Disease Burden in Patients with von Willebrand Disease Potentially Eligible for Prophylaxis: Post Hoc Analysis of a European Cross-Sectional Study

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Abstract
Recent international guidelines conditionally recommend von Willebrand factor (VWF) prophylaxis for von Willebrand disease (VWD) patients with a history of severe/frequent bleeds. This post hoc analysis of the Cost of VWD Across Europe, a Socioeconomic Study (CVESS; conducted in 2018), assessed patient characteristics and disease burden in patients aged >1 year with congenital VWD not receiving but potentially eligible for prophylaxis based on severe/frequent bleeds, and those receiving prophylaxis in the previous 12 months. Data were collected using medical records and a patient questionnaire. Patients considered potentially prophylaxis-eligible (n = 102) experienced more bleeds than patients receiving prophylaxis (n = 229) and were more likely to be admitted to the hospital due to bleeding events in the prior 12 months. Quality of life and work productivity were similar between the two groups. Logistic regression analysis showed that the prophylaxis-eligible group was more likely to have poor joint function and moderate chronic pain than the prophylaxis group. This retrospective study suggests that 1/7 patients not receiving VWF prophylaxis had a higher disease burden than patients receiving prophylaxis and would potentially benefit from prophylaxis.

Keywords
von Willebrand disease, von Willebrand factor, prophylaxis, disease burden, quality of life, healthcare resource utilization

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Introduction
von Willebrand disease (VWD) is a hereditary bleeding disorder caused by deficiency or dysfunction of von Willebrand factor (VWF), impairing both primary and secondary hemostasis (platelet adhesion and stabilization of factor VIII, respectively). The global prevalence of VWD is estimated to be 600-1300 per 100,000 individuals, with 10 per 100,000 individuals who have symptomatic VWD requiring treatment. There are three main types of VWD classified according to quantitative or qualitative defects in VWF activity. The most common bleeding phenotypes in patients with VWD are mucocutaneous bleeding—including epistaxis, easy bruising, and heavy menstrual bleeding—and bleeding after surgery or trauma. Bleeding phenotypes in VWD vary, however, depending on disease type, age, and sex. Patients with a severe bleeding phenotype (mostly those with VWD type 2 and type 3) have poorer health-related quality of life than the general population and are at increased risk of bleeds that are life-threatening or can lead to long-term complications. In the 2021 international guidelines on the management of VWD, long-term prophylactic VWF replacement was recommended in patients with a history of severe and frequent bleeds. However, this recommendation was conditional based on the

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low certainty in evidence of effects. In particular, there is limited real-world evidence demonstrating the health benefits of long-term prophylaxis in patients with VWD.

The Cost of von Willebrand Disease Across Europe, a Socioeconomic Study (CVESS) was initially established to describe the socioeconomic impact of VWD in five European countries. The objectives of this post hoc analysis of data from CVESS were to describe patient characteristics and disease burden in patients with VWD identified as potentially eligible for prophylaxis according to current VWD management guidelines but not receiving it compared with those patients receiving prophylaxis; and to assess whether the burden of disease differed significantly between these two identified patient groups.

Methods

Study Design

CVESS was a cross-sectional study conducted in 2018 in France, Germany, Italy, Spain, and the United Kingdom. The study was carried out by the University of Chester (Chester, UK) and overseen by an expert reference group that included medical experts and patient representatives. It was endorsed by The Haemophilia Society (London, UK) and the European Haemophilia Consortium (Brussels, Belgium), with ethical oversight from the University of Chester. This manuscript reports findings from a post hoc analysis focusing on a specific subset of CVESS patients with VWD and severe/frequent bleeds who were potentially eligible for VWF prophylaxis, as well as those who had received intermittent or continuous prophylaxis.

Hematologists who were directly responsible for the care of patients with VWD collected medical chart data from the 12 months before the index date (ie the date of consultation), including demographics, clinical information, and direct healthcare resource utilization. Patients (in conjunction with their parents or guardian for children aged <18 years) were invited to complete a paper-based questionnaire designed to capture the impact of VWD on their lives, such as direct and indirect non-medical costs, quality of life, and work impairment. Patients completed the questionnaire in the clinic or at a location of their choice around the time of the index date. The questionnaires were then returned to the investigators and passed on to the University of Chester for analysis.

Patient Population

The inclusion and exclusion criteria were approved by the expert review group and the University of Chester research ethical committee. Patients aged >1 year with a laboratory diagnosis of congenital VWD and known VWD classification were eligible, even if they were participating in a clinical trial at the time of the study. Patients were excluded for reasons such as language barriers, diagnosis of acquired von Willebrand syndrome, or, where applicable, the presence of a physical or mental condition resulting in diminished decision making. All patients (or their parent/guardian if aged <18 years) provided written informed consent.

Two patient subgroups were identified from the overall CVESS population based on prior prophylactic therapy with any product containing VWF. The group considered potentially eligible for prophylaxis (ie the prophylaxis-eligible group) comprised patients with severe and/or frequent bleeds in the 12 months before the index date who were not prescribed prophylaxis. This definition of prophylaxis eligibility was based on that used in the 2021 international guidelines on the management of VWD, in which frequent bleeding was categorized as at least three joint bleeds, at least two gastrointestinal bleeds, or at least five bleeds in total across a 12 month period. The definition of severe bleeding (hospitalization as the result of a bleed, or any bleed involving critical organs) was adapted to fit the data collected in CVESS from the major bleeding definition used in the 2021 VWD management guidelines: “bleeding requiring hospital admission, requiring surgical intervention, requiring blood transfusion (of at least 2 units), resulting in a drop of ≥2 g/dL in hemoglobin, or resulting in symptoms involving critical areas (intracranial, intraspin- nal, intraocular, retroperitoneal, intraarticular, pericardial, or intramuscular with compartment syndrome).” The prophylaxis group included patients who had received intermittent or continuous prophylaxis to prevent bleeding in the previous 12 months. Intermittent prophylaxis was defined as treatment given to prevent bleeding for periods not exceeding 45 weeks in a year, and continuous prophylaxis was defined as the intention of treating for 52 weeks/year and receiving 85% of the prior defined frequency of infusions for at least 45 weeks/year.

Outcome Measures and Statistical Analyses

The sample size for CVESS was based on the maximum feasible number of patients available for recruitment in each country, given that VWD is a rare disease. Missing data were excluded from the analysis and the numbers of patients with observations were reported.

VWD-related clinical outcomes (bleeding events, pain, and joint damage) and patient-reported outcomes (EuroQoL 5-dimension, five-level [EQ-5D-5L] score, using a published value set derived from the general population in England, and the Work Productivity and Activity Impairment questionnaire [WPAI]) were assessed in the two patient groups. Healthcare resource utilization, including the number of treated bleeds, was assessed during the 12 months before the index date.

Descriptive statistics were used to compare demographic and clinical characteristics between the prophylaxis-eligible and prophylaxis groups. Categorical variables were described as frequencies and percentages, and continuous variables were presented as mean (standard deviation [SD]). T-tests for continuous variables and chi² tests for categorical variables with two-sided p-values < 0.05 were used to assess statistical significance, with no correction for multiple comparisons.
Multivariable logistic regression models were performed to determine whether patient outcomes differed significantly between the prophylaxis-eligible and prophylaxis groups, controlling for demographic, clinical, and center-related factors. Stepwise selection was used to eliminate variables using the Wald test with a p-value threshold for inclusion set at 0.1. Following this, model goodness of fit statistics and variance inflation factor were assessed for the variables included in the model (Supplementary Table 4b and 4c).

Results

Patient Demographics and Clinical Characteristics

In total, 974 patients were enrolled in CVESS, of whom 229 were receiving intermittent or continuous VWF prophylaxis (Figure 1). Of the remaining 745 patients, 102 were considered potentially eligible for prophylaxis based on the predefined criteria in this analysis for severity and/or frequency of bleeding. Demographic and clinical characteristics of the prophylaxis-eligible and prophylaxis groups are presented in Table 1 and Supplementary Table 1. Mean age in the prophylaxis-eligible group was higher than in the prophylaxis group, with a higher percentage of patients aged ≥65 years. In the UK, there was a higher proportion of patients in the prophylaxis-eligible group; in Germany, more patients were in the prophylaxis group than in the prophylaxis-eligible group. With respect to VWD type distributions, there was a lower percentage of patients with type 3 VWD in the prophylaxis-eligible group than in the prophylaxis group. However, prophylaxis-eligible patients were more likely to have moderate disease as assessed by the treating physician (rather than mild disease, which was more frequently reported in the prophylaxis group), in addition to higher levels of chronic pain and/or joint damage than patients receiving prophylaxis. Overall, mental and behavioral disorders (including anxiety and depression) were the most reported concomitant conditions in both groups. In general, patients in the prophylaxis-eligible group were more likely to have comorbidities such as mental and behavioral disorders and diseases of circulatory system than those receiving prophylaxis (Supplementary Table 2).

Treated Bleeds and Healthcare Resource Utilization

Frequency of bleeding and bleed severity (defined on the basis of bleed-related hospitalization) were inclusion criteria for the prophylaxis-eligible group. As expected, therefore, the mean (SD) number of treated bleeds in the 12 months before the index date was significantly higher in prophylaxis-eligible patients (5.5 [4.3]) than in patients receiving prophylaxis (1.5 [2.2]); p < 0.001). Similarly, patients in the prophylaxis-eligible group were more likely to be admitted to hospital due to bleeding in the 12 months before the index date than patients receiving prophylaxis (p < 0.001), with correspondingly more days in hospital and intensive care units due to bleeding (p < 0.001; Table 2).

In the 12 months before the index date, the numbers of unplanned/emergency visits with treating physicians and...
### Table 1. Baseline Demographics and Disease Characteristics in Patients Considered Potentially Eligible for Prophylaxis but not Receiving it, Compared with Patients who Received Prophylaxis in the Previous 12 Months.

|                              | Patients Eligible for Prophylaxis (n = 102) | Patients who Received Prophylaxis (n = 229) | p-Valuea |
|------------------------------|--------------------------------------------|---------------------------------------------|---------|
| **Age, years**               |                                            |                                             |         |
| Mean (SD)                    | 38.0 (20.2)                                | 32.0 (15.5)                                 | 0.004   |
| Median (range)               | 36 (5–85)                                  | 31 (2–68)                                   | 0.818   |
| **Age group, n (%)**, years  |                                            |                                             |         |
| <18                          | 22 (21.6)                                  | 52 (22.7)                                   | 0.001   |
| 18–44                        | 39 (38.2)                                  | 123 (53.7)                                  | 0.009   |
| 45–64                        | 27 (26.5)                                  | 48 (21.0)                                   | 0.269   |
| ≥65                          | 14 (13.7)                                  | 6 (2.6)                                     | <0.001  |
| **Sex, n (%)**               |                                            |                                             |         |
| Male                         | 57 (55.9)                                  | 122 (53.5)                                  | 0.660   |
| Female                       | 45 (44.1)                                  | 107 (46.7)                                  | 0.660   |
| **Height, mean (SD), m**     | 1.7 (0.2)                                  | 1.7 (0.2)                                   | 0.226   |
| **Ethnicity**                |                                            |                                             |         |
| White/Caucasian              | 87 (85.3)                                  | 189 (82.5)                                  | 0.533   |
| Black/Afro-Caribbean         | 7 (6.9)                                    | 13 (5.7)                                    | 0.676   |
| Middle Eastern               | 4 (3.9)                                    | 11 (4.8)                                    | 0.722   |
| Asian                        |                                            |                                             |         |
| Indian subcontinent          | 1 (1.0)                                    | 6 (2.6)                                     | 0.338   |
| Other                        | 1 (1.0)                                    | 3 (1.3)                                     | 0.800   |
| Mixed                        | 1 (1.0)                                    | 5 (2.2)                                     | 0.449   |
| Prefer not to answer         | 1 (1.0)                                    | 2 (0.9)                                     | 0.924   |
| **Country, n (%)**           |                                            |                                             |         |
| Germany                      | 4 (3.9)                                    | 33 (14.4)                                   | 0.005   |
| Spain                        | 15 (14.7)                                  | 29 (12.7)                                   | 0.613   |
| France                       | 13 (12.7)                                  | 34 (14.8)                                   | 0.613   |
| UK                           | 35 (34.3)                                  | 33 (14.4)                                   | <0.001  |
| Italy                        | 35 (34.3)                                  | 100 (43.7)                                  | 0.110   |
| **VWD type, n (%)**          |                                            |                                             |         |
| Type 1                       | 33 (32.4)                                  | 63 (27.5)                                   | 0.370   |
| Type 2A                      | 19 (18.6)                                  | 47 (20.5)                                   | 0.690   |
| Type 2B                      | 18 (17.6)                                  | 29 (12.7)                                   | 0.230   |
| Type 2M                      | 14 (13.7)                                  | 27 (11.8)                                   | 0.622   |
| Type 2N                      | 5 (4.9)                                    | 15 (6.6)                                    | 0.561   |
| Type 2 unconfirmed subtype   | 3 (2.9)                                    | 1 (0.4)                                     | 0.054   |
| Type 3                       | 10 (9.8)                                   | 47 (20.5)                                   | 0.017   |
| **Physician-assessed disease severity, n (%)** | | | |
| Mild (does not interfere with most activities) | 28 (27.5) | 102 (44.5) | 0.003 |
| Moderate (interferes with many activities) | 64 (62.7) | 99 (43.2) | 0.001 |
| Severe (unable to engage in normal activities) | 10 (9.8) | 28 (12.2) | 0.523 |
| **Chronic pain level, n (%)** | | | |
| None                         | 19 (18.6)                                  | 71 (31.0)                                   | 0.019   |
| Mild                         | 44 (43.1)                                  | 108 (47.2)                                  | 0.498   |
| Moderate                     | 36 (35.3)                                  | 46 (20.1)                                   | 0.003   |
| Severe                       | 3 (2.9)                                    | 4 (1.7)                                     | 0.486   |
| **Joints with limited range of motion** | | | |
| ≥1 reported, n (%)           | 38 (37.3)                                  | 38 (16.6)                                   | <0.001  |
| Number of joints if ≥1 reported, mean (SD) | 2.3 (2.3) | 1.9 (1.2) | 0.347 |
| **Target joints**            |                                            |                                             |         |
| ≥1 reported, n (%)           | 24 (23.5)                                  | 24 (10.5)                                   | 0.002   |
| Number of joints if ≥1 reported, mean (SD) | 2.3 (2.6) | 1.6 (0.9) | 0.232 |
| **Chronically damaged joints** | | | |
| ≥1 reported, n (%)           | 36 (35.3)                                  | 44 (19.2)                                   | 0.002   |
| Number of joints if ≥1 reported, mean (SD) | 1.9 (2.2) | 1.6 (0.8) | 0.378 |

aP-value threshold for statistical significance set at <0.05. SD, standard deviation; VWD, von Willebrand disease.
nurse specialists, and planned visits with physicians were similar for the prophylaxis-eligible and prophylaxis groups (Table 2). Planned nurse specialist visits, however, were more common in patients eligible for prophylaxis but not receiving it (p < 0.001) (Table 2). Outpatient consultations in the 12 months before the index date for dentistry, emergency medicine and acute surgery, general practice, general surgery, immunology, otolaryngology, pain management, and physiotherapy were more common in prophylaxis-eligible patients than in patients receiving prophylaxis (p < 0.05; Supplementary Table 3).

**Table 2. Hospitalizations and Consultations in Patients Considered Potentially Eligible for Prophylaxis but not Receiving it, Compared with Patients who Received Prophylaxis in the Previous 12 Months.**

|                        | Patients Eligible for Prophylaxis (n = 102) | Patients who Received Prophylaxis (n = 229) | p-Valuea |
|------------------------|---------------------------------------------|---------------------------------------------|---------|
| **Hospitalizations**   |                                             |                                             |         |
| Hospitalized due to bleeding, n (%) | 78 (76.5)                                   | 64 (27.9)                                   | <0.001  |
| Days in hospital due to bleeding, mean (SD) | 7.1 (12.9)                                  | 1.3 (3.9)                                   | <0.001  |
| Days in ICU due to bleeding, mean (SD)   | 4.4 (12.0)                                   | 0.3 (1.8)                                   | <0.001  |
| **Consultation history, mean (SD)**      |                                             |                                             |         |
| Planned/routine visits |                                             |                                             |         |
| Treating physician     | 4.3 (2.3)                                    | 4.1 (3.0)                                   | 0.409   |
| Nurse specialist       | 2.5 (1.8)                                    | 1.5 (1.9)                                   | <0.001  |
| Unplanned/emergency visits |                                         |                                             |         |
| Treating physician     | 3.3 (3.1)                                    | 3.2 (4.2)                                   | 0.960   |
| Nurse specialist       | 2.1 (2.2)                                    | 1.6 (2.5)                                   | 0.053   |

*p-value threshold for statistical significance set at <0.05.
ICU, intensive care unit; SD, standard deviation.

**Figure 2.** Productivity at the index date in patients considered potentially eligible for prophylaxis but not receiving it, compared with patients who received prophylaxis in the previous 12 months.
SD, standard deviation; WPAI, Work Productivity and Activity Impairment questionnaire.

**Health-Related Quality of Life and Productivity**

Around the time of the index date, mean (SD) EQ-5D-5L score was similar in the prophylaxis-eligible group (0.7 [0.3]; n = 33) and prophylaxis group (0.7 [0.3]; n = 59; p = 0.345). WPAI scores were also similar in both groups (Figure 2).

**Multivariable Regression Analysis**

Logistic regressions were performed for outcomes of interest, controlling for factors identified in the stepwise model.
remained in the regression analysis when controlling for key demographic and clinical parameters, and center-related factors. The differences between groups with type 1 or 2 VWD, and only a small number of these patients had type 3 VWD. Patients considered potentially eligible for but not receiving prophylaxis (Table 3). In addition, patients in the prophylaxis-eligible group were more likely to have planned/routine nurse specialist consultations, pain management, and/or physiotherapy than patients receiving prophylaxis (Table 3).

Discussion

This post hoc analysis shows that one in seven patients with VWD could be eligible for long-term VWF prophylaxis according to the current VWD management guidelines. The study results suggest that long-term VWF prophylaxis could potentially reduce the burden of severe and frequent bleeds for those patients. This highlights that the common perception of VWD as a ‘mild’ bleeding disorder compared with hemophilia is misleading.

Patients identified as potentially eligible for prophylaxis in the present study mostly had moderate disease severity and type 1 or 2 VWD, and only a small number of these patients had type 3 VWD. Patients considered potentially eligible for but not receiving prophylaxis also tended to be older than those receiving prophylaxis and were found to have worse health outcomes and a higher disease burden than those receiving prophylaxis in the 12 months before the index date, including greater levels of pain, poorer joint function, more treated bleeds, and more medical consultations. The differences between groups with respect to joint function, chronic pain, and medical consultations remained in the regression analysis when controlling for key demographic and clinical parameters, and center-related factors (country and number of patients seen by physician per month).

The rate of hospitalization for bleeding events in the present analysis was similar to that seen in the randomized PRO.WILL study of VWF prophylaxis, in which 22% of patients receiving on-demand therapy and 20% of patients receiving prophylaxis were hospitalized in the 12 months before baseline. The finding in the present analysis of a greater rate of hospitalizations for bleeding events in patients potentially eligible for prophylaxis but not receiving it compared with those receiving prophylaxis is also consistent with previous data, including a national registry study from Sweden, in which initiation of prophylaxis was associated with a significant reduction in hospitalizations.

Prophylactic VWF replacement was initially recommended in the UK treatment guidelines in 2014 for specific patients, including those with type 3 disease plus hemarthroses, severe epistaxis, women with heavy menstrual bleeding, and those with an ongoing risk factor for bleeding (eg angiodysplasia). More recently, the 2021 international guidelines on the management of VWD recommended the use of prophylactic VWF replacement in patients with a history of severe and frequent bleeds. The recommendation was conditional, however, due to the low certainty of evidence for a net benefit of long-term prophylaxis in this patient population; most of the studies reviewed were observational, with only one randomized trial (the PRO.WILL study). Some researchers have noted that the recommendation is particularly valuable for countries such as the United States, where VWF prophylaxis is not part of routine practice. In addition, although VWF prophylaxis has been routinely used for many years in Europe, there is still evidence to suggest that in contrast to hemophilia, prophylaxis is under-utilized in patients with VWD and severe disease burden. Conversely, the applicability of the recommendation to low- or middle-income countries has been questioned, with authors noting that it will be challenging to implement the recommendation where resources are limited, even though the data from the present study indicate a high unmet need for patients with severe and/or frequent bleeds.

When interpreting the data from the present study, it should be borne in mind that it was a post hoc analysis for which data collection (medical chart review and patient questionnaire) was not specifically designed. As such, the definition for severe

| Table 3. Summary of the Logistic Regression Analysis Results. |
|---------------------------------------------------------------|
| Patient Outcome                                                |
| Chronic damaged jointsa                                      |
| Joints with limited range of motiona                         |
| Chronic painb                                                |
| Mild pain                                                     |
| Moderate pain                                                 |
| Severe pain                                                   |
| Planned/routine consultations: physiciana                     |
| Planned/routine consultations: nurse specialista              |
| Unplanned/emergency consultations: physiciana                 |
| Unplanned/emergency consultations: nurse specialista          |
| Outpatient consultations: emergency medicinea                 |
| Outpatient consultations: general practicea                   |
| Outpatient consultations: pain managementa                    |
| Outpatient consultations: physiotherapya                      |
| Odds Ratio (95% CI)                                           |
| 0.757 (0.556–1.031)                                          |
| 0.694 (0.467–1.033)                                          |
| 0.740 (0.566–0.966)                                          |
| 0.555 (0.263–1.175)                                          |
| 0.299 (0.127–0.703)                                          |
| 0.200 (0.024–1.634)                                          |
| 0.991 (0.885–1.110)                                          |
| 0.767 (0.650–0.906)                                          |
| 1.008 (0.926–1.097)                                          |
| 0.904 (0.793–1.031)                                          |
| 0.950 (0.859–1.050)                                          |
| 0.934 (0.840–1.039)                                          |
| 0.706 (0.520–0.958)                                          |
| 0.794 (0.624–1.010)                                          |
| p-Value                                                      |
| 0.077                                                        |
| 0.072                                                        |
| 0.027                                                        |
| 0.124                                                        |
| 0.006                                                        |
| 0.133                                                        |
| 0.874                                                        |
| 0.002                                                        |
| 0.854                                                        |
| 0.132                                                        |
| 0.314                                                        |
| 0.211                                                        |
| 0.026                                                        |
| 0.060                                                        |

One additional unit (ie increase in odds of being in prophylaxis group given one additional joint/consultation).

Versus no pain.
bleeding was not as broad as the major bleeding definition in the 2021 international guidelines on the management of VWD. In addition, relatively few patients, particularly from the prophylaxis group, completed the quality of life and productivity questionnaires. It should also be noted that the exact date when prophylaxis was started was not captured during the study, so patients in the prophylaxis group may not have received prophylaxis for the full 12 months before the index date. This is especially the case for patients who had received intermittent prophylaxis rather than continuous treatment. However, patients in the prophylaxis group must have received prophylaxis for sufficient time to satisfy the prophylaxis definitions used in the study. Also, the frequencies of bleeding and bleeding-related hospitalizations were used as criteria for prophylaxis-eligible patients and therefore results concerning the frequencies of treated bleeds and hospitalizations due to bleeds may be biased. Finally, it is also possible that treatment patterns may have changed since the study was conducted in 2018, and that the results of this European study may not be applicable to countries where VWF prophylaxis is not available or in routine clinical use.

Conclusions
This post hoc analysis of CVESS, which was conducted in five European countries, shows that a considerable number of patients with VWD and severe or frequent bleeding were not receiving VWF prophylaxis at the time of data collection, despite its availability in Europe. It should be noted that while this cross-sectional study found differences in the outcomes of patient receiving and not receiving but potentially eligible for prophylaxis, it cannot confirm a causal link between prophylaxis use and better health outcomes. The observed higher disease burden in patients considered potentially eligible but not receiving it than in those receiving prophylaxis, however, does suggest that long-term VWF prophylaxis may improve outcomes in patients with VWD and severe/frequent bleeds.

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Author Contributions
GM and SB contributed to the development of the statistical plan for post hoc analysis, analysis, and development of the report and the manuscript. PD and SXS contributed to conceptualization of the study, study design, critical reviews of the results, and development of the report and the manuscript. All authors approved the final version of the manuscript.

Data Availability
Due to the nature of this retrospective study, data are not available for sharing due to ethical/legal restrictions.

Declaration of Conflicting Interests
PD and SXS are employees of Takeda Development Center Americas, Inc., Cambridge, MA, USA, and hold stock in Takeda. GM and SB are employees of HCD Economics, Daresbury, UK, and received research support from Shire Human Genetic Therapies, Inc., a Takeda company, to perform this analysis.

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Ethics Approval
Ethical oversight for CVESS was provided by the University of Chester, Chester, United Kingdom.

Informed Consent
All patients (or their parent/guardian if aged <18 years) provided written informed consent.

Previous Presentation
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Supplemental Material
Supplemental material for this article is available online.

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