P-T-105

Long-term Efficacy of Recombinant Factor VIII Fc Fusion Protein (rFVIIIFc) in Adults/Adolescents With Severe Hemophilia A: United States Subgroup Analysis of A-LONG and ASPIRE

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INTRODUCTION

- The safety, efficacy, and prolonged half-life of rFVIIIFc were demonstrated in the Phase 3 A-LONG[1] and Kids A-LONG[2] studies of previously treated adults/adolescents and children with severe hemophilia A, respectively
- Eligible subjects who completed A-LONG or Kids A-LONG could enroll in the ongoing rFVIIIFc extension study ASPIRE; results from the first ASPIRE interim data cut (January 6, 2014) have been published[3]
- Longitudinal data from US adults/adolescents who enrolled in A-LONG and ASPIRE are reported here

OBJECTIVE

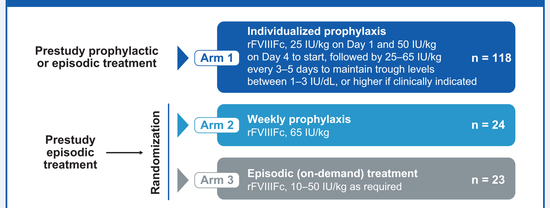
- To report the long-term efficacy of rFVIIIFc for US adults/adolescents from the start of A-LONG to the second ASPIRE interim data cut (December 8, 2014)

METHODS

Study Design

- Previously treated males (≥12 years of age) with severe hemophilia A (<1 IU/dL endogenous factor VIII [FVIII] activity) were eligible for A-LONG (ClinicalTrials.gov Identifier: NCT01181128; Figure 1)

Figure 1. A-LONG study design



- Eligible subjects who completed A-LONG could participate in 1 of 4 treatment groups in ASPIRE (NCT01454739; Table 1)
  - Subjects could change treatment groups at any point in ASPIRE; thus, subjects could be represented in >1 treatment group
- All data were analyzed from the first dose of rFVIIIFc in A-LONG to the second ASPIRE interim data cut
- Evaluated outcomes included rFVIIIFc exposure days (EDs), prophylactic dose and dosing interval, and annualized bleeding rates (ABRs)
- Median ABRs were analyzed by treatment regimen during A-LONG/ASPIRE
  - Subjects' ABRs were summarized by year for the duration during which they were on a given treatment regimen

Table 1. ASPIRE treatment groups

Treatment group	Dosing guidance per protocol
Individualized prophylaxis	rFVIIIFc 25–65 IU/kg every 3–5 days, OR twice-weekly rFVIIIFc (20–65 IU/kg on Day 1, 40–65 IU/kg on Day 4)
Weekly prophylaxis	rFVIIIFc 65 IU/kg every 7 days
Modified prophylaxis	Investigators could personalize dosing for subjects in whom optimal prophylaxis could not be achieved with individualized or weekly prophylaxis (eg, less frequent dosing, targeting a FVIII trough level of >3 IU/dL)
Episodic treatment	rFVIIIFc dosing based on type and severity of bleeding episode

RESULTS

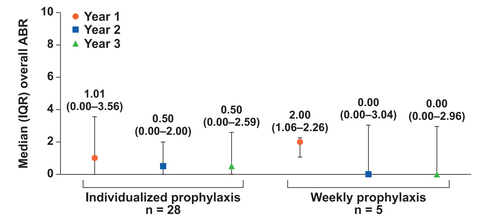
Study Population

- 54 US subjects from A-LONG/ASPIRE with available on-study data were included
- Among all 54 subjects from the beginning of A-LONG to the second interim data cut of ASPIRE on December 8, 2014:
  - Median (range) cumulative rFVIIIFc exposure was 234.5 (9.0–374.0) EDs
  - Median (range) cumulative efficacy duration of rFVIIIFc treatment in A-LONG/ASPIRE was as follows:
    - Individualized prophylaxis (n = 44): 2.70 (0.15–3.69) years
    - Weekly prophylaxis (n = 7): 2.09 (0.09–2.70) years
    - Modified prophylaxis (n = 4): 1.68 (1.26–1.79) years
    - Episodic treatment (n = 7): 2.60 (0.58–2.95) years

Annualized Bleeding Rates

- Median ABRs were low with rFVIIIFc prophylaxis (Table 2)
- Median overall ABRs remained low over time during A-LONG/ASPIRE (Figure 2)

Figure 2. Median overall ABRs over time during A-LONG/ASPIRE



- Overall, 98.5% of bleeding episodes were controlled with 1–2 infusions

Changes to Prophylactic Dosing Regimens

- 96.8% (30/31) of subjects lengthened and 3.2% (1/31) of subjects maintained their dosing interval on-study compared with prestudy (Figure 3), while median total weekly prophylactic factor consumption decreased (Figure 4)

Figure 3. Change in prophylactic dosing interval from pre–A-LONG to the second ASPIRE interim data cut[a]

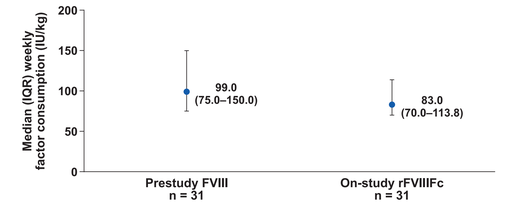
ASPIRE dosing interval (second interim data cut: December 8, 2014)

Pre–A-LONG dosing interval	Every 3 days n = 8 (25.8%)	Twice weekly n = 10 (32.3%)	Every 4 days n = 4 (12.9%)	Every 5 days n = 7 (22.6%)	Once weekly n = 2 (6.5%)
5 times weekly n = 1 (3.2%)	–	–	–	1	–
4 times weekly n = 2 (6.5%)	1	1	–	–	–
3 times weekly n = 24 (77.4%)	7	8	3	5	1
Twice weekly n = 4 (12.9%)	–	1	1	1	1

Change in dosing interval
- Lengthened (n = 30; 96.8%)
- No change (n = 1; 3.2%)
- Shortened (n = 0; 0.0%)

[a]Only subjects who were on prophylaxis both prior to A-LONG and during ASPIRE and who had both prestudy FVIII and on-study rFVIIIFc dosing interval data were included in this analysis.

Figure 4. Total weekly prophylactic factor consumption pre–A-LONG and at the second ASPIRE interim data cut[a]



[a]Only subjects who were on prophylaxis both prior to A-LONG and during ASPIRE and who had both prestudy FVIII and on-study rFVIIIFc dosing interval data were included in this analysis.

Safety Summary (Overall Study Population)

- No subjects developed an inhibitor during the completed A-LONG study or in ASPIRE as of the second interim data cut (December 8, 2014)
- As of the second interim data cut, the adverse event profile was generally similar to the background characteristics of the adult and pediatric hemophilia A population

Table 2. Summary of pooled ABRs from the start of A-LONG to the second ASPIRE interim data cut[a]

Treatment group[b]	Individualized prophylaxis (n = 44)	Weekly prophylaxis (n = 7)	Modified prophylaxis (n = 4)	Episodic treatment (n = 7)
ABR, median (IQR)				
Overall	0.90 (0.00–3.25)	2.39 (0.74–13.50)	2.37 (0.60–8.51)	19.64 (17.40–30.48)
Spontaneous	0.15 (0.00–0.81)	0.74 (0.00–1.43)	0.59 (0.30–1.09)	15.91 (12.21–23.47)
Traumatic	0.32 (0.00–2.27)	0.96 (0.51–4.76)	1.78 (0.30–7.42)	5.96 (1.49–11.92)
Joint	0.68 (0.00–1.89)	1.43 (0.43–9.13)	0.30 (0.00–6.63)	18.96 (11.94–27.33)
Spontaneous joint	0.00 (0.00–0.76)	0.37 (0.00–1.07)	0.00 (0.00–0.79)	12.43 (8.86–21.02)

IQR = interquartile range.
[a]The efficacy period reflects the sum of all intervals of time during which subjects were treated with rFVIIIFc according to the treatment regimens of the study, excluding major and minor surgical/rehabilitation periods and large dosing intervals.
[b]Subjects could change treatment groups at any point in ASPIRE; thus, subjects could be represented in >1 treatment group.

CONCLUSIONS

- These data confirm that previously treated US adults/adolescents receiving rFVIIIFc prophylaxis during A-LONG/ASPIRE maintained low ABRs over an extended time period while either lengthening or maintaining their dosing interval compared with prestudy FVIII
- The observed reduction in total weekly prophylactic dose may have resulted from high prestudy FVIII consumption among US subjects

References

1. Mahlangu J, et al. *Blood*. 2014;123(3):317-325.
2. Young G, et al. *J Thromb Haemost*. 2015;13(6):967-977.
3. Nolan B, et al. *Haemophilia*. 2016;22(1):72-80.

Disclosures

DVQ: speakers bureau for Baxalta, Biogen, CSL Behring, Grifols, and Novo Nordisk; advisory boards for Baxalta, Bayer, Biogen, and Novo Nordisk. GY: consultant for Novo Nordisk, Biogen, Baxalta, Bayer, Roche, Alnylam, and Kedrion; honoraria for speaking engagements from Novo Nordisk, Baxalta, and Biogen. MVR: grant/research support from Alnylam, Bayer, Biogen, Bristol-Myers Squibb, CSL Behring, Dimension, Genentech Roche, Pfizer, SPARK, Vascular Medicine Institute, and Biomarin; advisory boards for Baxalta, Shire, and Tacere Benitec; honoraria from Baxalta. BAK: grant/research support from Biogen, Baxalta, Novo Nordisk, and Octapharma; consultant for Biogen, Baxalta, Novo Nordisk, CSL Behring, and Pfizer. RK: grant/research support from Biogen, Baxter, Bayer, and Novo Nordisk; advisory boards for Baxter, Bayer, Novo Nordisk, Pfizer, Kedrion, and BPL; speakers bureau for Biogen and Novo Nordisk. ADS: grant/research support from Bayer HealthCare, Baxalta, Biogen, CSL Behring, Daiichi Sankyo, Kedrion Biopharma, Octapharma, OPKO, ProMetic Life Sciences, PTC Therapeutics, and Selexys; consultant for Baxalta, Novo Nordisk, Biogen, ProMetic Life Sciences, and Kedrion Biopharma; advisory boards for Baxalta, Novo Nordisk, and Biogen; speakers bureau for Biogen. JF, LMC: employees of and hold equity interest in Biogen. GA: former employee of and holds equity interest in Biogen.

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