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Predicting FVIII Activity in Patients Who Use Recombinant FVIII Fc Fusion Protein for Prophylaxis and Treatment of Bleeding Episodes

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INTRODUCTION

- Prophylaxis with replacement factor VIII (FVIII) is the standard of care for people with hemophilia A, and is known to reduce the frequency of bleeding episodes and prevent arthropathy[1]
- However, despite prophylactic factor replacement, patients may still be at risk for developing bleeding episodes[2]
- The Phase 3 A-LONG study demonstrated the prolonged half-life of recombinant factor VIII Fc fusion protein (rFVIIIFc; geometric mean, 19.0 hours) relative to recombinant FVIII (rFVIII; geometric mean, 12.4 hours), and the efficacy and safety of rFVIIIFc for routine prophylaxis and treatment of bleeding in people with severe hemophilia A[3]
- In the A-LONG study (including participants receiving either episodic or prophylactic treatment with rFVIIIFc), most acute bleeding episodes were resolved with a single rFVIIIFc infusion (87.3%), and the majority of participants rated their response to treatment as "excellent" or "good" (77.6%)[3]
  - A subanalysis of the efficacy of rFVIIIFc for the treatment of bleeding only in subjects receiving rFVIIIFc prophylaxis has not been performed to date
  - The magnitude of the peak factor activity following treatment of a bleeding episode and/or scheduled prophylaxis in subjects receiving rFVIIIFc prophylaxis has not yet been evaluated

OBJECTIVES

- The purpose of this post hoc analysis was to assess the efficacy of rFVIIIFc used for the treatment of bleeding in participants who received rFVIIIFc prophylaxis in the A-LONG study
- In addition, a population pharmacokinetic model of rFVIIIFc was used to predict FVIII activity in participants who use rFVIIIFc to treat bleeding episodes in close proximity to their next scheduled prophylaxis dose

METHODS

Study Design and Participants

- The A-LONG study was a Phase 3, open-label, multicenter, partially randomized study (ClinicalTrials.gov Identifier: NCT01181128)
- This study included male participants ≥12 years of age with severe hemophilia A (<1 IU/dL [1%] endogenous FVIII activity or severe genotype) who had been previously treated prophylactically, or episodically with ≥12 bleeding events in the 12 months prior to the study; participants with a history of inhibitors were excluded
  - Participants were enrolled into 1 of 3 treatment groups: individualized prophylaxis (twice-weekly rFVIIIFc dosing; 25 IU/kg on Day 1 and 50 IU/kg on Day 4 to start, followed by 25–65 IU/kg every 3–5 days to maintain trough levels between 1–3 IU/dL), weekly prophylaxis (65 IU/kg rFVIIIFc once weekly), or episodic treatment (10–50 IU/kg rFVIIIFc as needed for the treatment of bleeding episodes)
    - This analysis included only participants in A-LONG who received rFVIIIFc prophylaxis (enrolled in the individualized prophylaxis or weekly prophylaxis groups)
- Acute bleeding episodes were treated with 10 to 50 IU/kg of rFVIIIFc; dosing was based on the participant's clinical condition, type and severity of the bleeding event, and the participant's previous dosing history for a similar bleeding episode (Table 1)

Table 1. Recommended rFVIIIFc Dosing by Bleeding Episode Severity[a]

Bleeding episode severity	rFVIIIFc dose
Minor	10–20 IU/kg
Moderate to severe	15–30 IU/kg
Major to life threatening	40–50 IU/kg initial dose followed by 20–25 IU/kg every 12–24 hours until bleeding episode resolved

[a]If a bleeding episode occurred or was ongoing at the time a prophylactic dose of rFVIIIFc was scheduled, the participant was to treat the bleeding episode using a dose no less than his regular prophylaxis dose.

Outcomes

- Outcomes evaluated in this analysis included: number of bleeding episodes, location and type of bleeds, the average dose per infusion required to treat a bleed, the number of infusions required to resolve a bleed, participants' assessment of response to treatment (recorded within 8–12 hours of first infusion), and safety

Statistics

- Descriptive statistics were used to provide the median and interquartile range (IQR). Frequency and percent were summarized categorically

Pharmacokinetic Simulations

- A previously validated 2-compartment population pharmacokinetic model of rFVIIIFc,[4] developed based on activity-time profiles from participants enrolled in the Phase 1/2a study of rFVIIIFc (n = 16)[5] and the A-LONG study (n = 164),[3] was used to predict FVIII activity levels in 1,000 hypothetical patients
- FVIII activity was modeled under 2 scenarios in which a 25 IU/kg dose of rFVIIIFc was used to treat a bleeding episode 24 hours before a scheduled prophylactic dose for patients at steady state on a regimen of 50 IU/kg every 3 or 4 days
  - A dose of 25 IU/kg was selected to approximate the median dose per infusion used to treat a bleed
  - Twenty-four hours is likely to be the closest proximity to a scheduled prophylaxis dose that a separate dose would be used to treat a bleeding episode
  - The median total weekly prophylactic dose in Arm 1 of the A-LONG study was 77.9 IU/kg.[3] For this modeling exercise, the dose and intervals used were chosen because 50 IU/kg was one of the starting doses in A-LONG, 4 days was one of the starting interval lengths, and 3 days was the shortest interval used in A-LONG

RESULTS

Study Population

- Demographic and baseline characteristics in this study population were representative of a population with severe hemophilia A (Table 2). Additionally, most participants in the individualized prophylaxis and weekly prophylaxis groups reported similar or increased physical activity with the use of rFVIIIFc on-study

Table 2. Demographic and Baseline Characteristics

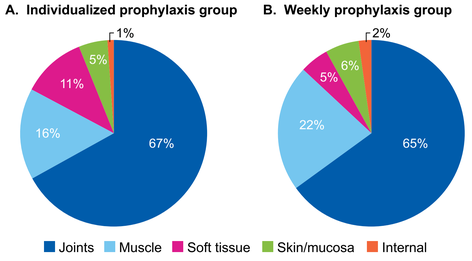
	Individualized prophylaxis group (n = 118)	Weekly prophylaxis group (n = 24)
Age, y, median (range)	29 (12–65)	31.5 (18–59)
Weight, kg, median (range)	71.65 (42.0–127.4)	75.85 (50.0–105.0)
Race, n (%)[a]		
White	79 (66.9)	12 (50.0)
Black	7 (5.9)	1 (4.2)
Asian	27 (22.9)	11 (45.8)
Other	5 (4.2)	0
Geographic location, n (%)		
Europe	34 (28.8)	3 (12.5)
North America	44 (37.3)	5 (20.8)
Other[b]	40 (33.9)	16 (66.7)
Prestudy FVIII regimen, n (%)		
Prophylaxis	87 (73.7)	0
Episodic treatment	31 (26.3)	24 (100)
Estimated bleeding events in prior 12 months, median (IQR)[c]		
Prior prophylaxis	6.0 (2–15)	–
Prior episodic treatment	27 (17–41)	29.5 (19–44)
1 or more target joint, n (%)		
Prior prophylaxis	47 (39.8)	–
Prior episodic treatment	26 (22.0)	22 (91.7)

[a]Percentages may not total 100.0% due to rounding.
[b]Other included Australia, New Zealand, Brazil, Hong Kong, India, Japan, Russia, and South Africa.
[c]Calculation was based on available data.

Bleeding Episodes by Type and Location

- In the individualized prophylaxis group, 209 bleeding episodes were reported in 64 participants (median annualized bleeding rate [ABR], 1.6; median spontaneous ABR, 0.0)
  - Of these, 119 were spontaneous and 87 were traumatic bleeds (for 3 bleeds, the type of bleed is unknown)
  - The location of bleeding episodes is shown in Figure 1A
- In the weekly prophylaxis group, 92 bleeding episodes were reported in 19 participants (median ABR, 3.59; median spontaneous ABR, 1.93)
  - Of these, 60 were spontaneous and 32 were traumatic bleeds
  - The location of bleeding episodes is shown in Figure 1B

Figure 1. Bleeding episodes by location.[a]

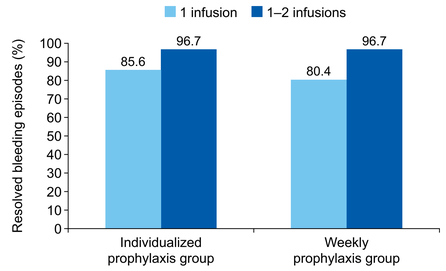


[a]A single bleeding episode could have been reported in ≥1 location.

Treatment of Bleeding

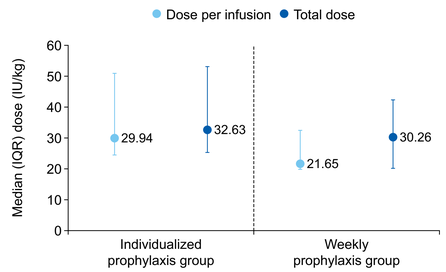
- The majority of bleeding episodes were resolved with 1 or 2 rFVIIIFc infusions in the individualized prophylaxis and weekly prophylaxis groups (Figure 2)

Figure 2. Percentage of bleeding episodes resolved with 1 or 1–2 rFVIIIFc infusions.



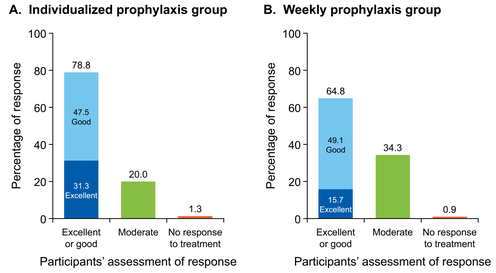
- The median number of infusions of rFVIIIFc required to resolve a bleeding episode was 1.0 in both the individualized prophylaxis and weekly prophylaxis groups
- The median (IQR) dose per infusion required to resolve bleeding episodes was similar in both treatment groups (Figure 3)

Figure 3. Median (IQR) dose per infusion and total dose (IU/kg) of rFVIIIFc required to resolve a bleeding episode.



- When evaluating their response to rFVIIIFc for the treatment of a bleeding episode, 78.8% and 64.8% of participants in the individualized prophylaxis and weekly prophylaxis groups, respectively, rated their response as either "excellent" or "good" (Figure 4)

Figure 4. Participants' assessment of response to treatment for all infusions.[a]



[a]Recorded within 8 to 12 hours of first infusion.

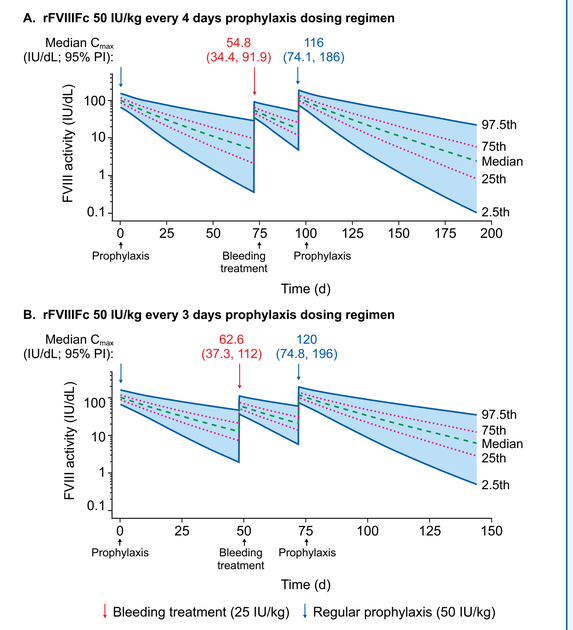
Safety

- rFVIIIFc was generally well tolerated and no serious vascular thrombotic events were reported
- No inhibitors were detected in any participant with an evaluable inhibitor test

Population Pharmacokinetic Simulations of the Treatment of Bleeding With rFVIIIFc

- Population pharmacokinetic simulations predicted that the majority of patients on prophylaxis who use rFVIIIFc to treat a bleeding episode in close proximity to their next scheduled prophylactic dose will have maximum factor activity levels that fall within the normal range (Figure 5)

Figure 5. Predicted FVIII activity versus time profiles when a bleeding episode is treated with rFVIIIFc (25 IU/kg, regardless of prophylaxis dosing regimen) 24 hours before a scheduled prophylactic dose.[a,b]



C_{max} = maximum concentration; PI = prediction interval.
[a]Based on the incremental recovery observed in A-LONG, a rFVIIIFc dose of 25 IU/kg is expected to increase factor activity by approximately 50 IU/dL.
[b]The median time to 1% with a single dose of rFVIIIFc 50 IU/kg is 4.9 days.[3] At steady state, a prophylaxis regimen of rFVIIIFc 50 IU/kg every 3 days would be predicted to maintain 89.4% of individuals above 1%, and a prophylaxis regimen of rFVIIIFc 50 IU/kg every 4 days would be predicted to maintain 67.2% of individuals above 1%.[4]

CONCLUSIONS

- Bleeding episodes among participants in the prophylaxis arms of the A-LONG study were rare
- rFVIIIFc was safe and effective when used to treat bleeding episodes in participants receiving routine prophylaxis, with most bleeds resolving with 1 or 2 rFVIIIFc infusions; efficacy for treatment of bleeding in the prophylaxis arms was consistent with that in the episodic treatment arm
- Clinical observations during A-LONG indicate that the maximal plasma factor activity level is reached immediately following infusion of rFVIIIFc. Population pharmacokinetic simulations demonstrate that predicted maximum FVIII activity levels are likely to fall within the normal range for a majority of patients using rFVIIIFc prophylaxis when a bleeding event is treated in close proximity to a scheduled prophylaxis dose

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