The safety analysis set (SAF): The safety analysis set will consist of all patients who received any amount of VONVENDI as obtained from the investigational product (IP) administration electronic diary (eDiary).
- The full analysis set (FAS): The FAS will consist of all patients who satisfy all entry criteria and received any amount of IP.
- The per protocol analysis set (PPAS): The PPAS will consist of all patients included in the FAS that have no major protocol violations that may have an impact on the efficacy of the IP.

Primary Analysis for Primary Efficacy Endpoint

The ABR for treated spontaneous BEs was analyzed descriptively, including 2-sided 95% Confidence Intervals (CI) around the mean and assessed on each cohort receiving prophylactic treatment.

Secondary Analysis for Secondary Efficacy Endpoint

- **Efficacy of Prophylaxis:** summarized through descriptive statistics by prophylactic cohort (Cohorts 1 to 4) and age group, accompanied by a 2-sided 95% CI. Summary statistics for the time to first bleeding event was to be provided by cohort and age group using Kaplan-Meier plots. The spontaneous ABR (as calculated for the primary endpoint) was also summarized by location of bleeding (GI, epistaxis, joint bleeding, menorrhagia, oral, muscle and soft tissue, etc.). Summary statistics for the total number of infusions, average number of infusions per week, as well as number (proportion) of patients on different prophylaxis dosing regimens was to be provided by cohort and age group. The total weight-adjusted consumption of VONVENDI (and of ADVATE [rFVIII, octocog alfa] if applicable) during prophylactic treatment was to be provided similarly. The count and proportion of patients that require no transfusion over time to maintain hemoglobin level were to be calculated and summarized by cohort and age group.
- **Efficacy of Treatment of Bleeding Episodes:** During the first 12 months of study treatment, efficacy will be evaluated by tracking the number of infusions and weight-adjusted consumption of both VONVENDI and ADVATE (rFVIII, octocog alfa) per bleeding episode, along with overall hemostatic efficacy ratings at bleed resolution. All bleeding episodes will be comprehensively characterized by cause, type, severity, and anatomical location, with categorization based on whether episodes occurred spontaneously or due to trauma, and summary statistics will be presented for all measured parameters.

Supplementary Analysis

- Subgroup Analysis: For primary efficacy group, subgroup analysis is conducted by age group and location of bleed.
- Sensitivity Analysis: The primary analysis will be repeated on the PPAS as sensitivity analysis.

Missing Data Analysis

Unless otherwise specified, missing data was not to be imputed.

6.2.10 Study Population and Disposition

6.2.10.1 Populations Enrolled/Analyzed

Of the 40 enrolled patients, 36 were categorized into 6 cohorts (10 in Cohort 1, 1 each in Cohorts 2 and 3, 5 in Cohort 4, 16 in Cohort 5, and 2 in Cohort 6), while 2 cases had unknown status and 2 were screen failures. The SAF, FAS, PPAS and PK sets were identical across the treatment arm for pediatric and adult populations: 18 pediatric and 4 adult participants. Among pediatric patients, 16 patients were enrolled in the OD treatment arm and 4 patients participated in the surgery arm, with 2 patients enrolled

in both arms. The adult population comprised 4 patients in total: 3 treatment-naïve patients in the prior OD treatment arm and 1 patient in the switch arm.

6.2.10.1.1 Demographics

Demographic characteristics for both pediatric and adult patients are summarized in Table 11. The pediatric OD group has the mean (SD) ages of 10.4(5) years with the majority being adolescents aged 12-18 years (38%), while the surgery group consisted of adolescent patients only aged 12-15 years (13 [2]). The prior OD group comprised 3 adult patients with mean age of 41(16), and the switch group contained a single 77-year-old patient. VWD Type 3 was most prevalent in the pediatric on-demand cohort (50%), followed by Type 1 (25%), while Type 1 was most common in the surgery group (50%). However, adult patients in both the prior OD and switch groups were exclusively diagnosed with VWD Type 2A.

Table 11. Demographics of Patients: Study SHP677-304 (Safety Analysis Set)

Characteristic	Pediatric OD N = 16[1]	Pediatric Surgery N = 4[1]	Adult Prior OD N = 3[1]	Adult Switch N = 1[1]
Age				
Mean (SD)	10 (5)	13 (2)	41 (16)	77 (NA)
Median (Min, Max)	11 (2, 18)	12 (12, 15)	35 (30, 59)	77 (77, 77)
Age Category				
Pediatric (<6 years)	3 (19%)	0 (0%)	0 (0%)	0 (0%)
Pediatric (>=6 to <12 years)	5 (31%)	0 (0%)	0 (0%)	0 (0%)
Pediatric (>=12 to <18 years)	6 (38%)	4 (100%)	0 (0%)	0 (0%)
Adult (>=18 years)	2 (13%)	0 (0%)	3 (100%)	1 (100%)
Sex				
Female	9 (56%)	0 (0%)	1 (33%)	0 (0%)
Male	7 (44%)	4 (100%)	2 (67%)	1 (100%)
Race				
White	14 (88%)	4 (100%)	3 (100%)	1 (100%)
Multiple	1 (6.3%)	0 (0%)	0 (0%)	0 (0%)
Other	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Not Reported	1 (6.3%)	0 (0%)	0 (0%)	0 (0%)
Ethnicity				
Hispanic or Latino	1 (6.3%)	0 (0%)	0 (0%)	1 (100%)
Not Hispanic or Latino	14 (88%)	4 (100%)	3 (100%)	0 (0%)
Not Reported	1 (6.3%)	0 (0%)	0 (0%)	0 (0%)
VWD Type				
Type 1	4 (25%)	2 (50%)	0 (0%)	0 (0%)
Type 2A	1 (6.3%)	0 (0%)	3 (100%)	1 (100%)
Type 2B	3 (19%)	1 (25%)	0 (0%)	0 (0%)
Type 3	8 (50%)	1 (25%)	0 (0%)	0 (0%)

[1]n (%).

Source: Adapted from sBLA 125577/691; SHP677-304 Clinical Study Report, Tables 14.1.4.1.1 and 14.1.4.1.2.1.

6.2.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

Disease type for pediatric and adult patients in the SAF can be found in Table 11. Regarding the adult patients specifically, mean coagulation parameters were within normal range at screening, with activated partial thromboplastin time slightly prolonged (normal range: 20.6-39.9 seconds). For the adult prior on-demand patients during the historical period, 28 spontaneous bleeding episodes were experienced: 17 (60.7%) were mild/minor, 8 (28.6%) were moderate, and 3 (10.7%) were severe/major bleeds. Additionally, 9 bleeds resulted from injury/trauma, with 8 (88.9%) being mild/minor and 1 (11.1%) moderate. Four bleeds were attributed to other causes, all of which (100.0%) were mild/minor.

6.2.10.1.3 Subject Disposition

The enrolled population consisted of 40 patients. After excluding 2 screening failures and 2 patients with unknown status, 36 patients remained for analysis. Following the removal of 3 undosed participants, the safety set included 16 pediatric OD patients, 4 surgical patients, 3 adults with prior OD experience, and 1 switch patient (See Table 12). All patients in the safety set received at least one dose of recombinant von Willebrand factor, with concomitant ADVATE administered in 50%, 75%, 67%, and 100% of each respective group. One pediatric surgical patient discontinued participation due to a physician's decision.

Table 12. Subject Disposition: Study SHP677-304 (All Enrolled Set)

Characteristic	Pediatric OD N = 19[1]	Pediatric Surgery N = 4[1]	Adult Prior OD N = 3[1]	Adult Switch N = 1[1]
All Subjects Enrolled	19	4	3	1
Not Yet Dosed	3	0	0	0
Safety Analysis Set	16 (100%)	4 (100%)	3 (100%)	1 (100%)
Received at Least 1 Dose of VONVENDI	16 (100%)	4 (100%)	3 (100%)	1 (100%)
Received at Least 1 Dose of ADVATE	8 (50%)	3 (75%)	2 (67%)	1 (100%)
End of Study Status				
Completed	14 (88%)	2 (50%)	1 (33%)	1 (100%)
Ongoing	2 (13%)	1 (25%)	2 (67%)	0 (0%)
Discontinued	0 (0%)	1 (25%)	0 (0%)	0 (0%)
Discontinuation Reason				
Physician Decision	0 (0%)	1 (100%)	0 (0%)	0 (0%)

[1]n(%); % = Percentage of subjects relative to the number of subjects in the Safety Analysis Set.
Source: Adapted from sBLA 125577/691; SHP677-304 Clinical Study Report, Tables 14.1.1.1.1 and 14.1.1.1.2.

6.2.11 Efficacy Analyses

6.2.11.1 Analyses of Primary Endpoint(s)

6.2.11.1.1 Pediatric Patients

On-Demand

Sixteen patients reported 164 bleeding episodes, all age subgroups experienced 100% treatment coverage (See Table 13). The overall efficacy rating was high, with 98% of episodes rated as excellent and 1.2% as good. Only 1.2% of ratings were missing. The mean number of VONVENDI infusions required per episode was low across all age groups (Mean±SD: 1.06 ±0.36). Use of ADVATE was minimal, with an overall mean (SD) of 0.27 (0.46). The mean (SD) amount of VONVENDI infused was consistent across groups with 52.78 (20.61).

Table 13. Efficacy Rating for Pediatric On-Demand Patients (Full Analysis Set)

Characteristic	Pediatric (<6 years) N = 35[1]	Pediatric (>=6 to <12 years) N = 46[1]	Pediatric (>=12 to <=18 years) N = 83[1]	Overall N = 164[1]
Treated Bleeding Episode	35 (100%)	46 (100%)	83 (100%)	164 (100%)
Efficacy Rating				
Excellent	34 (97%)	44 (96%)	82 (99%)	160 (98%)
Good	1 (2.9%)	1 (2.2%)	0 (0%)	2 (1.2%)
Missing	0 (0%)	1 (2.2%)	1 (1.2%)	2 (1.2%)
Actual Number of Infusions VONVENDI				
Mean (SD)	1.03 (0.17)	1.02 (0.15)	1.10 (0.48)	1.06 (0.36)
Median (Min, Max)	1 (1, 2)	1 (1, 2)	1 (1, 5)	1 (1, 5)
Actual Number of Infusions ADVATE				
Mean (SD)	0.03 (0.17)	0.02 (0.15)	0.51 (0.53)	0.27 (0.46)
Median (Min, Max)	0 (0, 1)	0 (0, 1)	0 (0, 2)	0 (0, 2)
Amount Infused of VONVENDI				
Mean (SD)	53.12 (19.72)	50.72 (10.65)	53.78 (24.85)	52.78 (20.61)
Median (Min, Max)	50 (0, 99)	48 (39, 97)	50 (5, 250)	50 (0, 250)
Amount Infused of ADVATE				
Mean (SD)	1.02 (6.06)	1.04 (7.07)	18.38 (19.24)	9.81 (16.83)
Median (Min, Max)	0 (0, 36)	0 (0, 48)	0 (0, 70)	0 (0, 70)

[1]n (%).

Source: Original sBLA 125577/691 SHP677-304 Clinical Study Report, Table 14.2.1.9.

Perioperative management

In Study SPH677-304, four patients underwent five elective procedures: four minor procedures and one oral procedure (See Table 14). Overall hemostatic efficacy was rated as “excellent” in four surgeries with one missing in one minor surgical procedure. Note that 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.

Table 14. Efficacy Rating for Pediatric Surgical Patients (Full Analysis Set)

Patient ID	Age	Procedure Category	Surgical Type	Hemostatic Efficacy
071102-(b) (6)	12	DENTAL	Oral	Excellent
071102-(b) (6)	15	DENTAL	Major	Good
071102-(b) (6)	15	ENDOSCOPIC	Minor	-
071102-(b) (6)	12	MINIMAL INVASIVE	Minor	Excellent
SHP677-304-(b) (6)	12	ENDOSCOPIC	Minor	Excellent
SHP677-304-(b) (6)	12	ENDOSCOPIC	Minor	Excellent

Source: Original sBLA 125577/691; SHP677-304 Clinical Study Report, Table 14.2.4.2.

6.2.11.1.1 Adult

The interim analysis supporting prophylaxis label extension evaluated the primary efficacy endpoint of sABR during the first 12 months of treatment. The overall population demonstrated a mean sABR of 1.77 (SD: 1.54), indicating effective bleeding control (See Table 15). Treatment efficacy was assessed for 16 bleeding episodes, with 88.9% of cases achieving excellent efficacy ratings, demonstrating consistently high treatment effectiveness across the study population. The prior OD group showed a reduction from a mean pre-study sABR of 9.3 (7.8) to an on-study sABR of 2.36 (1.21). The switch group had a mean of 0 (NA) for both pre-study sABR and on-study sABR.

Table 15. Pre-Study and On-study ABR for Treated Spontaneous Bleeding Events (Full Analysis Set)

Characteristic	Prior OD N = 3[1]	Switch N = 1[1]	Overall N = 4[1]
Efficacy Rating			
Excellent	15 (88.2%)	1 (100%)	16 (88.9%)
Good	2 (11.8%)	0	2 (11.1%)
Missing	0	0	0
Pre-Study Treated sABR			
Mean (SD)	9.3 (7.8)	0.00 (NA)	7.0 (7.9)
Median (Min, Max)	7.0 (3.0, 18.0)	0.00 (0.00, 0.00)	5.0 (0.0, 18.0)
12 Month On-Study Treated sABR			
Mean (SD)	2.36 (1.21)	0.00 (NA)	1.77 (1.54)
Median (Min, Max)	2.99 (0.96, 3.12)	0.00 (0.00, 0.00)	1.98 (0.00, 3.12)

[1] n (%).

Source: Adapted from sBLA 125577/691; SHP677-304 Clinical Study Report, Table 14.2.1.1.

6.2.11.3 Subpopulation Analyses

Please refer to Section 6.2.11.1 Analyses of Primary Endpoint(s).

6.2.11.4 Dropouts and/or Discontinuations

One pediatric surgical patient from FAS discontinued due to physician decision (See Table 12).

6.2.12 Safety Analyses

6.2.12.1 Methods

The safety analysis was performed using safety analysis set. Descriptive statistics were used to summarize adverse events in SAF.

6.2.12.3 Deaths

No deaths occurred during the study period.

6.2.12.4 Nonfatal Serious Adverse Events

Among 16 pediatric patients receiving OD treatment, TEAEs were reported in 15 patients (93.8%), with a total of 111 events. Serious TEAEs occurred in 2 patients (12.5%), accounting for 4 events. In contrast, within the surgery group (n = 4), only 1 (25%) patient experienced a single event of TEAE, and no serious TEAEs were observed.

Four adult patients in prophylactic cohorts experienced 53 TEAEs. A total of 4 Serious TEAEs were reported in 1 (33.3%) patient from Prior OD arm and 1 (100%) patient from Switch arm, however these SAEs were all considered unrelated to VONVENDI or ADVATE.

7. INTEGRATED OVERVIEW OF EFFICACY

7.1 Adult Patients with Type 1 and Type 2 VWD for Prophylaxis Treatment

To expand the current approved adult prophylaxis indication for type 3 VWD to include adults with type 1 and type 2 VWD, data from Studies 071301 and SHP677-304 were provided as supporting evidence.

Study 071301 was a prospective, phase 3, open-label, international multicenter study conducted to evaluate the efficacy and safety of prophylaxis with VONVENDI in severe von VWD. The treatment was initiated at a dose of 50 ± 10 IU/kg administered twice weekly, with dose escalation permitted according to protocol up to a maximum of 80 IU/kg per infusion, and infusion frequency was increased as needed. It consists of two cohorts:

- **Cohort1 - Prior OD (N = 13; N = 3 Types 1&2):** patients previously received on-demand treatment.
- **Cohort2 – Switch (N = 10; N = 3 Types 1&2):** patients switching from prophylactic treatment with pdVWF.

The exclusion of one patient (Subject ID = (b) (6)) was based on an FDA Information Request dated November 30, 2021 (BLA 125577/538), because the patient discontinued the study after receiving 2 doses of VONVENDI and was not considered evaluable for the assessment of the efficacy of regular prophylaxis. Thus, a total of 22 adult patients with severe VWD were included in the study. Of the 22 patients, there were 12 patients in prior on-demand group and 10 patients in the switch group. Within the prior OD group, one had severe Type 1, one had severe Type 2 VWD, and 10 had severe Type 3 VWD. Within the switch group, one had severe Type 1, one had severe Type 2 VWD, and 8 had severe Type 3 VWD. The primary efficacy outcome measure is the annualized bleeding rate (ABR) for treated spontaneous bleeding episodes.

7.1.1 Methods of Integration

Eleven patients are rolled over to SHP 677-304 from 071301 and after 12-36 month of prophylaxis treatment, and 7 patients with either Type 1 or Type 2 VWD were included in the overall integrated dataset for evaluation of the efficacy and the safety for adult patients with Type 1 or Type 2 VWD for prophylaxis treatment. Among these 7, 3 patients were newly enrolled in SHP 677-304 to initiate prophylaxis with VONVENDI; all had Type 2A VWD and belonged to the prior on-demand group.

7.1.2 Demographics and Baseline Characteristics

The integrated dataset comprised 7 patients with a mean age of 52 years, where patients in the switch arm were older than those in the prior OD arm (See Table 16). All patients were white (100%), and the cohort included 2 patients with Type 1 and 5 patients with Type 2.

Table 16 . Demographics of Adult Patients (Integrated Full Analysis Set)

Characteristic	Prior OD N=5[1]	Switch N=2[1]	Overall N=7[1]
Age			
Mean (SD)	42.2 (19.9)	76.5 (0.7)	52.0 (23.4)
Median (Min, Max)	35.0 (20.0, 67.0)	76.5 (76.0, 77.0)	59.0 (20.0, 77.0)
Age Category			
>=18 to < 65 years	1 (20.0%)	0 (0.0%)	1 (14.3%)
>65 years	1 (20.0%)	2 (100.0%)	3 (42.9%)
Unknown	3 (60.0%)	0 (0.0%)	3 (42.9%)
Sex			
Female	1 (20.0%)	0 (0.0%)	1 (14.3%)
Male	4 (80.0%)	2 (100.0%)	6 (85.7%)
BMI			
Mean (SD)	24.9 (0.5)	26.4 (3.1)	25.7 (2.0)
Median (Min, Max)	24.9 (24.6, 25.3)	26.4 (24.2, 28.6)	24.9 (24.2, 28.6)
VWD Type			
Type 1	1 (20.0%)	1 (50.0%)	2 (28.6%)
Type 2A	3 (60.0%)	1 (50.0%)	4 (57.1%)
Type 2B	1 (20.0%)	0 (0.0%)	1 (14.3%)
Type 3	0 (0.0%)	0 (0.0%)	0 (0.0%)
Race			
White	5 (100.0%)	2 (100.0%)	7 (100.0%)
Asian	0 (0.0%)	0 (0.0%)	0 (0.0%)
Multiple	0 (0.0%)	0 (0.0%)	0 (0.0%)
Not Reported	0 (0.0%)	0 (0.0%)	0 (0.0%)
Ethnicity			
Hispanic or Latino	0 (0.0%)	2 (100.0%)	2 (28.6%)
Not Hispanic or Latino	5 (100.0%)	0 (0.0%)	5 (71.4%)
Not Reported	0 (0.0%)	0 (0.0%)	0 (0.0%)

[1]n (%).

Source: Adapted from sBLA 125577/691; Application Orientation Meeting (AOM) slides dated on April 23, 2025, p 51-52.

7.1.4 Analysis of Primary Endpoint(s)

From the integrated dataset, five patients (one Type 1 and four Type 2) previously received on-demand treatment experienced a reduction in median spontaneous annualized bleeding rate (sABR) from 3.0 to 1.0 after 12 months of VONVENDI prophylaxis (See Table 17). Two patients (one Type 1 and one Type 2) switching from prophylactic treatment with pdVWF to VONVENDI prophylaxis maintained a sABR of 0.

Table 17. Pre-Study and On-study ABR for Treated Spontaneous Bleeding Events (Integrated Full Analysis Set)

	Prior OD N=5	Switch N=2
Pre-Study Treated sABR		
Mean (SD)	6.8 (6.50)	0 (0)
Median (Min, Max)	3.0 (3.1, 18.0)	0 (0, 0)
12 Month On-Study Treated sABR		
Mean (SD)	1.4 (1.55)	0 (0)
Median (Min, Max)	1.0 (0, 3.1)	0 (0, 0)

Source: Adapted from sBLA 125577/691; Application Orientation Meeting (AOM) slides dated on April 23, 2025, p 52.

7.1.10 Additional Efficacy Issues/Analyses

As a supplementary material, the sponsor provided pre-study and on-study of sABR by bleeding sites from Study 071301 consisting of 22 patients to support the efficacy profile for adult in the prescribing information (See Table 18).

Table 18. Demographics of Adult Patients: Study 071301 (Full Analysis Set)

Characteristic	Prior OD N = 12[1]	Switch N = 10[1]	Overall N = 22[1]
Sex			
Female	7 (58%)	3 (30%)	10 (45%)
Male	5 (42%)	7 (70%)	12 (55%)
Age	39; 38 (18)	44; 34 (22)	41; 34 (19)
Race			
White	12 (100%)	9 (90%)	21 (95%)
Not Reported	0 (0%)	1 (10%)	1 (4.5%)
Ethnicity			
Hispanic or Latino	0 (0%)	2 (20%)	2 (9.1%)
Not Hispanic or Latino	12 (100%)	7 (70%)	19 (86%)
Not Reported	0 (0%)	1 (10%)	1 (4.5%)
Type of VWD			
Type 1	1 (8.3%)	1 (10%)	2 (9.1%)
Type 2A	0 (0%)	1 (10%)	1 (4.5%)
Type 2B	1 (8.3%)	0 (0%)	1 (4.5%)
Type 3	10 (83%)	8 (80%)	18 (82%)

[1]n (%).

Source: Adapted from sBLA 125577/616; 071301 Clinical Study Report, Table 15.

The pre-study and on-study of sABR by bleeding sites for these patients were presented in Table 19. The bleeding event analysis demonstrated that prior OD patients experienced substantial reductions in bleeding rates, with median ABR for treated spontaneous and traumatic bleeds decreasing from 4.0 pre-study to 0.0 on-study, and joint bleeds reducing from 1.5 to 0.0. Switch patients maintained low treated bleeding rates at 0.0, though all spontaneous and traumatic bleeds (including untreated bleeds) increased from 1.0 to 3.6.

Table 19. Efficacy of Routine Prophylaxis with VONVENDI: Study 071301 (Full Analysis Set)

Type or Site of Bleeding Event	Number of BEs Pre-Study / On-Study	Pre-Study ABR		On-Study ABR	
		Mean (SD)	Median (Min, Max)	Mean (SD)	Median (Min, Max)
Prior OD Patients (N=12)					
Treated Spontaneous Bleeds	197/9	16.4 (43.7)	3.0 (3.0, 155.0)	0.7 (1.8)	0.0 (0.0, 5.8)
Treated Spontaneous and Traumatic Bleeds	203/12	16.9 (43.8)	4.0 (3.0, 156.0)	1.0 (1.8)	0.0 (0.0, 5.8)
All Spontaneous Bleeds	202/33	16.8 (44.5)	3.5 (3.0, 158.0)	14.5 (45.2)	0.0 (0.0, 158.0)
All Spontaneous and Traumatic Bleeds	208/38	17.3 (44.6)	4.5 (3.0, 159.0)	14.9 (45.1)	0.5 (0.0, 158.0)
All Joint Bleeds	23/3	1.9 (2.3)	1.5 (0.0, 7.0)	0.2 (0.6)	0.0 (0.0, 1.9)
Switch Patients (N=10)					
Treated Spontaneous Bleeds	50/18	5.0 (14.4)	0.0 (0.0, 46.0)	1.7 (3.9)	0.0 (0.0, 12.1)
Treated Spontaneous and Traumatic Bleeds	53/19	5.3 (14.7)	0.0 (0.0, 47.0)	1.8 (3.8)	0.0 (0.0, 12.1)
Treated Joint Bleeds	1/1	0.1 (0.3)	0.0 (0.0, 1.0)	0.1 (0.3)	0.0 (0.0, 1.0)
All Spontaneous Bleeds	54/43	5.4 (14.3)	1.0 (0.0, 46.0)	4.2 (8.3)	1.5 (0.0, 27.0)
All Spontaneous and Traumatic Bleeds	57/47	5.7 (14.6)	1.0 (0.0, 47.0)	4.8 (8.1)	3.6 (0.0, 27.0)
All Joint Bleeds	2/3	0.2 (0.4)	0.0 (0.0, 1.0)	0.3 (0.7)	0.0 (0.0, 2.0)

Source: Adapted from sBLA 125577/616; 071301Clinical Study Report, Table 18.

7.1.11 Efficacy Conclusions

Overall, the data demonstrate that prophylactic treatment with VONVENDI reduced bleeding frequency.

10. CONCLUSIONS

10.1 Statistical Issues and Collective Evidence

Efficacy

For the pediatric on-demand treatment and control of bleeding episode indication, Study 071102 demonstrated 100% treatment success in 104 evaluable non-surgical bleeding episodes among all 18 pediatric patients (95% CI: 81.5–100%), with 94% (98 out of 104) of the episodes rated as "excellent" (97) or "good" (1). In Study SHP677-304, 16 patients experienced 164 bleeding episodes, of which 160 were rated "excellent" and 2 "good" with 2 missing ratings. For the pediatric perioperative management of bleeding indication, Study 071102 reported "excellent" hemostatic efficacy in two minor surgeries across two patients, and four were rated "excellent" with one rating missing across five elective procedures in four patients in Study SPH677-304.

For the Type 3 VWD adult routine prophylaxis indication, Study 071301 showed substantial benefit in patients transitioning from on-demand therapy (n=12 including 2 Types 1 and 2 patients), with median annualized bleeding rates (ABRs) for treated spontaneous and traumatic bleeds decreasing from 4.0 to 0.0, all spontaneous and traumatic bleeds from 4.5 to 0.5, and joint bleeds from 1.5 to 0.0. Patients switching from other prophylaxis regimens (n=10 including 2 Types 1 and 2 patients) maintained low treated bleed rates at 0.0, though all spontaneous and traumatic bleeds (including untreated bleeds) increased from 1.0 to 3.6, with joint bleeds remaining at 0.0. Integrated data from Studies 071301 and SPH 677-304 confirmed these findings in seven adult patients with Type 1 and Type 2 VWD. Five patients (one Type 1 and four Type 2) previously received on-demand treatment experienced a reduction in median spontaneous annualized bleeding rate (sABR) from 3.0 to 1.0 after 12 months of rVWF prophylaxis. Two patients (one Type 1 and one Type 2) switching to rVWF prophylaxis maintained a sABR of 0.

Safety

For safety evaluation, 5 (19.2%) pediatric patients in Study 071102 experienced 6 serious treatment-emergent adverse events (TEAEs). In Study SHP677-304, 4 serious TEAEs were reported by 2 (11%) pediatric patients, and 4 serious TEAEs occurred in 2 (50%) adult patients. The applicant determined that all these serious TEAEs were unrelated to the investigational products. Further evaluation of safety data is deferred to the clinical team.

10.2 Conclusions and Recommendations

Overall, there were no major statistical issues related to the submission. The primary and secondary efficacy result have been verified and the evidence is sufficient to support for the indication expansions: (1) 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, and (2) the current approved adult prophylaxis indication for type 3 VWD to include adults with type 1 and type 2 VWD. No major safety concerns were identified. I defer to the clinical team on the acceptance of overall safety profile of VONVENDI.

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