

Efficacy and safety of full-length pegylated recombinant factor VIII with extended half-life in previously treated patients with hemophilia A: comparison of data between the general and Japanese study populations

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Abstract Ruriococog alfa pegol (BAX 855) is a novel third-generation recombinant factor VIII whose active ingredient is chemically modified with polyethylene glycol. A global multicenter phase 2/3 study of the product in 137 patients (including 11 patients from Japan) with severe hemophilia A aged 12–65 years, reported an extended half-life and a good tolerability profile, as well as a significantly lower annualized bleeding rate in the prophylactic treatment arm than in the on-demand treatment arm. Using descriptive statistics, a post hoc analysis was performed to compare the pharmacokinetics, safety, and efficacy profiles of the product in the Japanese subpopulation and the overall population. Extended half-life was demonstrated in the Japanese subpopulation. The mean [standard deviation (SD)] annualized bleeding rates in the prophylactic treatment arm were 3.7 (4.7) for the overall population ($n = 120$) and 4.0 (3.4) for the Japanese subpopulation ($n = 11$). The proportion of bleeds reported as excellent or good was 94.9% (149/157) in the overall population,

whereas that in the Japanese subpopulation was 92.3% (12/13). No FVIII inhibition or anaphylactic reaction was reported in the Japanese subpopulation. The post hoc comparisons demonstrated similar pharmacokinetic, safety, and efficacy profiles between the overall population and the Japanese subpopulation.

Keywords Hemophilia A · Previously treated patients · Pegylated full-length recombinant factor VIII · Phase 2/3 clinical study · Annualized bleeding rate

Introduction

Hemophilia A is an X chromosome-linked recessive, congenital bleeding disorder caused by a quantitative or qualitative abnormality in coagulation factor VIII (FVIII). A deficiency of plasma FVIII activity results in a prolonged clotting time, and patients with hemophilia A suffer from

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frequent bleeding episodes in joints and muscles over a lifetime unless they receive proper treatment. Current management of severe hemophilia A includes prophylactic therapy with FVIII replacement, which involves the long-term regular administration of FVIII products. Prophylactic therapy offers a certain level of plasma FVIII activity and thus markedly reduces bleeding episodes. As a result, the development of chronic arthropathy, a disease caused by frequent bleeding episodes into joints, can be prevented, which will contribute to an improved quality of life (QOL) in patients with hemophilia A [1, 2].

Current prophylaxis in patients with hemophilia A often uses the so-called the third-generation recombinant FVIII (rFVIII) products which require no addition of proteins of human or animal origin at any stage of their manufacturing process. The mean half-life of current rFVIII products ranges from 10 to 14 h [3–6]; and thus generally requires an infusion of FVIII every other day, or 3 days per week to maintain the FVIII trough level of 1% or above. Frequent intravenous infusions for a long period of time have become an obstacle to continuing treatment and maintaining adherence. Therefore, the development of an rFVIII product with more extended half-life than the currently available FVIII products is considered to reduce burden imposed on patients and lead to an improved adherence to treatment.

Rurioctocog alfa pegol (hereinafter, BAX 855) is a novel third-generation full-length rFVIII product, manufactured by covalent binding of a branched polyethylene glycol (PEG) reagent with a molecular weight of 20 kDa to ADVATE, a currently available rFVIII, to extend half-life [7–9].

Two clinical studies of BAX 855 were conducted in patients with severe hemophilia A. A phase 1, crossover, dose-escalation (2 doses: 30 ± 3 and 60 ± 6 IU/kg) study compared the safety and pharmacokinetic (PK) profile between BAX 855 and ADVATE. The study demonstrated that the mean half-life of BAX 855 was 1.4- to 1.5-fold longer than that of ADVATE. On the basis of this result, an international, multicenter, phase 2/3 study (PROLONG-ATE) was conducted to evaluate the PK parameters, safety, and efficacy of BAX 855 administered as twice weekly prophylaxis at a fixed dose of 45 ± 5 IU/kg. The study demonstrated that BAX 855 was well efficacious in the prophylactic treatment evaluated on the basis of annualized bleeding rate (ABR) as well as in the treatment of bleeding episodes. In addition, no inhibitor development against BAX 855 was reported, and the study also demonstrated that BAX 855 was safe and well-tolerated [10].

In this research, data on the 11 subjects from eight participating institutions in Japan were separately analyzed to assess the consistency in PK parameters, safety, and

efficacy between the Japanese subpopulation ($N = 11$) and the overall population ($N = 137$).

Materials and methods

Study design

The phase 2/3 study was conducted in patients with severe hemophilia A aged 12–65 years who had been previously treated with plasma-derived FVIII or rFVIII products for ≥ 150 exposure days (EDs). A total of 159 patients with severe hemophilia A, from 72 study sites in 20 countries, including 12 Japanese patients at eight study sites in Japan, underwent the screening for eligibility. Patients were considered ineligible for the study if they met any of the following conditions: having detectable FVIII inhibitory antibodies at screening as confirmed by the central laboratory, having a history of FVIII inhibitory antibodies at any time prior to screening, or having known hypersensitivity to mouse or hamster proteins, PEG, or Tween 80. As a result of the screening, 21 patients (including one Japanese patient) were found ineligible and 138 patients (including 11 Japanese patients) were found eligible to participate in the study.

Assignment of the subjects to study arms was based on their treatment regimens prior to enrollment. That is, those who had been receiving prophylaxis regimens prior to enrollment ($N = 100$) were assigned to the prophylaxis arm, and those who had been receiving on-demand regimens prior to enrollment ($N = 17$) were assigned to the on-demand arm until the first 17 continuous subjects were assigned to the on-demand arm; the 18th and subsequent subjects ($N = 21$) were assigned to the prophylaxis arm. Eventually, 121 subjects were assigned to the prophylaxis arm, where BAX 855 was administered at 45 ± 5 IU/kg twice weekly. For the treatment of bleeding, BAX 855 was administered at $10\text{--}60 \pm 5$ IU/kg depending on the severity of bleeding irrespective of treatment arm. PK parameters were evaluated in 26 (including 2 Japanese subjects) of 121 subjects in the prophylaxis arm after administration of BAX 855 at a fixed dose of 45 ± 5 IU/kg. PK evaluation was performed three times: a single dose administration of ADVATE (PK-1), an initial single dose administration of BAX 855 (PK-2), and re-administration of BAX 855 after at least 50 EDs to BAX 855 or 6 months of prophylactic treatment (PK-3), whichever occurred last. Plasma half-life ($T_{1/2}$), mean residence time (MRT), total body clearance (CL), and incremental recovery (IR) were selected as the primary PK parameters. PK parameters were calculated on the basis of plasma FVIII levels obtained with the use of the one-stage clotting assay.

To evaluate the efficacy in prophylaxis of BAX 855, the primary endpoint was annualized bleeding rate (ABR), and the key secondary endpoint was the proportion of success in the treatment of bleeding episodes. Effectiveness of treatment with BAX 855 in each bleeding episode was rated by subjects with a 4-point efficacy rating scale (i.e., “excellent”, “good”, “fair”, or “none”) 24 ± 2 h after the infusion of BAX 855. Hemostatic efficacy was defined as success if it was rated as either “excellent” or “good”, and the proportion of success was calculated. To evaluate the safety of BAX 855, the incidence of adverse events (AEs) and immunogenicity were assessed. To evaluate the immunogenicity of BAX 855, the Nijmegen modification of the Bethesda assay was used to measure inhibitory antibodies against FVIII at each study visit. Enzyme-linked immunosorbent assay was used to examine the development of binding antibodies to FVIII, PEG-FVIII, and PEG, as well as antibodies to Chinese hamster ovary (CHO) proteins. Furthermore, the effects of BAX 855 on vital signs and changes in laboratory values were examined.

This study was conducted in accordance with the Declaration of Helsinki and International Conference on Harmonisation Good Clinical Practice (ICH-GCP) guidelines. The study protocol, informed consent form, and all the relevant documents were reviewed and approved by the relevant ethics committees/institutional review boards and relevant regulatory authorities, and a written informed consent was obtained from all subjects and/or their legal representatives prior to the study implementation. The details of the study were registered at Clinical Trials.gov (NCT01736475) prior to the study initiation.

Statistical analysis

In this research, PK parameters were compared between 26 subjects from the overall population and the two subjects from Japan who underwent the PK assessment. To evaluate the efficacy of BAX 855, 101 subjects of the 121 subjects in the twice weekly prophylaxis arm with BAX 855 were included in per-protocol analysis set (PPAS) because they adhered to the pre-specified requirements in the protocol. All of the 11 Japanese subjects were previously treated prophylactically, enrolled to the prophylactic treatment arm, and included in the PPAS. To evaluate the safety of BAX 855, 137 subjects who received BAX 855 at least once were included in the safety analysis. For efficacy, we compared ABRs during the prophylactic treatment period with

BAX 855 and hemostatic efficacy against breakthrough bleeds between the Japanese subpopulation and the overall population.

The comparisons of PK parameters, safety, and efficacy between the Japanese subpopulation and the overall population were not pre-specified in the protocol. Therefore, the comparisons were made as post hoc analyses. Given that the small sample size of Japanese subjects of 11 (accounting for 11% of the overall population), which would give an insufficient statistical power to compare between the two populations, this post hoc analysis used a descriptive statistical approach.

Results

Of the 138 patients who were enrolled to the study, 121 subjects were assigned to the prophylaxis arm. Of the 121 subjects, 120 subjects received BAX 855 during the study; one subject received only ADVATE and discontinued the study for screen failure before receiving BAX 855. Of the 120 subjects, 101 subjects were treated with BAX 855 in accordance with the dosing requirements as pre-specified in the study protocol without major protocol deviations; the mean age was 30.9 (range 12–58) years, and the mean body weight was 76.5 (range 39.5–137.5) kg (Table 1). Of the 101 subjects, 11 subjects participated from sites in Japan; the mean age was 34.2 (range 19–50) years and the mean body weight was 67.7 (range 51.8–88.0) kg (Table 2). In total, 82 (81.2%) subjects were found to have had at least one target joint at screening, 6 (54.5%) subjects of whom were from the sites in Japan.

Primary PK parameters were obtained from the single dose of ADVATE for PK-1 ($N = 26$), the single dose of BAX 855 for the initial PK-2 prior to prophylaxis with BAX 855 ($N = 26$), and the re-administration of BAX 855 after 50 EDs for PK-3 ($N = 22$). Of the 26 subjects, 4 subjects were not included in PK-3 assessment due to discontinuation or withdrawal from the study. The mean (SD) half-life ($T_{1/2}$) of BAX 855 was 14.3 (3.8) hours for PK-2 and 16.0 (4.9) hours for PK-3, each demonstrating a longer half-life than ADVATE with fold changes of BAX 855 to ADVATE of 1.4- to 1.5-fold higher. The fold change for CL and AUC were 0.5- to 0.6-fold (decrease) and 1.7- to 1.8-fold (increase), respectively. However, similar results were obtained for the mean (SD) of IR: 2.37 (0.536) (IU/dL)/(IU/kg) for PK-1, 2.49 (0.694) (IU/dL)/(IU/kg) for PK-2,

Table 1 Patient background data for total population (per-protocol analysis set, $N = 101$)

	Mean	SD	Median	Q1	Q3	Min	Max
Age (years)	30.9	12.53	28	20	36	12	58
Weight (kg)	76.5	18.78	73	62	83.6	39.5	137.5

Table 2 Patient background data for subjects in Japan ($N = 11$)

No.	Age (years)	Weight (kg)	Previous treatment	Number of target joints at screening	Arthropathy at screening
1	30	57.1	Prophylaxis	0	Yes
2	47	67.8	Prophylaxis	0	Yes
3	24	65.9	Prophylaxis	1	Yes
4	47	66.6	Prophylaxis	1	Yes
5	29	88.0	Prophylaxis	5	Yes
6	49	70.1	Prophylaxis	3	Yes
7	19	73.0	Prophylaxis	0	Yes
8	22	51.8	Prophylaxis	1	Yes
9	50	76.0	Prophylaxis	0	Yes
10	34	61.8	Prophylaxis	4	Yes
11	25	66.3	Prophylaxis	0	Yes
Mean	34.2	67.7	N/A	1.4	N/A
Range	19–50	51.8–88.0	N/A	0–5	N/A

No.	Age (years)	Weight (kg)	Blood type	Number of target joints at screening	Arthropathy at screening
1	30	57.1	B	0	Yes
2	47	67.8	A	0	Yes
3	24	65.9	AB	1	Yes
4	47	66.6	B	1	Yes
5	29	88.0	O	5	Yes
6	49	70.1	A	3	Yes
7	19	73.0	A	0	Yes
8	22	51.8	O	1	Yes
9	50	76.0	B	0	Yes
10	34	61.8	O	4	Yes
11	25	66.3	AB	0	Yes
Mean	34.2	67.7	N/A	1.4	N/A
Range	19–50	51.8–88.0	N/A	0–5	N/A

ABR annualized bleeding rate, N/A not applicable

and 2.30 (0.638) (IU/dL)/(IU/kg) for PK-3 [10]. Of the 2 subjects from Japan [19 years old (no. 7) and 25 years old (no. 11)] who participated in the PK study, the 19-year-old subject experienced muscle hemorrhage due to a traffic accident and did not participate in PK-3 assessment. The remaining subject completed PK-1, PK-2, and PK-3. For PK-2, the two subjects from Japan demonstrated similar PK trends to the overall subjects (Table 3).

For the evaluation of efficacy, the mean (SD) total ABRs were comparable between the Japanese subpopulation and the overall population, with 4.0 (3.4)/year for the Japanese subpopulation and 3.7 (4.7)/year for the overall population. The median ABRs [1st quartile; 3rd quartile (Q1; Q3)] were 4.0/year (0.0; 5.8) for the Japanese subpopulation and 1.9/year (0.0; 5.8) for the overall population, showing a higher median value for the Japanese subpopulation than that of the overall population. In this study, 13 breakthrough bleeds developed in 8 (72.7%) subjects in the Japanese subpopulation, whereas 157 breakthrough bleeds

developed in 61 (60.4%) subjects in the overall population. The proportions of bleeds rated “excellent” or “good” were 92.3% (12/13 bleeds) for the Japanese subpopulation and 94.9% (149/157 bleeds) for the overall population, showing a high hemostatic efficacy in both populations. The proportions of subjects in whom hemostasis was achieved with 1 or 2 infusions were 100% (13/13 bleeds) in the Japanese subpopulation and 93.0% (146/157 bleeds) in the overall population, showing that breakthrough bleeds were in the most cases treated successfully with no more than 2 infusions in both populations. The mean (SD) doses to achieve hemostasis were 33.5 (14.9) IU/kg in the Japanese subpopulation and 35.5 (10.6) IU/kg in the overall population, whereas the medians (Q1; Q3) were 32.5 (21.6; 37.7) IU/kg in the Japanese subpopulation and 37.7 (26.1; 43.7) IU/kg in the overall population (Table 4).

Safety was assessed in 137 subjects who received at least 1 dose of BAX 855 (Table 5). Overall, 171 adverse events (AE) developed in 73 subjects (53.3%). On the other

Table 3 Comparison of PK parameters for the Japanese subjects ($n = 2$) with mean (SD) PK parameters for the overall population

Subject no.	PK cohort	$T_{1/2}$ (h)	MRT (h)	CL [dL/(kg h)]	IR (IU/dL)/(IU/kg)	AUC _{0-∞} (IU h/dL)
PK parameters for the Japanese subjects ($n = 2$)						
No. 7 (aged 19)	PK-1	8.9	13.0	0.0343	2.58	1278
	PK-2	17.2	22.8	0.0171	2.72	2769
	PK-3	–	–	–	–	–
No. 11 (aged 25)	PK-1	15.6	20.8	0.0251	2.62	1928
	PK-2	24.0	33.1	0.0142	2.43	3001
	PK-3	20.7	33.6	0.0153	2.20	2541
Mean (SD) PK parameters for the overall population						
Overall	PK-1 ($n = 26$)	10.4 (2.24)	12.9 (3.04)	0.0455 (0.02173)	2.37 (0.536)	1168 (425.4)
	PK-2 ($n = 26$)	14.3 (3.84)	19.6 (5.32)	0.0276 (0.02029)	2.49 (0.694)	2073 (778.4)
	PK-3 ($n = 22$)	16.0 (4.92)	20.7 (4.82)	0.0247 (0.00823)	2.30 (0.638)	2009 (631.5)

The PK parameters were based on FVIII measurements obtained using the one-stage assay

PK-1: ADVATE, PK-2: BAX 855 (initial), and PK-3: BAX 855 (second)

PK-3 for the 19-year-old subject is missing due to an adverse event (intramuscular bleeding caused by a traffic accident leading to discontinuation before 50 EDs)

– data not available

Table 4 Hemostatic efficacy data in Japanese subjects and overall subjects (per-protocol analysis set: PPAS)

	Subjects from Japan ($n = 11$)	Overall subjects ($n = 101$)
ABR (bleeds/year)		
Mean (SD)	4.0 (3.4)	3.7 (4.7)
Median (Q1; Q3)	4.0 (0.0; 5.8)	1.9 (0.0; 5.8)
Number of bleeds treated with BAX855	13 (11)	157 (100)
Number of infusions needed to treat a bleed		
1	12 (92.3%)	125 (79.6%)
2	1 (7.7%)	21 (13.4%)
3	0 (0.0%)	8 (5.1%)
≥4	0 (0.0%)	3 (1.9%)
Efficacy rating in the treatment of bleeding episodes ^a		
Excellent	12 (92.3%)	68 (43.3%)
Good	0 (0.0%)	81 (51.6%)
Fair	0 (0.0%)	5 (3.2%)
None	0 (0.0%)	1 (0.6%)
Not reported	1 (7.7%)	2 (1.3%)
Dose per infusion to treat bleeds (IU/kg)		
Mean (SD)	33.5 (14.9)	35.5 (10.6)
Median (Q1; Q3)	32.5 (21.6; 37.7)	37.7 (26.1; 43.7)

The PPAS included those who were on the prophylactic treatment arm

^a Efficacy rating on the treatment of bleeding episodes is classified into “Excellent”, “Good”, “Fair”, and “None”

Table 5 Incidence of adverse events

	Subjects from Japan ($n = 11$) <i>E, N (%)</i>	Overall subjects ($n = 137$) <i>E, N (%)</i>
All adverse events	12, 7 (63.6%)	171, 73 (53.3%)
Serious adverse events	1, 1 (9.1%)	5, 5 (3.6%)
Adverse drug reactions	1, 1 (9.1%)	12, 10 (7.3%)

E number of events, *N* number of patients, % percent of patients with adverse events

hand, 12 AEs developed in 7 Japanese subjects (63.6%). A total of 5 serious adverse events (SAE) developed in 5 subjects (each one event of osteoarthritis, muscle hemorrhage, neurological herpes zoster infection, humerus fracture, and neuroendocrine carcinoma); the muscle hemorrhage developed in one Japanese subject. There was no causal relationship between each SAE and BAX 855. Of the AEs experienced by the overall population, 12 AEs (Adverse drug reactions: ADR) experienced by 10 subjects were considered related to the use of BAX 855 by the investigator or sponsor. Of these ADRs, 11 ADRs were experienced by 9 subjects of the prophylactic treatment arm (4 events of headaches in three subjects, 2 events of injection site pain in one subject, and one event each of diarrhea, nausea, transaminase increased, arthralgia, and flushing); the nausea was experienced by one Japanese subject. No marked changes in vital signs, no thrombosis-associated events, or no allergic reactions considered related to BAX 855 were reported during the study period in the overall population. Moreover, no inhibitory antibodies (≥ 0.6 BU/mL) developed against FVIII. A total of 7 subjects experienced transient binding IgG antibodies (no Japanese subjects included) who had been tested negative for antibodies at screening; 4 subjects experienced IgG against FVIII and 3 subjects against PEG-FVIII at 1 or 2 consecutive visits after exposures to BAX 855. All of these binding antibodies were transient and became undetectable at subsequent visits or at the end of the study. There was no temporal relationship to impaired IR or hemostatic efficacy.

Discussion

In this research, PK parameters, the prophylactic as well as treatment effect on bleeding, and the safety with the use of BAX 855 in the treatment of patients with severe hemophilia A were compared between the Japanese subpopulation and the overall population in the multicenter phase 2/3 study. Generally, no racial or ethnical difference is considered to exist in the epidemiology and pathophysiology of hemophilia A as well as the treatment with FVIII products. Because hemophilia A is a rare disease, phase 3 clinical trials involving new recombinant FVIII products have been conducted as a global multicenter clinical study to include a sufficient number of patients [11–15]. In these global multicenter clinical studies, the number of subjects enrolled across the participating countries was limited, making it difficult to demonstrate the study results statistically by race and ethnicity. In this study, while taking these limitations into account, we performed a post hoc comparison between the overall subjects ($N = 101$) and the Japanese subpopulation ($N = 11$) who were assigned to the prophylactic treatment in the PROLONG-ATE study.

PK parameters were measured in two subjects from Japan. A total of 26 subjects participated in the PK assessment. The fold changes demonstrated in the 26 subjects were 1.4- to 1.5-fold (increase) for $T_{1/2}$, 1.7- to 1.8-fold (increase) for $AUC_{0-\infty}$, and 0.5- to 0.6-fold (decrease) for CL; IR was comparable between BAX 855 and ADVATE. Although the number of subjects participating in the PK analysis from the sites in Japan was limited to two, the fold changes for the PK parameters did not contradict those obtained from the overall population.

We compared the mean (SD) and median (Q1; Q3) ABRs in the prophylactic regimen between the Japanese subpopulation and the overall population. The results showed a similar mean ABR (SD) [Japanese: 4.0 (3.4) vs. overall: 3.7 (4.7)] but a slightly higher median ABR in the Japanese subpopulation [Japanese: 4.0 (0.0; 5.8) vs. overall: 1.9 (0.0; 5.8)]. The interpretation of the results requires the consideration that the number of Japanese subjects was limited to 11. Given that the interquartile range was the same and that the mean (SD) was comparable between the two populations, there seemed to be no obviously clinically significant difference in the effect of BAX 855 on the prophylactic control of bleeding between the two populations.

The proportions of hemostatic efficacy rated either “excellent” or “good” on breakthrough bleeds were 92.3% (12/13 bleeds) in the Japanese subpopulation and 94.9% (149/157 bleeds) in the overall population, both populations demonstrating a high hemostatic efficacy. In addition, hemostasis was achieved with one or two infusions of BAX 855 in all Japanese subjects (100%), demonstrating a good efficacy, similar to that of the overall population (93.0%). The mean and median doses to achieve hemostasis with a BAX 855 infusion were similar between the two populations, and thus, the hemostatic efficacy with BAX 855 was considered comparable.

The development of FVIII inhibitor due to the use of blood coagulation factor products is a clinically significant issue in the treatment of hemophilia A. No development of inhibitors against FVIII was reported during the study period in the overall population. Furthermore, neither persistent binding antibodies against FVIII, PEG, or PEG-FVIII nor antibodies against CHO-derived proteins were reported in the overall population. There were no large differences in the incidences of AEs, SAEs, or ADRs, and no AEs were considered specific to the Japanese subpopulation. Of the reported AEs, no marked changes in vital signs, no thrombotic events, or allergic reactions considered related to BAX 855 were observed, and therefore, BAX 855 was considered safe and well-tolerated in the Japanese subpopulation as well.

In conclusion, there were no marked differences between the Japanese subpopulation and the overall population in the safety and efficacy of BAX 855 although there

was a limitation in the number of subjects in the Japanese subpopulation ($N = 11$), accounting for approximately 8% of the overall population ($N = 137$).

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Author contributions KN, MS, KF, TF, MT, TM, SH, TS, and MS made their contributions in data collection, data interpretation, and revising the manuscript. BAK made her contribution in data interpretation and revising the manuscript. WE made his contribution in statistical analyses, data interpretation, and revising the manuscript. BA, HU, and MA made their contributions in data interpretation as well as drafting and revising the manuscript. All authors had a full editorial control of the manuscript and provided their written approval forms for the content of the manuscript.

Compliance with ethical standards

Conflict of interest Keiji Nogami, Midori Shima, Katsuyuki Fukutake, Hideji Hanabusa, Teruhisa Fujii, Masashi Taki, Tadashi Matsushita, Satoshi Higasa, Tetsuji Sato, and Michio Sakai were investigators in this clinical trial. Keiji Nogami has received grants from Baxalta. Midori Shima has received grants and personal fees from Baxalta outside the submitted work. Katsuyuki Fukutake has received grants and personal fees from Baxalta outside the submitted work. Teruhisa Fujii has received honoraria from Baxalta and Chugai Pharmaceutical. Masashi Taki has received an honorarium from Pfizer outside the submitted work. Tadashi Matsushita has received personal fees from Baxalta for the submitted work; grants and personal fees from Bayer, Baxalta, Novo Nordisk, Kaketsuken, and Biogen-idec outside the submitted work. Satoshi Higasa has received honoraria from Baxalta, Bayer, Pfizer, CSL Behring, Novo Nordisk, Biogen, and Chugai Pharmaceutical. Tetsuji Sato and Michio Sakai have declared no conflict of interest. Barbara A. Konkle has received research funding from Shire, Biogen, and Octapharma and serves as a consultant for Shire, Biogen, CSL Behring, and Pfizer. Werner Engl, and Brigitt Abbuehl, Haruhiko Uchikawa, and Morio Arai are full-time employees of Baxalta.

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