Japanese subject subpopulation analysis of B-LONG: a Phase 3 study of long-acting recombinant factor IX Fc fusion protein

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Abstract: The multinational Phase 3 B-LONG study demonstrated the prolonged half-life of recombinant factor IX Fc fusion protein (rFIXFc) versus native recombinant factor IX (rFIX), and the safety and efficacy of rFIXFc for treatment of bleeding and routine prophylaxis in subjects with hemophilia B. This post hoc subgroup analysis of B-LONG evaluated the safety, efficacy, and pharmacokinetics of rFIXFc in Japanese subjects. Previously treated males with moderately severe to severe hemophilia B (endogenous FIX ≤2 IU/dL) received weekly prophylaxis (starting at 50 IU/kg/week, with dose adjustment), individualized interval prophylaxis (starting at 100 IU/kg every 10 days, with interval adjustment), episodic treatment, or perioperative management with rFIXFc. Primary endpoints were annualized bleeding rates (ABRs) and safety. rFIXFc pharmacokinetics were comparable between Japanese subjects (n=6) and non-Japanese subjects. Median ABRs for Japanese subjects in the weekly prophylaxis (n=4) and individualized interval prophylaxis (n=2) groups were 3.27 and 4.28, respectively, which were within the range for non-Japanese subjects. For Japanese subjects, most (95.8%) bleeding episodes were resolved with 1 or 2 rFIXFc infusions, and no treatment-related adverse events or inhibitors were observed. rFIXFc was safe and efficacious for prophylaxis and treatment of bleeding in Japanese subjects with outcomes and pharmacokinetics comparable to non-Japanese subjects.

Key words: hemophilia B, recombinant factor IX Fc fusion protein, pharmacokinetics, bleeding, efficacy

Introduction

Hemophilia B is an X-linked hereditary bleeding disorder resulting from deficiency of functional coagulation factor IX (FIX).⁵ Hemophilia B affects approximately 1 in every 50,000 live births and is found in all racial and ethnic groups.¹⁻³ It is characterized by recurrent, spontaneous bleeding episodes, primarily involving the joints

Received March 12, 2015; Revision accepted July 9, 2015

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and muscles, which may lead to joint destruction and disabling arthritis. Prophylactic FIX replacement is considered the preferred treatment regimen for patients with hemophilia, as it has demonstrated improvement in long-term outcomes (eg, reduced rates of bleeding and arthropathy) compared with the episodic use of FIX to control acute bleeding events. However, the half-life of conventional FIX products necessitates intravenous infusions approximately 2 times weekly, which limits acceptance of and adherence to prophylaxis.

Recombinant factor IX Fc fusion protein (rFIXFc) was developed to have a prolonged half-life compared with conventional FIX products. rFIXFc is composed of a single molecule of recombinant FIX (rFIX) covalently fused to the Fc domain of human immunoglobulin G1 (IgG1), which binds to the neonatal Fc receptor (FcRn) to prolong its half-life. A prolonged half-life has been demonstrated for rFIXFc in both Phase 1/2a and Phase 3 (B-LONG) global studies, with a reported geometric mean terminal half-life of 82.1 hours in the Phase 3 B-LONG study. In both clinical studies, rFIXFc was well tolerated, and no inhibitors (neutralizing antibodies) were reported in previously treated subjects. In the Phase 3 B-LONG study, rFIXFc prophylaxis was associated with low annualized bleeding rates (ABRs) when dosed every 1 to 2 weeks.

Long-acting coagulation factors, such as rFIXFc, have the potential to reduce the frequency of infusions required for prophylactic therapy, and consequently, to improve adherence to these regimens, which may lead to decreased bleeding episodes and improved patient outcomes. Currently, rFIXFc is the only long-acting FIX product approved in Japan.

The objective of this post hoc analysis was to confirm that the safety, efficacy, and pharmacokinetics of rFIXFc in Japanese subjects enrolled in the multinational Phase 3 B-LONG study were comparable to those obtained for non-Japanese subjects in B-LONG.

### Materials and Methods

#### Subjects

The study design of B-LONG has previously been described in detail. Briefly, subjects were males ≥12 years of age with moderately severe to severe hemophilia B (≤2 IU/dL [2%] endogenous FIX) who had previously been treated either prophylactically, or had been treated episodically with a history of ≥8 bleeding events in the year prior to enrollment. Subjects with a history of inhibitors were excluded. The study was conducted in accordance with the International Conference on Harmonisation Guidelines for Good Clinical Practice, and registered with ClinicalTrials.gov (NCT01027364). All subjects (or their guardians) gave written informed consent.

#### Study Design

Subjects were assigned to 1 of 4 treatment groups: weekly prophylaxis, individualized interval prophylaxis, episodic treatment, or perioperative management. Subjects in the weekly prophylaxis group received a starting dose of 50 IU/kg weekly, with dose adjustment to maintain FIX trough levels 1 to 3 IU/dL above baseline (or higher if clinically necessary). Subjects in the individualized interval prophylaxis group received a starting dose of 100 IU/kg every 10 days, with interval adjustment to maintain FIX trough levels 1 to 3 IU/dL above baseline (or higher if clinically necessary). Subjects in the episodic treatment group received 20 to 100 IU/kg of rFIXFc as needed for bleeding episodes (dose adjusted for severity of bleeding event). Subjects in the perioperative management group received rFIXFc for perioperative care (subjects in this group could be enrolled from any other study group or as new subjects). Results from the primary analysis of B-LONG, detailed results from the perioperative management group, and a post hoc analysis of subjects switching from conventional to rFIXFc prophylaxis have previously been published.

A subgroup of participants in the weekly prophylaxis group underwent sequential pharmacokinetic assessment, during which subjects received a single dose of 50 IU/kg of rFIX (BENEFIX®; Pfizer, Philadelphia, PA, USA),
followed by a 50 IU/kg dose of rFIXFc (administered after a 120-hour washout period). Standard pharmacokinetic evaluation was completed for all other Japanese and non-Japanese subjects following 50 or 100 IU/kg doses of rFIXFc. Pharmacokinetics were evaluated for up to 96 hours for rFIX and for 240 or 336 hours for rFIXFc, depending on the dose of rFIXFc used (for 1 Japanese subject, pharmacokinetic assessment could only be completed through 168 hours due to the occurrence of a spontaneous bleed on Day 7).

Inhibitor testing was performed at screening, just prior to the first rFIXFc infusion, and at every study visit. Details of inhibitor testing have been published previously.\(^\text{13}\)

The primary endpoints of B-LONG were ABR, the incidence of adverse events, and the development of inhibitors. Key secondary endpoints included in this subanalysis were pharmacokinetics, rFIXFc dose (weekly prophylaxis group) and dosing interval (individualized interval prophylaxis group), and the dose and number of rFIXFc infusions required to stop a bleeding episode.

**Analyses**

In this post hoc analysis, descriptive statistics were used to describe efficacy and safety endpoints for Japanese and non-Japanese subjects enrolled in B-LONG; the small sample size prevented statistical comparisons between groups. A noncompartmental pharmacokinetic analysis was performed to characterize baseline rFIXFc pharmacokinetic parameters of Japanese subjects and the non-Japanese subjects in the sequential pharmacokinetic subgroup.

**Results**

Of the 123 subjects enrolled in the B-LONG study, 6 subjects were Japanese. Of the 6 Japanese subjects, 4 were enrolled in the weekly prophylaxis group and 2 were enrolled in the individualized interval prophylaxis group. There were no Japanese subjects enrolled in the episodic or perioperative management groups. The remaining 117 subjects were non-Japanese; of these, 59 subjects were enrolled in the weekly prophylaxis group, 27 subjects were enrolled in each of the individualized interval prophylaxis and episodic treatment groups, and 4 subjects were only enrolled in the perioperative management group (another 8 subjects participated in the perioperative management group in addition to another treatment group, and these subjects are accounted for in their other treatment groups).

Demographic and baseline characteristics for Japanese subjects, non-Japanese subjects, and for the overall B-LONG population are shown in Table 1. The median (range) age of Japanese subjects was 44.0 (32–62) years. Five Japanese subjects (83.3%) had a baseline FIX activity level of <1%. The FIX genotypes in Japanese subjects were either missense (66.7%; 4 subjects) or nonsense (33.3%; 2 subjects) mutations. Three Japanese subjects (50%) reported use of a prophylactic prestudy regimen, and 3 Japanese subjects (50%) reported the use of an episodic prestudy regimen. All 3 subjects who received prestudy prophylaxis reported the use of plasma-derived FIX products (twice weekly [n = 2] and thrice weekly [n = 1]).

**rFIXFc Exposure and Compliance**

Five Japanese subjects received at least 50 exposure days (EDs) of rFIXFc. The median (range) of EDs to rFIXFc for Japanese subjects in the weekly prophylaxis group was 54.5 (52–57) days; EDs for the 2 Japanese subjects in the individualized interval prophylaxis group were 35 and 55 days. The median (range) of EDs to rFIXFc in non-Japanese subjects was 55.0 (1–73) days and 37.0 (1–54) days in the weekly prophylaxis and individualized interval prophylaxis groups, respectively. The majority of Japanese subjects (83.3%) were compliant with both the prescribed dose (at least 80% of their doses were taken within 80–125% of the prescribed dose) and prescribed dosing interval (at least 80% of their dosing intervals were within 36 hours of the prescribed interval).

**Pharmacokinetics**

Pharmacokinetic data were available for all 6 Japanese subjects. Two of these Japanese subjects were enrolled in the sequential pharmacokinetic subgroup; the other 4 subjects also had pharmacokinetics assessed but were not in the sequential pharmacokinetic subgroup. All major pharmacokinetic parameters were comparable be-
between Japanese subjects and the 20 non-Japanese subjects in the sequential pharmacokinetic subgroup, including the elimination half-life, mean residence time (MRT), clearance, volume of distribution at steady state (Vss), area under the curve (AUC), and incremental recovery (Table 2). The geometric mean (95% confidence interval [CI]) elimination half-life for Japanese subjects was 79.4 (59.4–106.1) hours compared with 78.0 (69.7–87.3) hours in non-Japanese subjects. The geometric mean (95% CI) AUC/dose was 30.1 (23.6–38.6) IU*h/dL per IU/kg for Japanese subjects compared with 32.3 (28.9–36.0) IU*h/dL per IU/kg for non-Japanese subjects. The geometric mean (range) incremental recovery for Japanese subjects was 0.92 (0.75–1.13) IU/dL per IU/kg compared with 0.94 (0.77–1.14) IU/dL per IU/kg for non-Japanese subjects.

### Table 1 Demographic and Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Non-Japanese subjects (n = 86)</th>
<th>Japanese subjects (n = 6)</th>
<th>Overall B-LONG population (n = 123)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Weekly prophylaxis group (n = 59)</td>
<td>Individualized interval prophylaxis group (n = 27)</td>
<td>Weekly prophylaxis group (n = 4)</td>
</tr>
<tr>
<td><strong>Age, y, median (min-max)</strong></td>
<td>28.0 (12–71)</td>
<td>33.0 (12–62)</td>
<td>45.5 (32–62)</td>
</tr>
<tr>
<td><strong>Weight, kg, median (min-max)</strong></td>
<td>72.0 (47.9–186.7)</td>
<td>76.0 (58.6–128.0)</td>
<td>55.0 (45.2–60.4)</td>
</tr>
<tr>
<td><strong>Baseline FIX level, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1 IU/dL</td>
<td>47 (79.7)</td>
<td>20 (74.1)</td>
<td>3 (75.0)</td>
</tr>
<tr>
<td>1–2 IU/dL</td>
<td>12 (20.3)</td>
<td>7 (25.9)</td>
<td>1 (25.0)</td>
</tr>
<tr>
<td><strong>Genotype, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Missense mutation</td>
<td>30 (50.8)</td>
<td>19 (70.4)</td>
<td>4 (100.0)</td>
</tr>
<tr>
<td>Nonsense mutation</td>
<td>11 (18.6)</td>
<td>4 (14.8)</td>
<td>0</td>
</tr>
<tr>
<td><strong>Prestudy FIX regimen, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prophylaxis</td>
<td>31 (53.4)*</td>
<td>14 (51.9)</td>
<td>2 (50.0)</td>
</tr>
<tr>
<td>Episodic</td>
<td>27 (46.6)*</td>
<td>13 (48.1)</td>
<td>2 (50.0)</td>
</tr>
<tr>
<td>≥1 target joint, n (%)</td>
<td>33 (55.9)</td>
<td>7 (25.9)</td>
<td>3 (75.0)</td>
</tr>
<tr>
<td>HIV positive, n (%)</td>
<td>3 (5.1)</td>
<td>1 (3.7)</td>
<td>2 (50.0)</td>
</tr>
<tr>
<td>HCV positive, n (%)</td>
<td>34 (57.6)</td>
<td>13 (48.1)</td>
<td>4 (100.0)</td>
</tr>
</tbody>
</table>

*FIX, factor IX; HCV, hepatitis C virus; HIV, human immunodeficiency virus.
*Weekly prophylaxis, individualized interval prophylaxis, episodic treatment, and perioperative management groups.
*"n = 58.
*"n = 122.

### Prophylactic Dose and Interval

For Japanese subjects in the weekly prophylaxis group, the median average (range) rFIXFc dose was 57.3 (42.7–72.8) IU/kg; the range of average rFIXFc doses in Japanese subjects was slightly less when analyzed for the last 3 months on-study once subjects’ dosing regimens had stabilized (38.8–65.5 IU/kg). The range of doses used by Japanese subjects on-study was within the dosing range for non-Japanese subjects in the last 3 months on-study (median average [range], 40.3 [16.7–87.6] IU/kg). For the 2 Japanese subjects in the individualized interval prophylaxis group, the average dosing intervals were 11.9 and 10.4 days for the overall study period; intervals were similar when analyzed for the last 3 months on-study. These dosing intervals were within the range of dosing intervals observed for non-Japanese subjects during the
last 3 months on-study (median average [range], 14.0 [7.7–20.8] days).

**Annualized Bleeding Rate**

The median ABRs for Japanese subjects in the weekly prophylaxis and individualized interval prophylaxis groups were 3.27 and 4.28, respectively. Individual ABRs for the 4 Japanese subjects in the weekly prophylaxis group were 2.1, 3.2, 3.3, and 5.6; individual ABRs for the 2 Japanese subjects in the individualized interval prophylaxis group were 0.0 and 8.6. ABRs for Japanese subjects were within the range observed for non-Japanese subjects in both the weekly prophylaxis and individualized interval prophylaxis groups, with median (interquartile range [IQR]) ABRs of 2.30 (0.99–4.35) and 1.38 (0.00–3.27), respectively (Fig. 1). In addition, the ABRs for Japanese subjects, who were all enrolled in prophylactic treatment groups, were numerically lower than the median ABRs observed for non-Japanese subjects enrolled in the episodic treatment group (median [IQR], 17.69 [10.77–23.24]).

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**Table 2  Pharmacokinetics of rFIXFc in Non-Japanese and Japanese Subjects**

<table>
<thead>
<tr>
<th>Pharmacokinetic parameter (geometric mean, 95% CI)</th>
<th>Non-Japanese subjects</th>
<th>Japanese subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n = 20</td>
<td>n = 6</td>
</tr>
<tr>
<td>AUC/dose, IU*h/dL per IU/kg</td>
<td>32.25 (28.92–35.98)</td>
<td>30.14 (23.55–38.57)</td>
</tr>
<tr>
<td>Terminal t&lt;sub&gt;1/2&lt;/sub&gt;, h</td>
<td>77.98 (69.68–87.26)</td>
<td>79.37 (59.39–106.08)</td>
</tr>
<tr>
<td>Clearance, mL/h/kg</td>
<td>3.100 (2.779–3.458)</td>
<td>3.318 (2.592–4.247)</td>
</tr>
<tr>
<td>MRT, h</td>
<td>96.78 (86.48–108.31)</td>
<td>83.46 (67.20–103.66)</td>
</tr>
<tr>
<td>V&lt;sub&gt;ss&lt;/sub&gt;, mL/kg</td>
<td>300.1 (270.7–332.6)</td>
<td>276.9 (221.6–346.1)</td>
</tr>
<tr>
<td>Incremental recovery, IU/dL per IU/kg</td>
<td>0.9351 (0.7704–1.1350)</td>
<td>0.9216 (0.7509–1.1311)</td>
</tr>
</tbody>
</table>

rFIXFc, recombinant factor IX Fc fusion protein; AUC, area under the curve; t<sub>1/2</sub>, half-life; MRT, mean residence time; V<sub>ss</sub>, volume of distribution at steady state.

*a*Noncompartmental pharmacokinetic analysis.

*b*All non-Japanese subjects from the sequential pharmacokinetic subgroup who had an evaluable pharmacokinetic profile for baseline rFIXFc.

*c*All Japanese subjects, regardless of their treatment group, with an evaluable pharmacokinetic profile for baseline rFIXFc.

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**Fig. 1  Annualized bleeding rates for non-Japanese and Japanese subjects**

*Horizontal line represents the median; box, interquartile range; whiskers, min-max data.*
Treatment of Bleeding Events

A total of 24 bleeding episodes were reported in the 6 Japanese subjects during the study period. Of these, 87.5% (21 bleeding episodes) were resolved with 1 infusion; 95.8% (23 episodes) were resolved with 1 or 2 infusions (Table 3). The median (IQR) dose used to treat a bleeding episode was 65.2 (49.6–108.9) IU/kg for spontaneous bleeds and 55.6 (40.0–55.6) IU/kg for traumatic bleeds in Japanese subjects. These results were comparable to those observed for non-Japanese subjects, for whom 90.5% of bleeding episodes were resolved after 1 infusion and 97.4% were resolved with 1 or 2 infusions. The median (IQR) dose used to treat a bleeding episode was 44.7 (30.3–54.8) IU/kg for spontaneous bleeds and 52.2 (37.1–75.4) IU/kg for traumatic bleeds in non-Japanese subjects.

Safety

Safety findings observed for Japanese subjects were similar to non-Japanese subjects; there were no unique safety issues observed in Japanese subjects. All Japanese subjects had valid inhibitor tests and no inhibitors were observed (in addition, no inhibitors were detected in non-Japanese subjects). All Japanese subjects experienced at least 1 adverse event; none were considered by the investigator to be related to treatment with rFIXFc. The most common adverse event experienced by Japanese subjects was nasopharyngitis (5 subjects; 83.3%). Other adverse events experienced by more than 1 Japanese subject (2 subjects each) included abdominal discomfort, bronchitis, and hemorrhoids. One Japanese subject experienced a serious adverse event of cellulitis, which was classified by the investigator as unrelated to rFIXFc treatment. This subject experienced moderate cellulitis of the forearm on Day 82, which was considered serious on Day 83 and resolved on Day 89. At the time of the event, the subject had 16 EDs to rFIXFc; no action was taken with rFIXFc as a result of the event; the subject completed the study with a total of 56 EDs and enrolled in the rFIXFc extension study. Adverse events observed in Japanese subjects in this study were typical for a population with severe hemophilia B.

Discussion

The study design of B-LONG enabled a direct comparison of data from Japanese and non-Japanese subjects because both populations were included in this multinational study and followed the same protocol. This post hoc analysis of B-LONG demonstrated that rFIXFc was safe and efficacious in Japanese subjects, with pharmacokinetic and outcome parameters comparable to those observed in non-Japanese subjects. Exposure to rFIXFc was similar in Japanese and non-Japanese subjects. Furthermore, rFIXFc dose in the weekly prophylaxis group and dosing interval in the individualized interval prophylaxis group for Japanese subjects were within the range of those of non-Japanese subjects. Japanese subjects demonstrated low ABRs (median ABR, 3.27 and 4.28 in the weekly prophylaxis and individualized interval prophylaxis groups, respectively), which were within the range.

Table 3  Summary of Control of Bleeding in Non-Japanese and Japanese Subjects

<table>
<thead>
<tr>
<th></th>
<th>Non-Japanese subjects</th>
<th>Japanese subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n = 113</td>
<td>n = 6</td>
</tr>
<tr>
<td>Total bleeding episodes</td>
<td>612</td>
<td>24</td>
</tr>
<tr>
<td>Bleeding episodes resolved with</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 infusion</td>
<td>554 (90.5%)</td>
<td>21 (87.5%)</td>
</tr>
<tr>
<td>1 or 2 infusions</td>
<td>596 (97.4%)</td>
<td>23 (95.8%)</td>
</tr>
<tr>
<td>Total dose (IU/kg) to treat a bleeding episode&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spontaneous</td>
<td>44.7 (30.3–54.8)</td>
<td>65.2 (49.6–108.9)</td>
</tr>
<tr>
<td>Traumatic</td>
<td>52.2 (37.1–75.4)</td>
<td>55.6 (40.0–55.6)</td>
</tr>
</tbody>
</table>

<sup>a</sup>Data are reported as median (interquartile range).
of ABRs observed for non-Japanese subjects (median ABR, 2.30 and 1.38 in the weekly prophylaxis and individualized interval prophylaxis groups, respectively), when rFIXFc was dosed prophylactically every 1 to 2 weeks. Moreover, the ABRs for Japanese and non-Japanese subjects in the prophylaxis treatment groups were lower than the ABRs of subjects in the episodic treatment group (which included non-Japanese subjects only; median ABR, 17.69). In addition, most acute bleeding events were resolved with 1 or 2 rFIXFc infusions in both Japanese (95.8%) and non-Japanese (97.4%) subjects. There were no unique treatment-related adverse events reported in Japanese subjects, and no inhibitors were detected.

The findings in Japanese subjects reported here are consistent with those observed in the overall B-LONG subject population (N = 123), including a similar mean geometric terminal half-life (79.4 hours for the Japanese subpopulation vs 82.1 hours for the sequential pharmacokinetic subgroup of the global population), a low median ABR in the weekly prophylaxis and individualized interval prophylaxis groups (3.27 and 4.28, respectively in the Japanese subpopulation vs 2.95 and 1.38, respectively in the overall population), and similar proportions of bleeding episodes resolved with 1 or 2 rFIXFc infusions (95.8% in the Japanese subgroup and 97.3% in the overall population). Additionally, a post hoc analysis of data from B-LONG showed that subjects transitioning from prophylaxis with a conventional FIX product to prophylaxis with rFIXFc decreased their infusion frequency and FIX consumption, while experiencing fewer bleeding episodes; moreover, population pharmacokinetic modeling was used to show that these patients have a greater likelihood of maintaining FIX activity above 1 IU/dL while using rFIXFc prophylaxis.

Unlike small molecule drugs, whose therapeutic effect and toxicity are mediated through their interaction with enzymes and receptors in target tissues (eg, liver or kidney) and are cleared by metabolism in the liver or filtration via the kidney, Fc fusion proteins are largely confined to the blood and interstitial spaces and cleared by proteolysis or other unknown mechanisms following target-mediated disposition (receptor-mediated endocytosis following drug-receptor binding). Given these mechanistic differences, Fc fusion proteins, like monoclonal antibodies, are less likely than small molecule drugs to be affected by ethnic genotypic variations. Polymorphisms of the FCGRT gene, the gene that encodes the neonatal Fc receptor (FcRn), have been reported in Japanese subjects and in other ethnic groups; however, no functional differences in FcRn due to these polymorphisms were observed, consistent with the similar pharmacokinetic profiles observed.

Direct comparisons of the pharmacokinetics, efficacy, and safety of an Fc fusion protein between Japanese and non-Japanese subjects in a global study have been limited, and global Phase 3 studies of coagulation factors have not been published until now. As discussed above, this analysis demonstrated no differences in pharmacokinetic parameters between Japanese and non-Japanese subjects. Similarly, studies evaluating the pharmacokinetics and pharmacodynamics of other approved Fc fusion proteins, including etanercept and romiplostim, have reported similar findings in studies conducted in Japanese subjects compared with those reported in non-Japanese populations. In addition, this study and prior studies of etanercept and romiplostim have also demonstrated comparable efficacy and safety between Japanese and non-Japanese subjects. Thus, to date, no differences in approved Fc fusion proteins have been demonstrated between Japanese and non-Japanese subjects.

Studies comparing pharmacokinetics, drug response, and safety for coagulation factors across ethnicities are limited; to date, no differences in the aforementioned parameters between Japanese and non-Japanese subjects have been reported for recombinant factor VIII (FVIII) or FIX products. Clinical and post-marketing observational studies for sucrose-formulated recombinant FVIII (KOGENATE® FS) suggest comparable safety and efficacy between Japanese subjects and North American and European subjects. Post-marketing observational studies for KOGENATE® FS suggest differences in the total number of units (IU) consumed monthly between Japanese and European populations; this may be a result of differences in average body weight in the study popula-
tions being compared, or of differences in prescribing patterns between Japan and Western countries.29

This analysis is not without limitations. Comparison of Japanese and non-Japanese subjects in B-LONG was not prespecified, and thus this was a post hoc analysis. In addition, the number of Japanese subjects was small, so it was not possible to perform statistical comparisons between groups. However, given the rarity of hemophilia B, this analysis provides useful information in the absence of a larger trial of Japanese subjects. The number of subjects in the current analysis is similar to a previous study evaluating a rFIX product in a Japanese population.32

Furthermore, the Japanese subjects in this analysis were all on a prophylactic rFIXFc regimen, the majority of subjects were compliant with both the prescribed dose and dosing interval, and all but 1 subject had at least 50 EDs to rFIXFc.

rFIXFc is the first long-acting rFIX product approved for the control and prevention of bleeding episodes in hemophilia B in Japan.15 Although prophylaxis is considered the preferred therapy for hemophilia patients, a recent survey published in 2015 reported only approximately 44% of individuals with hemophilia B in Japan had received a prophylactic regimen.33 Other recent Japanese surveys (both published in 2009) have also reported low prophylaxis rates overall (26%; hemophilia A and B combined) and specifically for patients with hemophilia B (16%).5,34 Problems associated with prophylaxis initiation in these studies included difficulty with venous access (young children), caregiver unwillingness, and poor adherence.5 rFIXFc provides a treatment regimen requiring less frequent dosing, which may improve clinical outcomes by increasing adherence rates and adoption of prophylaxis.

Conclusions

This post hoc analysis of B-LONG demonstrated that rFIXFc was safe and efficacious for the control and prevention of bleeding in Japanese subjects. rFIXFc prophylaxis was associated with low ABRs, and most acute bleeds were resolved with 1 rFIXFc infusion. No Japa-
nese subject–specific safety concerns were identified. All pharmacokinetic, safety, and efficacy parameters were found to be comparable between Japanese and non-Japanese subjects. Given these results, rFIXFc may allow for less frequent dosing and reduce the treatment burden for hemophilia B compared with conventional rFIX products, ultimately increasing acceptance and compliance to prophylactic treatment.

Acknowledgements

This study was funded by Biogen. Editorial support for the writing of this manuscript was provided by Melissa Yuan, MD, of MedErgy, and was funded by Biogen. We would like to acknowledge Aoife Brennan, Geoffrey Allen, Alison Innes, and Wildon Farwell of Biogen for their contributions to this analysis.

Conflict of Interest

M. Shima, K. Fukutake, H. Hanabusa, T. Matsushita, M. Taki, and M. Sakai have participated as investigators in clinical trials of Biogen. T. Hirakata is an employee of Biogen Japan Ltd. Y. Dong, S. Li, L.M. Cristiano, and B. Mei are employees of and hold equity interest in Biogen. G.F. Pierce is a shareholder and a former employee of Biogen.

References


