

Comparison of Real-World Dose and Consumption for Two Extended Half-Life Recombinant Factor VIII Products for the Treatment of Hemophilia A in the United States

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Background: US patients with hemophilia A can receive prophylaxis with extended half-life recombinant factor VIII (rFVIII) products, including efmoctocog alfa (fragment crystallizable fusion protein) and rurioctocog alfa pegol (antihemophilic factor [recombinant], PEGylated).

Objective: To evaluate dosing patterns and weekly consumption of extended half-life rFVIII products in the United States.

Methods: We performed a retrospective analysis using the US Specialty Pharmacy Database (2015–2018). Included patients had a diagnosis of hemophilia A, ≥ 2 consecutive monthly claims for efmoctocog alfa or rurioctocog alfa pegol for prophylaxis, and weight data. Outcome measures included weekly dosing frequency and dispensed weekly dose.

Results: The analysis included 774 patients (efmoctocog alfa, 506; rurioctocog alfa pegol, 268). Mean (SD) age was 24.2 (15.8) and 26.3 (14.9) years for patients receiving efmoctocog alfa and rurioctocog alfa pegol, respectively; mean (SD) weight was 68.4 (36.8) and 79.8 (37.7) kg, respectively. The most frequent efmoctocog alfa regimen was twice weekly (45.7%), followed by every 4 days (20.6%), every 3 days (9.1%), and 3 times per week (7.5%). The most frequent rurioctocog alfa pegol regimen was twice weekly (72.4%), followed by 3 times per week (8.7%), every 4 days (7.6%), and every 3 days (5.5%). The proportion of efmoctocog alfa twice-weekly dispensing records increased from 31.5% to 50.9%, and every 4 days dispensing records decreased from 31.3% to 14.5% (2015–2018). The proportion of rurioctocog alfa pegol dispensing records remained broadly stable (2016–2018). Overall, mean (SD; median) weekly prophylactic dose was 105.4 (77.9; 92.6) IU/kg with efmoctocog alfa, and 96.8 (41.9; 90.9) IU/kg with rurioctocog alfa pegol.

Conclusion: In this database study, the most frequently observed dosing frequency was twice weekly for patients receiving efmoctocog alfa or rurioctocog alfa pegol. The observed mean weekly consumption was slightly higher, and variation was greater, in patients receiving efmoctocog alfa versus rurioctocog alfa pegol.

Keywords: hemophilia A, fragment crystallizable fusion protein, efmoctocog alfa, antihemophilic factor (recombinant), PEGylated, rurioctocog alfa pegol, dosing patterns

Introduction

Hemophilia A is a recessive congenital bleeding disorder caused by a deficiency of factor VIII (FVIII).¹ The estimated worldwide prevalence is 17.1 cases per 100,000 males.² The recommended care for patients with severe hemophilia A is prophylactic replacement therapy with recombinant FVIII (rFVIII) to prevent bleeding and maintain joint health.^{3,4} However, conventional factor concentrates have a short half-life of 8–12 hours,⁵ which necessitates frequent intravenous infusions. Therefore, standard half-life (SHL) rFVIII concentrates can result in a high treatment burden for patients, which can have a negative impact on treatment adherence,⁶ potentially leading to poorer bleeding outcomes. Extended

half-life (EHL) rFVIII products with improved pharmacokinetic profiles have been developed, allowing patients to extend the interval between treatments.⁷

The plasma half-life of FVIII has been extended through recombinant technology, either by fusion with the fragment crystallizable (Fc) region of the immunoglobulin G1 molecule or by conjugation with the polymer polyethylene glycol (PEG).⁸ Efmoroctocog alfa (Eloctate; Bioverativ Therapeutics Inc., Waltham, MA, USA) is a rFVIII-Fc fusion protein.⁹ A phase 3 trial analyzed the pharmacokinetics of efmoroctocog alfa and reported that the terminal half-life was extended 1.5-fold versus a commercially available rFVIII product, octocog alfa (antihemophilic factor [recombinant], plasma/albumin-free method [Advate [Europe]; Takeda Manufacturing Austria AG] geometric mean = 19.0 vs 12.4 hours, respectively).¹⁰ Rurioctocog alfa pegol, antihemophilic factor (recombinant), PEGylated (Adynovate [United States]/Adynovi [Europe]; Baxalta Inc., a Takeda company, Lexington, MA, USA) is a recombinant full-length human coagulation FVIII covalently conjugated with at least one molecule of PEG.¹¹ A pivotal study showed that the half-life for rurioctocog alfa pegol increased 1.4-fold versus octocog alfa (14.3 vs 10.4 hours, respectively) in patients aged ≥ 12 years.¹²

Efmoroctocog alfa was approved in the United States in 2014 for use in adults and children with hemophilia A.⁹ According to the product label, the recommended starting regimen for prophylaxis (at the time of the study) in patients aged ≥ 6 years is 50 IU/kg administered every 4 days. The dose can be adjusted, based on the patient response, within a range of 25–65 IU/kg every 3–5 days. For patients aged < 6 years, the recommended starting regimen is 50 IU/kg administered twice weekly. The regimen can be adjusted based on patient response, with dosing in the range of 25–65 IU/kg at 3–5-day intervals, with more frequent or higher doses up to 80 IU/kg if required. A pivotal phase 3 study of males aged ≥ 12 years with severe hemophilia A found that prophylaxis with efmoroctocog alfa was well tolerated and effective in the prevention and treatment of bleeding and did not result in increased immunogenicity.¹⁰

Rurioctocog alfa pegol was first approved for use in November 2015.¹¹ The prescribing information recommends a dose of 40–50 IU/kg twice weekly for patients aged ≥ 12 years. For patients aged < 12 years, the recommended starting dose is 55 IU/kg twice weekly. The dose can be adjusted based on the patient's clinical response, with a maximum of 70 IU/kg.¹¹ A phase 3b study among patients with severe hemophilia A found that rurioctocog alfa pegol as long-term prophylaxis provided good hemostatic efficacy and had a similar safety and immunogenicity profile to previously published data.¹³

There is a lack of published studies of real-world treatment patterns for EHL rFVIII among patients with hemophilia A. In 2020, an observational study of US patients with hemophilia A reported a reduction in the frequency of treatment administration (mean days/week) after patients switched from an SHL rFVIII to rurioctocog alfa pegol (from 2.8 to 2.2 days).¹⁴ The authors also reported lower consumption by patients who switched from SHL rFVIII to rurioctocog alfa pegol (from 109.8 to 100.6 IU/kg). A Canadian report of efmoroctocog alfa utilization for the first 8 months following availability in 2014 showed a 19% reduction in factor utilization (based on weekly IU/kg) among patients with severe hemophilia A who switched from SHL rFVIII to efmoroctocog alfa.¹⁵ Another Canadian study reported a retrospective analysis of pharmacokinetic data from 23 patients with hemophilia A who were switched from efmoroctocog alfa to rurioctocog alfa pegol.¹⁶ The results showed minor differences in the pharmacokinetic profile of the two agents, which were statistically significant ($p < 0.05$ for all) for in vivo recovery (mean 2.73 vs 2.41 IU/dL per IU/kg), clearance (mean 0.163 vs 0.194 mL/h), and volume of distribution at steady state (mean 42.5 vs 49.8 mL/kg), respectively. The authors commented, however, that the clinical implications of these differences are uncertain.¹⁶ Indeed, an earlier study from the same centers showed that the pharmacokinetic profiles of efmoroctocog alfa to rurioctocog alfa pegol in adolescents with hemophilia A were almost identical (mean [range] terminal half-life 16.1 (10.4–23.4) hours vs 16.7 (11.0–23.6) hours, respectively [$p = \text{NS}$]).¹⁷

There is a need for further real-world evidence on EHL products to improve the understanding of prophylaxis dosing patterns associated with each EHL rFVIII to inform health care decision-making and identify the most appropriate treatment regimens for different patient groups. We therefore undertook a retrospective analysis of US specialty pharmacy data to evaluate real-world dosing patterns (weekly dose, infusion frequency) of efmoroctocog alfa and rurioctocog alfa pegol for the prophylactic treatment of patients with hemophilia A without inhibitors.

Methods

Study Design and Data Source

This study was a retrospective analysis of prescription dispensing data from the US Specialty Pharmacy Database and includes >2400 patients with hemophilia from all 50 states. The database comprises de-identified data including patient demographics, detailed prescription information, and clinical data such as diagnosis, disease severity, and inhibitor status, and is fully compliant with regulations from the Health Insurance Portability and Accountability Act (HIPAA) of 1996. De-identified prescription dispensing data were collected for the period between January 1, 2015 and December 31, 2018.

Patient Population

Patients were included in the analysis if they had a diagnosis of hemophilia A using International Classification of Diseases (ICD)-9 code 286.0 or ICD-10 code D66. For registration in the database, patients were required to have received medication for hemophilia A from one of the Specialty Pharmacy Providers included in the database. This study included patients from the database that had at least two consecutive monthly pharmacy dispensing records for efmoctocog alfa or rurioctocog alfa pegol administered for prophylaxis during the study period. Body weight data and valid dispensing units in the patient record were also required. Patients were excluded if they received immune tolerance induction therapy or more than one dose per day, because this is given to patients receiving immune tolerance induction therapy or could be a coding error. Patients receiving perioperative management were not included in the database.

Outcome Measures

We evaluated the weekly consumption (IU/kg) of efmoctocog alfa or rurioctocog alfa pegol. The frequency of dosing was evaluated according to the number and percentage of patients with a prophylactic dose recorded (once weekly, twice weekly, 3 times per week, every 3 days, every 4 days, every 5 days). Infusion frequency data for efmoctocog alfa were available from 2015 to 2018; data for rurioctocog alfa pegol were available from 2016 to 2018. We evaluated the number and percentage of pharmacy dispensing records with doses ≤ 50 and >50 IU/kg. For the purposes of comparison between the two drugs, this threshold was chosen because 50 IU/kg is the starting dose for efmoctocog alfa, per the label. The above outcomes (consumption, frequency of dosing) were analyzed for patients in each treatment group; consumption was also analyzed by age category (<12 and ≥ 12 years).

Statistical Analyses

Descriptive analyses were performed for patient demographic characteristics and clinical conditions. Patient characteristics were summarized using mean (SD) for continuous outcomes and counts, while proportions and counts described categorical variables. Consumption was described by the mean (SD) and median (interquartile range). Between-group comparisons were made using *t*-test for the weekly consumption (continuous variable) and chi-square test for dosing frequency (categorical variable).

Mean weekly prophylaxis was calculated based on the following:

$$\frac{\text{dispensed units}}{\text{number of days between pharmacy dispensing records} \times \text{patient weight}} \times 7$$

The dose from the last observed pharmacy dispensing claim was excluded because the number of days covered by that record could not be calculated. Only consecutive claims were included; claims with more than a 1-month gap to the next claim were excluded.

The proportion of patients receiving efmoctocog alfa and rurioctocog alfa pegol doses that were above, below, and equal to the prophylactic dose of 50 IU/kg was calculated. Subgroup analyses according to age groups (<12 and ≥ 12 years) were performed for patients who received efmoctocog alfa or rurioctocog alfa pegol using pharmacy dispensing records from 2017, when both EHL products had been approved for use in the United States for ≥ 1 year.

Results

Patient Characteristics

A total of 774 patients were included in the study (efmoroctocog alfa, n=506; rurioctocog alfa pegol, n=268) (Table 1). The mean (SD) ages of patients who received efmoroctocog alfa and rurioctocog alfa pegol were 24.2 (15.8) and 26.3 (14.9) years, respectively.

A higher proportion of patients aged 0 to <12 years was observed in the efmoroctocog alfa group versus the rurioctocog alfa pegol group (24.3% vs 14.6%, respectively). Among patients aged ≥ 12 years, the mean age was 31.2 years in the efmoroctocog alfa group and 29.7 years in the rurioctocog alfa pegol group, with a similar age distribution between groups. The mean (SD) weight was 68.4 (36.8) and 79.8 (37.7) kg for patients receiving efmoroctocog alfa and rurioctocog alfa pegol, respectively. A higher proportion of patients receiving rurioctocog alfa pegol had severe hemophilia A versus those receiving efmoroctocog alfa (79.9% vs 57.5%). The states with the most patients in the database were California, Florida, Massachusetts, and Ohio. Florida had the highest proportion of patients receiving efmoroctocog alfa (20.2%), while Ohio had the highest proportion of patients receiving rurioctocog alfa pegol (16.0%).

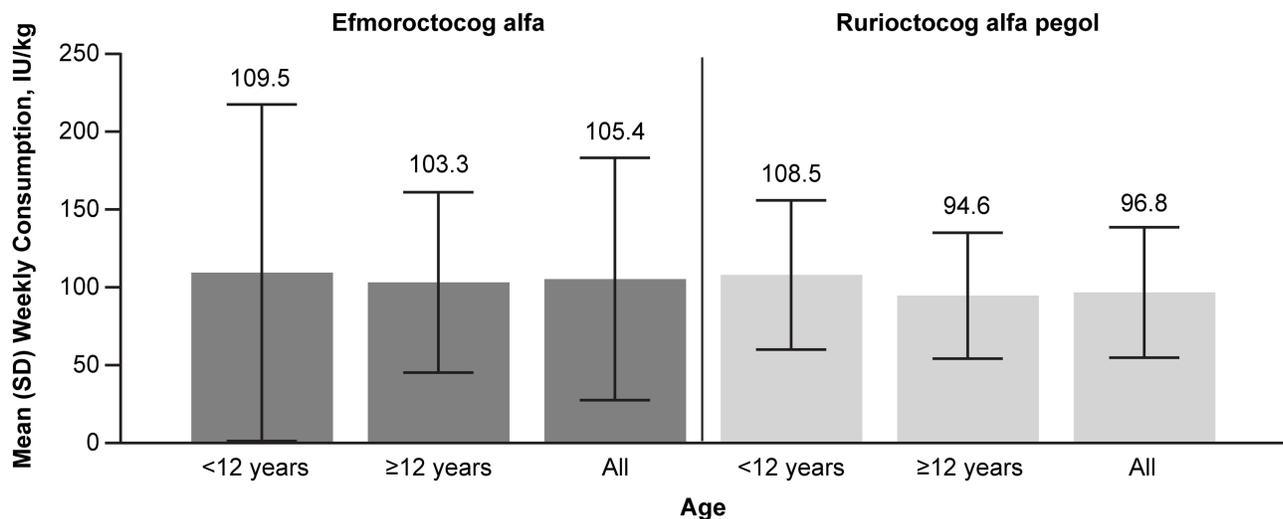
Dosing Frequency

From 2015 to 2018, the most frequent dosing regimens overall were twice weekly for both efmoroctocog alfa (45.7%) and rurioctocog alfa pegol (72.4%) (Supplementary Figure 1). For efmoroctocog alfa, this was followed by every 4 days (20.6%), every 3 days (9.1%), and 3 times per week (7.5%). For rurioctocog alfa pegol, it was followed by 3 times per week (8.7%), every 4 days (7.6%), and every 3 days (5.5%) ($p < 0.001$ for distribution of dose frequencies between efmoroctocog alfa and rurioctocog alfa pegol). During 2015–2018 (after US approval in June 2014), the proportion of efmoroctocog alfa twice-weekly dispensing records increased from 31.5% in 2015 to 50.9% in 2018, and every 4 days dispensing records decreased from 31.3% in 2015 to 14.5% in 2018. During 2016–2018 (after US approval in November 2015), the proportion of rurioctocog alfa pegol dispensing records remained broadly stable.

Table 1 Patient Characteristics by Treatment Group

Characteristic	Efmoroctocog Alfa n=506	Rurioctocog Alfa Pegol n=268
Age group (as of 2018), n (%)		
0 to <6 years	38 (7.5)	10 (3.7)
6 to <12 years	85 (16.8)	29 (10.8)
12 to <18 years	75 (14.8)	45 (16.8)
≥ 18 years	267 (52.8)	182 (67.9)
Missing	41 (8.1)	2 (0.8)
Hemophilia A severity, n (%) ^a		
Mild (>5–30%) ^b	10 (2.0)	4 (1.5)
Moderate (1–5%) ^b	26 (5.1)	15 (5.6)
Severe (<1%) ^b	291 (57.5)	214 (79.9)
Unknown	179 (35.4)	35 (13.1)
Top four health care provider states, n (%) ^c		
California	48 (9.5)	26 (9.7)
Florida	102 (20.2)	23 (8.6)
Massachusetts	23 (4.6)	27 (10.1)
Ohio	41 (8.1)	43 (16.0)

Notes: ^aDisease severity as recorded in the database records. ^bValues in parentheses indicate FVIII levels, percentage of normal. ^cBased on data from all 50 states.



n	1029	2473	3803	214	1227	1448
Mean	109.5	103.3	105.4	108.5	94.6	96.8
95% CI	102.9–116.1	101.0–105.6	102.9–107.9	102.1–115.0	92.4–96.9	94.6–99.0
SD	108.2	57.9	77.9	48.0	40.4	41.9
Median	89.1	93.4	92.6	100.4	89.8	90.9
IQR	68.0–119.9	72.0–116.8	71.4–117.0	75.8–130.1	70.5–111.7	71.2–114.5

Figure 1 Mean (SD) Weekly Consumption (2015–2018), by age category.

Notes: The n values for both of the “All” columns include records with age missing: 301 missing records for efmoroctocog alfa and seven missing records for rurioctocog alfa pegol.

Abbreviation: n, number of pharmacy dispensing records.

Weekly Consumption

Overall, for patients receiving efmoroctocog alfa, the mean (SD) weekly consumption was 105.4 (77.9) IU/kg; the weekly consumption for patients receiving rurioctocog alfa pegol was 96.8 (41.9) IU/kg ($p < 0.001$ vs efmoroctocog alfa). Mean weekly consumption was slightly higher in patients aged <12 versus ≥ 12 years for both efmoroctocog alfa and rurioctocog alfa pegol from 2015 to 2018. By age category, mean weekly consumption was 109.5 (108.2) IU/kg for patients aged <12 years and 103.3 (57.9) IU/kg for patients aged ≥ 12 years receiving efmoroctocog alfa. For patients receiving rurioctocog alfa pegol, mean weekly consumption was 108.5 (48) IU/kg for patients aged <12 years and 94.6 (40.4) IU/kg for patients aged ≥ 12 years (Figure 1).

Subgroup Analysis

The subgroup analysis using 2017 data showed higher mean weekly consumption for patients who received efmoroctocog alfa versus those who received rurioctocog alfa pegol. By age category, the mean consumption for patients aged ≥ 12 years or <12 years was higher for patients receiving efmoroctocog alfa versus rurioctocog alfa pegol (Supplementary Table 1).

Discussion

This analysis of the US Specialty Pharmacy Database showed that the most frequently observed dispensed treatment regimen between 2015 and 2018 was twice weekly for both efmoroctocog alfa and rurioctocog alfa pegol. This aligns with previously published clinical trial efficacy data, where twice-weekly prophylaxis regimens of efmoroctocog alfa and rurioctocog alfa pegol resulted in low annualized bleeding rates.^{7,10,12} Further, in separate trials prophylaxis with rurioctocog alfa pegol twice-weekly or efmoroctocog alfa every 3–5 days resulted in 40% and 45% of patients, respectively, having zero bleeds.^{10,12} It seems likely that the choice of twice-weekly dosing was made for convenience

reasons, as it is less challenging for patients than dosing every 4 days. The advantage of dosing every 4 days, however, is the reduction in the number of total infusions by 1–2 per month, particularly as reduction in dosing frequency is seen as highly desirable by patients and caregivers.¹⁸ In patients who are highly active or have other clinical needs, more frequent dosing than every 4 days may be necessary even with EHL products, and studies have demonstrated the importance of individualized dosing.^{19,20}

In the present study, overall weekly consumption was slightly higher for efmoctocog alfa versus rurioctocog alfa pegol. Twice-weekly dosing for efmoctocog alfa increased from 31.5% in 2015 to 50.9% in 2018 but remained broadly stable for rurioctocog alfa pegol (67.0% to 72.2%). A possible explanation for this is that efmoctocog alfa was approved in June 2014 and clinicians may have become familiar with its use before rurioctocog alfa was approved ~1.5 years later. It has been estimated that the use of EHL rFVIII products results in a 30% reduction in the numbers of annual infusions versus SHL products.²¹ The results of the current study provide real-world evidence to support the finding that EHL rFVIII allows patients with hemophilia A to extend the time periods between intravenous injections.

Notably, most patients receiving efmoctocog alfa and rurioctocog alfa pegol resided in Florida and Ohio, respectively, likely due to different drug formularies between regions/states. A higher mean weekly consumption was observed for patients receiving efmoctocog alfa (105.4 IU/kg) versus rurioctocog alfa pegol (96.8 IU/kg), a finding that is meaningful economically. These results are broadly consistent with a published real-world exploratory analysis of SHL products (moctocog alfa, octocog alfa, simoctocog alfa, turoctocog alfa) versus EHL products (efmoctocog alfa and rurioctocog alfa pegol).²²

Our consumption results for efmoctocog alfa are very similar to those presented previously, where the authors reported a mean weekly consumption (all ages) of 104 (79.4) IU/kg.²³ Our observed consumption findings for rurioctocog alfa pegol are also similar to the findings of a real-world study published in 2020 of patients with hemophilia A who received rurioctocog alfa pegol after switching from an SHL rFVIII (overall mean weekly dose, 100.6 IU/kg).¹⁴ The slight increase in consumption for patients receiving efmoctocog alfa versus rurioctocog alfa pegol in the current study is likely explained by the higher dose and infusion frequency recommended in the prescribing information for efmoctocog alfa (according to the label, the dosing frequency for adults is every 4 days).⁹ In contrast to the prescribing information, our real-world data show that twice weekly is the most frequently used infusion frequency, which is likely due to convenience as it is less challenging for patients to follow than dosing every 4 days.

The proportion of children aged <12 years was substantially higher in the efmoctocog alfa group than the rurioctocog alfa pegol group. We observed that mean weekly consumption was slightly higher in patients aged <12 versus ≥12 years for both efmoctocog alfa and rurioctocog alfa pegol, which could have affected our observed results, given the possibility of age-dependent pharmacokinetic variation and the shorter half-life of FVIII in young children than in adults.^{3,24} Our finding of greater consumption variability among patients receiving efmoctocog alfa suggests less predictable utilization and indicates differences in the prescribing information for efmoctocog alfa versus rurioctocog alfa pegol (eg, different dosing frequencies for patients aged ≥6 vs <6 years). It may also reflect greater use of personalized treatment regimens with efmoctocog alfa, based on its longer period of availability and data obtained from clinical trials and presented in the prescribing information.

Limitations

We acknowledge some limitations that are inherent to database analyses. The US Specialty Pharmacy Database does not include all specialty pharmacy providers and therefore may not be representative of the total US population with hemophilia A. The recording of treatment regimen, infusion frequency, and disease severity may be inconsistent in a pharmacy dispensing records database. For example, no information on disease severity was recorded for 35% of patients in the efmoctocog alfa group and 13% in the rurioctocog alfa pegol group. In addition, the treatment selection and clinical response may affect dosing patterns. These factors were not investigated owing to lack of information in the pharmacy dispensing records data. The current analysis focused on FVIII utilization (frequency of infusions, consumption), but did not link the data to clinical outcomes. Finally, it should be noted that there were important differences between the two treatment groups, potentially affecting comparisons between the two agents. For example, there were

almost twice as many patients in the efomoroctocog alfa group than the rurioctocog alfa pegol group, reflecting the longer availability, and therefore potential study period, of efomoroctocog alfa. There was also a higher percentage of children aged <12 years in the efomoroctocog alfa group (24%) compared with the rurioctocog alfa pegol group (15%), and a higher proportion of patients receiving rurioctocog alfa pegol had severe hemophilia A (79.9%) versus those receiving efomoroctocog alfa (57.5%).

Conclusions

This retrospective database analysis provides additional evidence to increase the understanding of real-world dosing and utilization patterns of EHL rFVIII in patients with hemophilia A without inhibitors, which may help providers to understand clinical effectiveness implications for these therapies. Together, the results of this real-world study and those of clinical trial data suggest that the use of EHL rFVIII may reduce the treatment burden for patients. Additional research is needed to evaluate the reasons for changes in dosing patterns over time and the associated clinical outcomes.

Abbreviations

EHL, extended half-life; FVIII, factor VIII; HIPAA, Health Insurance Portability and Accountability Act; ICD, International Classification of Diseases; IQR, interquartile range; PEG, polyethylene glycol; rFVIII, recombinant factor VIII; SHL, standard half-life.

Data Sharing Statement

The data that support the findings of this study are available from Specialty Pharmacy Database records from individual states, but restrictions apply to the availability of these data due to applicable privacy laws and data use agreements. The data were used pursuant to data use agreements between Shire US Inc., a Takeda company, and the individual states.

Ethics Approval and Informed Consent

No institutional review board approval was required for this retrospective database analysis because only de-identified data were used. All data analyzed in the present study complied with the requirements of the Health Insurance Portability and Accountability Act (HIPAA) of 1996 for fully de-identified datasets.

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Author Contributions

All authors made a significant contribution to the conception, study design, execution, acquisition of data, analysis and/or interpretation of the manuscript. In addition, all authors took part in drafting, revising, and critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

Y. Wu and S.X. Sun are employees of Takeda Development Center Americas, Inc., Cambridge, MA, USA, and Takeda stock owners. T. Fan is an employee of Takeda Pharmaceuticals USA, Inc., Lexington, MA, USA, and Takeda stock owner. The authors report no other conflicts of interest in this work.

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