Recombinant factor VIII Fc fusion protein: extended-interval dosing maintains low bleeding rates and correlates with von Willebrand factor levels

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Summary. Background: Routine prophylaxis with replacement factor VIII (FVIII) – the standard of care for severe hemophilia A – often requires frequent intravenous infusions (three or four times weekly). An FVIII molecule with an extended half-life could reduce infusion frequency. The A-LONG study established the safety, efficacy and prolonged pharmacokinetics of recombinant FVIII Fc fusion protein (rFVIIIFc) in previously treated adolescents and adults with severe hemophilia A. Objective: In this post hoc analysis, we investigated the relationship between subjects’ prestudy (FVIII) and on-study (rFVIIIFc) regimens. Methods: We analyzed two subgroups of subjects: prior prophylaxis and on-study individualized prophylaxis (n = 80), and prior episodic treatment and on-study weekly prophylaxis (n = 16). Subjects’ prestudy dosing regimens and bleeding rates were compared with their final rFVIIIFc regimens and annualized bleeding rates (ABRs) in the last 3 months on-study. Dosing regimen simulations based on population pharmacokinetics models for rFVIII and rFVIIIFc were performed. Results: As compared with their prestudy regimen, 79 of 80 (98.8%) subjects on individualized rFVIIIFc prophylaxis decreased their infusion frequency. Overall ABRs were low, with comparable factor consumption. Longer dosing intervals, including 5-day dosing, were associated with higher baseline von Willebrand factor antigen levels. Simulated dosing regimens predicted a greater proportion of subjects with steady-state FVIII activity trough levels of ≥ 1 IU dL⁻¹ (1%) with rFVIIIFc than with equivalent rFVIII regimens. Conclusion: These results suggest that patients on rFVIIIFc prophylaxis can reduce their infusion frequency as compared with their prior FVIII regimen while maintaining low bleeding rates, affording more patients trough levels of ≥ 1 IU dL⁻¹ than with rFVIII products requiring more frequent dosing regimens.

Keywords: drug; administration schedule; factor VIII; hemophilia A; pharmacokinetics; recombinant fusion proteins.

Introduction

Patients with hemophilia A frequently experience spontaneous and traumatic bleeding, particularly into joints and
adolescents and adults with severe hemophilia A [13,14]. In the phase 3 A-LONG study conducted in use of the neonatal Fc receptor and IgG recycling pathway from FVIII [11,12]. The half-life of rFVIIIFc is extended via use of the neonatal Fc receptor and IgG recycling pathway [13,14]. In the phase 3 A-LONG study conducted in adolescents and adults with severe hemophilia A (< 1 IU dL⁻¹ [1%] endogenous FVIII activity or severe genotype), rFVIIIFc had a 1.53-fold longer half-life than rFVIII (Advate) (19.0 vs. 12.4 h; P < 0.001), and resulted in low annualized bleeding rates (ABRs) when dosed prophylactically one or two times weekly (median weekly on-study consumption with individualized prophylaxis was 77.90 IU kg⁻¹ [15].

The development of new dosing strategies for FVIII replacement therapies with extended half-lives, including rFVIIIFc, is essential for optimal clinical use. In this post hoc analysis of data from the A-LONG study, we sought to understand the relationship between subjects’ prestudy (FVIII) and on-study (rFVIIIFc) dosing regimens. Previously developed population pharmacokinetic (PK) models for rFVIIIFc and rFVIII [16,17] were used to simulate FVIII activity–time profiles following various dosing regimens and to predict the proportion of patients on each regimen with steady-state FVIII trough levels of ≥ 1 IU dL⁻¹. The relationship between subjects’ PK characteristics and on-study rFVIIIFc dosing interval, including the association of baseline von Willebrand factor (VWF) level with dosing interval extension, was also explored. On the basis of these analyses, the possibility of empiric conversion from FVIII to rFVIIIFc prophylaxis is discussed.

Materials and methods
Study population
The A-LONG study [15] enrolled previously treated males aged ≥ 12 years with severe hemophilia A who were treated prophylactically (defined per protocol as two or more injections weekly with any FVIII product), or episodically with a history of ≥ 12 bleeding events in the 12 months prior to the study. This analysis focused on two subgroups of subjects treated on-study with rFVIIIFc for at least 6 months: those previously on prophylactic therapy and receiving individualized prophylaxis (arm 1 dosing subgroup; n = 80), and those previously treated episodically and receiving weekly prophylaxis (arm 2 dosing subgroup; n = 16). For some analyses, the arm 1 dosing subgroup was further stratified by subjects’ dosing interval at the end of the study (i.e. every 3 days, twice weekly, every 4 days, and every 5 days).

Study design and outcome measures
The A-LONG study [15] was a phase 3, open-label, multicenter, partially randomized study of the safety, efficacy and PK of rFVIIIFc in patients with severe hemophilia A (Fig. S1). Information collected at the time of study enrollment from patient logs and/or hospital records included prestudy prophylactic FVIII dose and dosing frequency (recorded as number of infusions per week), and the number of bleeding episodes in the 12 months prior to the study. On-study parameters documented included rFVIIIFc dose and dosing interval (recorded as number of days between infusions), and ABR. Both spontaneous and traumatic bleeding episodes, including joint bleeds, were recorded [15].

Dosing regimen simulations
To construct FVIII activity–time profiles at steady state following various rFVIII and rFVIIIFc dosing regimens, Monte Carlo simulations were conducted in NONMEM (ICON Development Solutions, Ellicott City, MD, USA) with population PK models for rFVIII and rFVIIIFc [16,17]. The rFVIII and rFVIIIFc models were generated from pooled PK data from the phase 1/2a [18] (rFVIII, n = 16; rFVIIIFc, n = 16) and phase 3 [15] (rFVIII, n = 30; rFVIIIFc, n = 164) studies.

The population PK model for rFVIIIFc used a validated method (the M3 method) [19] for handling data values below the limit of quantification (BLQ). In the rFVIII dataset, there were very few BLQ data; these values were removed. The majority of the data used to construct the population PK models for rFVIII and rFVIIIFc were drawn from the phase 3 study, given its larger size. Thus, the rFVIII and rFVIIIFc dosing regimen simulations were based on the PK parameters and associated variability (e.g. additive error and proportional error) related to the phase 3 study (Table S1), with 1000 individuals modeled per dosing scenario. Sampling points were chosen on the basis of the PK properties of rFVIII and rFVIIIFc and the selected dosing scenarios. The body weight distribution of the simulated individuals was similar to that of subjects enrolled in the two clinical studies of rFVIIIFc. On the basis of the simulated activity–time profiles, the proportion of patients with predicted steady-state FVIII trough levels of ≥ 1 IU dL⁻¹ was estimated.
for each rFVIII and rFVIIIFc regimen. The analysis of simulated data and graphs was performed with S-PLUS (v.8.2; Insightful Corporation, Seattle, WA, USA).

Statistical analyses

Descriptive statistics, including the median and interquartile range (IQR) values for demographic characteristics, estimated number of prestudy bleeding events, and on-study ABR for the prophylactic dosing subgroups of arms 1 and 2, are provided.

To evaluate changes in dosing frequency, subjects in the arm 1 dosing subgroup were stratified according to their prestudy FVIII infusion frequency, and their dosing interval at the end of the study was examined. To evaluate the change in prophylactic factor consumption, the median weekly prestudy FVIII dose was compared with the median weekly rFVIIIFc dose averaged over the last 3 months on-study. The Wilcoxon signed-rank test was used for both comparisons.

The Wilcoxon signed-rank test was also used to evaluate the relationship between the median number of bleeding episodes in the 12 months prior to the study and the median on-study ABR based on the number of bleeding episodes in the last 3 months of the study, once subjects’ treatment regimens had stabilized. Efficacy analyses were based on subjects’ end-of-study dosing interval classification, as the overall ABR was not substantially affected by subjects whose dosing interval classification changed in the last 3 months (data not shown).

The relationships between baseline VWF antigen (VWF:Ag) levels and FVIII and rFVIIIFc half-lives were examined in A-LONG subjects enrolled in the sequential PK subgroup (rFVIII, n = 28) and subjects treated on-study with rFVIIIFc and who had available half-life and VWF:Ag data (n = 158). Subjects in the arm 1 dosing subgroup were classified by their final on-study rFVIIIFc dosing interval (< 5 days vs. every 5 days), and logistic regression was used to evaluate the association between baseline VWF:Ag level and dosing interval. The probability of achieving a 5-day dosing interval was calculated with the formula \( P = \exp(\text{log odds})/(1 + \exp(\text{log odds})) \).

Results

Subject demographics and clinical characteristics

Baseline characteristics of subjects in the prophylactic dosing subgroups of arms 1 and 2 were generally consistent with the overall A-LONG study population, and were representative of a population with severe hemophilia A (Table 1). Products used prior to study entry included both rFVIII and plasma-derived FVIII (Table 1). More than 80% of subjects on a prestudy prophylaxis regimen reported being on their regimen for at least 12 months prior to study entry.

Prophylactic dosing subgroup analyses

All subjects in arm 1 of the A-LONG study started on a twice-weekly prophylactic regimen (25 IU kg\(^{-1}\) on day 1 and 50 IU kg\(^{-1}\) on day 4; total weekly dose, 75 IU kg\(^{-1}\) week\(^{-1}\)), with subsequent dose and interval adjustments based on individual PK information and bleeding [15]. In the arm 1 dosing subgroup, 22 of 80 subjects (27.5%) remained on this regimen at study end. The most common dose per infusion at the end of the study was 50 IU kg\(^{-1}\) (37/80; 46.3%), which was most commonly administered at a frequency of every 5 days (19/37; 51.4%) or every 3 days (16/37; 43.2%).

All but one subject in the arm 1 dosing subgroup (79/80; 98.8%) had a decrease in the number of prophylactic infusions administered weekly (Fig. 1A; Table 2). Examination of prestudy prophylactic dose and frequency data for the subject who required an on-study increase in dosing frequency suggested that the prestudy regimen (12 IU kg\(^{-1}\) twice weekly) was not adequate for suppression of bleeding (see Fig 1A and Table 2 footnotes); however, this situation was effectively corrected on-study.

The final on-study rFVIIIFc prophylactic dosing intervals for the arm 1 dosing subgroup were every 3 days (29/80; 36.3%), twice weekly (23/80; 28.8%), every 4 days (4/80; 5.0%), and every 5 days (24/80; 30.0%). Prior to entering the study, the majority of these subjects (65/80; 81.3%) had reported a prophylactic FVIII infusion frequency of three times weekly, equivalent to ~156 infusions per year. Most of the subjects treated ‘three times weekly’ prestudy reduced their infusion frequency on rFVIIIFc to every 3 days (24/65; 36.9%) or twice weekly (22/65; 33.8%) or every 5 days (15/65; 23.1%) by the end of the study – approximate reductions in annual infusions of 21.8%, 33.3%, and 53.2%, respectively (Table 2).

Although the majority of subjects in the arm 1 dosing subgroup reduced their prophylactic dosing frequency, their weekly factor consumption remained consistent. The prestudy median weekly dose for FVIII was 78.0 IU kg\(^{-1}\) (IQR 60.0, 102.5); the on-study median weekly dose for rFVIIIFc averaged over the last 3 months on-study was 79.2 IU kg\(^{-1}\) (IQR 72.1, 111.5). The median difference in weekly dose (last 3 months on-study minus prestudy) was 4.4 IU kg\(^{-1}\) weekly (Fig. 1B). On an annual basis, this would translate to 4056.0 IU kg\(^{-1}\) yearly prestudy for FVIII vs. 4118.4 IU kg\(^{-1}\) yearly on-study for rFVIIIFc. Per protocol, subjects in arm 2 of the A-LONG study were treated with a prophylactic rFVIIIFc dose of 65 IU kg\(^{-1}\) every 7 days, which was not changed during the course of the study. In the arm 2 dosing subgroup, the median weekly dose for rFVIIIFc at the end of the study was 65.9 IU kg\(^{-1}\) (IQR 63.6, 67.8), which translates to 3426.8 IU kg\(^{-1}\) yearly.

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Efficacy analysis: ABRs

In the arm 1 dosing subgroup, the median on-study ABR was 2.1 overall and 0.0 in the last 3 months on-study (these ABRs were not statistically different from one another; \( P = 0.85 \)). Both the overall and last 3 months on-study median ABRs were significantly lower than the 12-month prestudy median number of bleeding episodes \( (P < 0.001 \) for both comparisons). The lower on-study ABR persisted when these subjects were stratified according to their end-of-study rFVIIIfc dosing interval (Fig. 2). Subjects in the arm 2 weekly dosing subgroup markedly lowered their ABR as compared with their prestudy bleeding rate; the median reported number of bleeding episodes in the 12 months prior to the study was 29.0, whereas in the last 3 months on-study the median ABR with rFVIIIfc was 4.0 \( (P = 0.003; \) Fig. 2).

Efficacy analysis: dosing regimen simulations

The proportion of individuals with predicted steady-state FVIII trough levels of \( \geq 1 \) IU dL\(^{-1} \) for various simulated regimens is shown in Fig. 3 and Table 3. For each simulated prophylactic regimen, higher steady-state FVIII troughs were predicted with rFVIIIfc than with rFVIII for the same dosing regimen. For example, an rFVIIIfc regimen of 50 IU kg\(^{-1} \) every 3–5 days (i.e. the most common end-of-study regimens in the arm 1 dosing subgroup) would maintain trough levels of \( \geq 1 \) IU dL\(^{-1} \) in 89.4% (3 days) to 42.8% (5 days) of individuals, as compared with 58.1% (3 days) to 4.6% (5 days) of individuals on equivalent rFVIII regimens. Similarly, in simulations of 50 IU kg\(^{-1} \) infusions administered twice weekly (e.g. on Monday and Thursday), the proportions of individuals with steady-state trough FVIII levels of \( \geq 1 \) IU dL\(^{-1} \) over both the short (3-day) and long (4-day) portions of the weekly dosing period would be higher for rFVIIIfc (89.5% and 70.3%, respectively) than for rFVIII (55.1% and 18.5%, respectively).

The arm 2 dosing regimen in the A-LONG study (65 IU kg\(^{-1} \) every 7 days) was designed to inform therapeutic decision-making for patients previously on episodic therapy who had been unwilling or unable to manage a regular prophylaxis regimen. Median overall ABR was markedly lower with weekly rFVIIIfc prophylaxis than with episodic rFVIIIfc treatment (3.6 and 33.6, respectively) [15], suggesting that once-weekly prophylaxis can provide positive clinical outcomes for some patients. In the Monte-Carlo dosing regimen simulations for rFVIII and rFVIIIfc, a once-weekly rFVIIIfc dose of...
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*Subject-reported number of infusions per week (12 months prior to start of study).

†Subject reported a prestudy FVIII regimen of 12 IU kg⁻¹ twice weekly, began the study on the initial twice-weekly rFVIIIFc regimen, and ended the study on a regimen of 30 IU kg⁻¹ every 3 days; VWF:Ag level at baseline was 160; prestudy bleeding rate was 42.0; overall on-study ABR was 7.5; ABR in the last 3 months on-study was 0.0.

‡Consumption data not shown for one subject in the analysis. Subject reported a prestudy FVIII regimen of 125 IU kg⁻¹ administered four times per week, began the study on the initial twice-weekly rFVIIIFc regimen, and ended the study on 60 IU kg⁻¹ rFVIIIFc every 3 days.

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Fig. 1. Infusion frequency and change in weekly factor consumption for FVIII (prestudy) and recombinant FVIII Fc fusion protein (rFVIIIFc) (on-study) among subjects in the arm 1 prophylactic dosing subgroup (n = 80). (A) To evaluate changes in dosing frequency, subjects previously on FVIII prophylaxis who received individualized rFVIIIFc prophylaxis on-study were grouped according to their previous FVIII prophylaxis frequency and their dosing interval at the end of the study (recorded as number of infusions per week and number of days between infusions, respectively). All but one subject decreased the number of prophylactic infusions administered per week from prestudy to on-study.† (B) Weekly prophylactic factor consumption in the arm 1 dosing subgroup was calculated as the number of annual infusions, on-study estimate/number of annual infusions, prestudy estimate.‡ Weekly prophylactic factor consumption remained consistent with decreased on-study dosing frequency for rFVIIIFc. The median difference in weekly dose (rFVIIIFc dose in the last 3 months on-study minus FVIII prestudy dose) was 4.4 IU kg\(^{-1}\) weekly (dashed line). Consumption data are not shown for one subject with a non-standard prestudy dosing regimen; this subject’s data did not affect the median change in weekly dose. ABR, annualized bleeding rate; VWF:Ag, von Willebrand factor antigen.

65 IU kg\(^{-1}\) would maintain trough levels of ≥ 1 IU dL\(^{-1}\) in 15.5% of individuals; comparatively, 0.2% of individuals on 65 IU kg\(^{-1}\) rFVIII once weekly would be expected to achieve this trough level.

**Relationship between dosing interval and baseline VWF:Ag level**

As VWF:Ag level was found to be a major covariate in the rFVIIIFc population PK model [17], further analyses were conducted on the relationship of VWF:Ag with rFVIII and rFVIIIFc half-lives. Data collected from A-LONG subjects in the sequential PK subgroup (rFVIII) and subjects receiving rFVIIIFc indicated correlations between baseline VWF:Ag level and rFVIII and rFVIIIFc half-lives (Fig. 4A). Logistic regression analysis revealed a positive association between baseline VWF:Ag level and the probability of a subject having a 5-day dosing interval with rFVIIIFc (P < 0.001), with higher VWF:Ag level being associated with a greater probability of patients achieving a longer dosing interval (Fig. 4B,C).

**Discussion**

This **post hoc** analysis of data from A-LONG study subjects receiving individualized or weekly rFVIIIFc prophylaxis demonstrates that patients were able to effectively change from their previous FVIII therapy to treatment with rFVIIIFc, while maintaining low bleeding rates and consistent levels of factor consumption. The data suggest that it is possible to convert patients who are stable on ‘three times weekly’ or ‘every other day’ FVIII prophylactic regimens to an rFVIIIFc regimen with dosing every 3–5 days. Although the median dose per infusion (IU kg\(^{-1}\)) was slightly higher for rFVIIIFc than for FVIII, owing to a lower number of injections with rFVIIIFc, total weekly factor consumption remained consistent for the majority of subjects. On the basis of population PK model dosing simulations, rFVIIIFc regimens with prolonged dosing intervals can be expected to maintain steady-state FVIII trough levels of ≥ 1 IU dL\(^{-1}\) in a greater proportion of patients than FVIII regimens with more frequent dosing. This may lead to a reduction in the proportion of prophylactically treated patients who experience bleeding episodes, although further investigation is needed.

New dosing strategies are essential for optimal clinical use of FVIII replacement therapies with a prolonged half-life. The current paradigm for prophylactic FVIII dosing is primarily empiric – adjustments to dose and dosing interval are made in response to bleeding events or, more rarely, to achieve desired trough levels, with treatment recommendations being designed to minimize break-through bleeding. The A-LONG study describes the use of FVIII replacement therapies with a prolonged half-life in a population of patients with FVIII deficiency who were selected to be stable on their previous FVIII therapy. The study aimed to determine the feasibility of converting patients from prophylactic FVIII therapy to rFVIIIFc therapy with dosing intervals recommendations being designed to minimize break-through bleeding.

**Table 2** Comparison of the number of prophylactic infusions for FVIII (prestudy) and recombinant factor VIII Fc fusion protein (rFVIIIFc) (last on-study) among subjects in the arm 1 prophylactic dosing subgroup (n = 80)

| FVIII prestudy infusion frequency | n | Number of annual infusions, prestudy estimate | rFVIIIFc dosing interval, last on-study | n (%) | Number of annual infusions, on-study estimate | Approximate % change in annual infusions |
|---|---|---|---|---|---|---|
| Twice weekly | 9 | 104 | Every 5 days | 8 (88.9) | 73 | – 29.8 |
| | | | Every 3 days§ | 1 (11.1) | 122 | + 17.3 |
| Three times weekly | 65 | 156 | Every 3 days | 24 (36.9) | 122 | – 21.8 |
| | | | Twice weekly¶ | 22 (33.8) | 104 | – 33.3 |
| | | | Every 4 days | 4 (6.2) | 91 | – 41.7 |
| | | | Every 5 days | 15 (23.1) | 73 | – 53.2 |
| Four times weekly | 5 | 208 | Every 3 days | 4 (80.0) | 122 | – 41.3 |
| | | | Twice-weekly¶ | 1 (20.0) | 104 | – 50.0 |
| Five times weekly | 1 | 260 | Every 5 days | 1 (100.0) | 73 | – 71.9 |

*Percentages refer to the proportion of subjects from each prestudy dosing group who converted to the specified on-study regimen. †Calculated by dividing 365.25 by the number of days in the final on-study rFVIIIFc dosing interval. ‡Calculated as [(number of annual infusions, on-study estimate – number of annual infusions, prestudy estimate)/number of annual infusions, prestudy estimate] × 100. §Examination of the subject’s prestudy and on-study bleeding rates revealed that the subject was not dosed appropriately prestudy to manage breakthrough bleeds (prestudy bleeding rate, 42.0; overall on-study annualized bleeding rate [ABR], 7.5; ABR in the last 3 months on study, 0.0). ¶Variable dosing intervals of 3 days and 4 days in a week-long period.

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Comparison of 12-month prestudy bleeding events and on-study median annualized bleeding rate (ABR) (last 3 months), stratified by final on-study dosing interval. The change in ABR when switching to an rFVIIIFc regimen was evaluated by comparing the median number of bleeding episodes in the 12 months prior to the study to the median on-study ABR for the last 3 months of the study (among subjects with ≥6 months on study). Subjects in the arm 1 and arm 2 prophylactic dosing subgroups showed reduced median ABRs in the last 3 months on-study with rFVIIIFc as compared with the prestudy median number of bleeding episodes with FVIII (arm 1, 0.0 vs. 6.0; arm 2, 4.0 vs. 29.0; \( P \leq 0.003 \) for both). On-study bleeding rates were consistently lower than prestudy rates when subjects were classified by their dosing interval at the end of the study. IQR, interquartile range (25th to 75th percentile).

![Graph showing bleeding episodes and dosing intervals](image)

**Fig. 2.** Comparison of 12-month prestudy bleeding events and on-study median annualized bleeding rate (ABR) (last 3 months), stratified by final on-study dosing interval. The change in ABR when switching to an rFVIIIFc regimen was evaluated by comparing the median number of bleeding episodes in the 12 months prior to the study to the median on-study ABR for the last 3 months of the study (among subjects with ≥6 months on study). Subjects in the arm 1 and arm 2 prophylactic dosing subgroups showed reduced median ABRs in the last 3 months on-study with rFVIIIFc as compared with the prestudy median number of bleeding episodes with FVIII (arm 1, 0.0 vs. 6.0; arm 2, 4.0 vs. 29.0; \( P \leq 0.003 \) for both). On-study bleeding rates were consistently lower than prestudy rates when subjects were classified by their dosing interval at the end of the study. IQR, interquartile range (25th to 75th percentile).

Data from the A-LONG study suggest a simple informed empiric approach to converting patients from their current FVIII product to one with a prolonged half-life. All A-LONG subjects showed an extended half-life for rFVIIIFc as compared with rFVIII (Fig. 4A), indicating that patients can expect to achieve longer dosing intervals with rFVIIIFc than with conventional FVIII products. Additionally, the observation that a prophylactic rFVIIIFc dose of 50 IU kg\(^{-1}\) (the most common dose at the end of the study) with variably prolonged infusion intervals (3–5 days) was sufficient to maintain on-study FVIII steady-state trough levels of ≥1 IU dL\(^{-1}\) in most A-LONG subjects [15] is supported by the population PK-based dosing simulations detailed here (Table 3). Although a recent comparison of two rFVIII prophylaxis regimens designed to maintain FVIII trough levels of ≥1 IU dL\(^{-1}\) (standard dosing every second day and PK-tailored dosing every third day) indicated similar efficacy for the two regimens [29], consideration of these results in the context of population PK modeling data for rFVIII and rFVIIIFc [17] suggests that dosing conventional FVIII products with a lengthened interval may not achieve consistent FVIII trough levels of ≥1 IU dL\(^{-1}\) in many patients. Thus, given the demonstrated correlation between increased time spent below 1 IU dL\(^{-1}\) and increased breakthrough bleeding [21], extended-interval dosing for conventional FVIII products may be protective for a limited proportion of prospectively identified patients.
In patients for whom PK-based dose optimization is not possible or not practical, an empiric approach to initial rFVIIIFc dosing could be expected to have a high degree of success. As weekly factor consumption remained fairly consistent in subjects changing from a prophylactic regimen with FVIII to one with rFVIIIFc, the analyses presented here provide a rationale for empiric dosing of rFVIIIFc, assuming that the patient is stable on the current regimen. For example, for a patient treated with 100 IU kg\(^{-1}\) FVIII weekly, with doses divided for Monday/Wednesday/Friday administration (i.e. 25/50/50 IU kg\(^{-1}\)), a possible starting regimen for rFVIIIFc might be twice-weekly dosing, with 50 IU kg\(^{-1}\) administered on Monday and Thursday, to maintain a weekly dose of 100 IU kg\(^{-1}\). Our data indicate that this approach appears to be viable for the majority of patients, and suggest that individual PK analyses for patients starting treatment with rFVIIIFc may not be necessary.

As most FVIII in circulation is from a prophylactic regimen with FVIII to one with rFVIIIFc, the analyses presented here provide a rationale for empiric dosing of rFVIIIFc, assuming that the patient is stable on the current regimen. For example, for a patient treated with 100 IU kg\(^{-1}\) FVIII weekly, with doses divided for Monday/Wednesday/Friday administration (i.e. 25/50 IU kg\(^{-1}\)), a possible starting regimen for rFVIIIFc might be twice-weekly dosing, with 50 IU kg\(^{-1}\) administered on Monday and Thursday, to maintain a weekly dose of 100 IU kg\(^{-1}\). Our data indicate that this approach appears to be viable for the majority of patients, and suggest that individual PK analyses for patients starting treatment with rFVIIIFc may not be necessary.

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with the half-lives of rFVIII and rFVIIIFc – subjects with lower VWF:Ag levels showed shorter half-lives for both rFVIII and rFVIIIFc, and those with higher VWF:Ag levels showed longer half-lives for both agents [15,18]. Thus, VWF appears to similarly affect the half-lives of both conventional FVIII products and rFVIIIFc, suggesting that individuals on a less frequent rFVIII dosing regimen would probably require less frequent rFVIIIFc dosing.

In some subjects in this study, baseline VWF:Ag levels were high. Factors potentially influencing VWF plasma levels include catecholamines, vasopressin, and physical activity [37], and variability in VWF gene expression related to ethnicity has been observed [38]. Studies have also shown differences in plasma VWF levels related to ABO blood group status [39,40], with individuals with blood group O having lower mean VWF:Ag levels. In addition, VWF is associated with the early stages of inflammation [41], and it has been postulated that the elevated VWF:Ag levels observed in patients with severe hemophilia A result from chronic endothelial cell activation or chronic inflammation, either in joints or as a result of chronic hepatitis C infection [42,43]. Further investigation is required to determine the causes of increased VWF:Ag levels in subjects in this study. Nonetheless, the high correlation between rFVIII half-life, VWF:Ag level and rFVIIIFc half-life provides additional support for the use of current FVIII regimens as a guide for prolonged dosing regimens with rFVIIIFc.

Potential limitations of the analyses detailed here include the small number of participants in each prestudy dosing interval group and the self-reported nature of the prestudy data. However, the prestudy information recorded in the A-LONG study, which included information from patient charts and infusion logs, was generally consistent with previously published factor consumption and reported bleeding rates [29,44,45]. Additionally, examination of prestudy bleeding rates suggests that some patients had suboptimal prestudy prophylaxis regimens, as is often the case in clinical practice; however, this situation was effectively resolved with rFVIIIFc prophylaxis on-study. Regardless of prestudy regimen, subjects treated with rFVIIIFc generally achieved favorable outcomes, including improved control of bleeding with longer dosing scheduling.

Table 3 Simulated recombinant factor VIII (rFVIII) and rFVIII Fc fusion protein (rFVIIIFc) dosing regimens: predicted proportion of individuals with steady-state FVIII trough levels of ≥1 IU dL⁻¹

| Simulated dosing regimen                  | Total calculated weekly dose (IU kg⁻¹) | Proportion of patients with ≥1 IU dL⁻¹ (1%) |
|------------------------------------------|---------------------------------------|-------------------------------------------|
|                                          | rFVIII*                              | rFVIIIFc†                                |
| 40 IU kg⁻¹ three times weekly             | 120                                   | 91.4% (Wednesday, Friday trough)         |
| (Monday/Wednesday/Friday)                |                                       | 98.4% (Wednesday, Friday trough)         |
| 50 IU kg⁻¹ every 3 days                  | 117                                   | 58.1%                                    |
|                                          |                                       | 89.4%                                    |
| 30 IU kg⁻¹ every other day               | 105                                   | 88.4%                                    |
|                                          |                                       | 98.6%                                    |
| 50 IU kg⁻¹, twice weekly                 | 100                                   | 55.1% (Thursday trough)                  |
| (Monday/Thursday)                        |                                       | 89.5% (Thursday trough)                  |
| 40 IU kg⁻¹ every 3 days                  | 93.3                                 | 50.5%                                    |
|                                          |                                       | 86.4%                                    |
| 25 IU kg⁻¹ three times weekly             | 75                                    | 81.2% (Wednesday, Friday trough)         |
| (Monday/Wednesday/Friday)                |                                       | 96.3% (Wednesday, Friday trough)         |
| 25/50 IU kg⁻¹, twice weekly              | 75                                    | 28.3% (Thursday trough)                  |
| (Monday/Thursday)                        |                                       | 79.4% (Thursday trough)                  |
| 50 IU kg⁻¹ every 5 days                  | 70                                    | 4.6%                                     |
|                                          |                                       | 42.8%                                    |
| 65 IU kg⁻¹ every 7 days§                 | 65                                    | 0.2%                                     |
|                                          |                                       | 15.5%                                    |

* rFVIII model parameters based on pharmacokinetic data from the A-LONG phase 3 study. † rFVIIIFc base model using the M3 method for handling below the limit of quantification data and parameters based on the A-LONG phase 3 study. § Dosing interval of 3–4 days; equivalent to the arm 1 starting study regimen of 25 IU kg⁻¹ on day 1 (Monday) and 50 IU kg⁻¹ on day 4 (Thursday).
**A**

Half-life (h) vs. Baseline VWF: Ag (%)

- rFVIIIFc (n = 158)
- rFVIII (n = 28)

rFVIIIFc, $R = 0.617$

rFVIII, $R = 0.669$

**B**

Last on-study dosing interval

- < 5 day (n = 55)
- 5 day (n = 24)

Probability of achieving 5-day dosing interval at end of study

**C**

End-of-study dosing interval*

- < 5 day (n = 55)
- 5 day (n = 24)

Proportion of subjects (%)

*N = 79 for this analysis; one subject in the arm 1 dosing subgroup with a recorded baseline VWF value of < 10 was excluded, as this value was inconsistent with later testing and deemed erroneous (in later testing, the subject was found to have a VWF level of 100).
projected annual number of infusions by 21.8 in the arm 1 dosing subgroup were able to reduce their laxis, particularly as patients age or their treatment stratified less than optimal rates of adherence to prophylaxis. Previous elses and less frequent weekly administration. Prior joint damage, some patients may choose an rFVIIIFc prophylactic regimen. Considering activity levels and episodically and have resisted initiating an intensive prophylaxis regimen. This study also suggest that a weekly regimen may be of benefit in conjunction with the dosing simulation data presented here, suggest that a weekly regimen may be of benefit for some patients, especially those who are currently treated episodically and have resisted initiating an intensive prophylaxis regimen. Considering activity levels and prior joint damage, some patients may choose an rFVIIIFc regimen with more frequent dosing to achieve higher trough levels, whereas others may choose lower trough levels and less frequent weekly administration.

A reduction in infusion frequency may help to improve the adoption of and adherence to prophylaxis. Previous studies within the hemophilia population have demonstrated less than optimal rates of adherence to prophylaxis, particularly as patients age or their treatment regimen becomes more intensive. Poor adherence to a prescribed prophylactic regimen was shown to be an important determinant of low FVIII levels and a corresponding increase in breakthrough bleeding among patients with severe hemophilia A. Additionally, a recent cost-of-illness analysis found that severe hemophilia and arthropathy are associated with higher healthcare costs

In conclusion, in-depth analyses of A-LONG phase 3 clinical study data, including individual PK, population PK and dosing regimen simulations, and analysis of the correlation between VWF:Ag level and rFVIIIFc half-life, have revealed that patients may be empirically converted from an FVIII regimen to rFVIIIFc without the need for extensive individual PK analyses. The data also suggest that this empiric conversion to rFVIIIFc prophylaxis can maintain low bleeding rates, extend dosing intervals, and enable a greater proportion of patients to maintain trough levels of ≥1 IU dL⁻¹ than with patients’ prior FVIII regimens. An rFVIIIFc dosing regimen with reduced infusion frequency may increase adherence to prophylaxis and potentially improve therapeutic outcomes.

Addendum

G. F. Pierce and H. Jiang contributed to the design and conceptualization of the research, design of data analyses, interpretation of data, and drafting and revision of the manuscript. S. Neelakantan and I. Nestorov contributed to the design and conceptualization of the study. A. D. Shapiro, M. V. Ragni, R. Kulkarni, J. Oldenberg, A. Srivastava, D. V. Quon, K. J. Pasi, H. Hanabusa, I. Pabinger, J. Mahlangu, and P. Fogarty contributed to the data collection, interpretation of data, and drafting and revision of the manuscript. D. Lillicrap contributed to interpretation of data, and drafting and revision of the manuscript. S. Kulke, S. Neelakantan, I. Nestorov, J. A. Dumont, H. Jiang, A. Brennan, and G. F. Pierce contributed to the design of data analyses, interpretation of data, and drafting and revision of the manuscript. J. Potts performed the statistical analyses and contributed to the interpretation of data and revision of the manuscript.

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Disclosure of Conflict of Interests

A. D. Shapiro has served on speakers’ bureaus for Baxter and Novo Nordisk; has served on advisory boards for Baxter, Novo Nordisk, Bayer, and Biogen Idec; has served on global steering committees for Baxter and Bayer; has received consulting fees from Baxter, Novo Nordisk,
Biogen Idec, Chugai Pharma USA, and Kedrion Biopharma; and has received research funding from Baxter, Bayer, CSL Behring, Biogen Idec, Novartis, Octapharma, Cambridge Pharmaceuticals, PTC Therapeutics, and Kedrion Biopharma; all consulting fees and honoraria are directed to the Indiana Hemophilia and Thrombosis Center, and are not accepted personally. M. V. Ragni has served on advisory boards for Biogen Idec; has been a consultant for Tacere Binettec; and has received research support from Baxter, Bayer, Biogen Idec, Bristol-Myers Squibb, CSL Behring, Merck, and Novo Nordisk. R. Kulkarni has served on advisory boards for Biogen Idec and received consulting fees from Biogen Idec. J. Oldenberg has received reimbursement for attending symposia/congresses and/or honoraria for speaking and/or honoraria for consulting, and/or funds for research from Baxter, Bayer, Biogen Idec, Biotest, CSL-Behring, Grifols, Novo Nordisk, Octapharma, Swedish Orphan Biovitrum, and Pfizer. D. V. Quon reports involvement in the A-LONG clinical trial. K. J. Pasi has served on advisory boards for Bayer, BPL, Octapharma, Biogen Idec, and Pfizer; and has received educational and travel grants from Octapharma, Pfizer, Biogen Idec, and Novo Nordisk. H. Hanabusa has received honoraria from Novo Nordisk, Bayer, and Pfizer; and has served on advisory boards for Baxter, Biogen Idec, and KakeksuKen. J. Mahlangu has served as an advisor for Amgen, Bayer, and Novo Nordisk; and has received funding for clinical trials from Bayer, Novo Nordisk, Biogen Idec, and Inspiration. P. Fogarty has received research funding from Baxter, Biogen Idec, and Pfizer; and has received honoraria from Bayer, Biogen Idec, and Pfizer. D. Lillicrap has received research funding from Bayer, Baxter, CSL Behring, and Biogen Idec. S. Kulke, J. Potts, S. Neelakantan, I. Nestorov, S. Li, J. A. Dumont, H. Jiang, A. Brennan and G. F. Pierce are employees of and hold equity interest in Biogen Idec. A. Srivastava and I. Pabinger state that they have no conflict of interest.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Fig. S1. A-LONG study design and dosing analysis subgroups.

Table S1. Summary of population pharmacokinetic model parameters.

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