P-T-82

Dosing Regimens Before and Following Long-term Treatment With Recombinant Factor VIII Fc Fusion Protein (rFVIIIFc) in Adults and Adolescents With Severe Hemophilia A

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INTRODUCTION

- Long-term safety and efficacy of rFVIIIFc in individuals with severe hemophilia A have been demonstrated in the Phase 3 A-LONG (adults/adolescents)[1] and Kids A-LONG (children)[2] studies, as well as in the ongoing rFVIIIFc extension study, ASPIRE
  - Results from the first interim data cut of ASPIRE (January 6, 2014) have been published[3]

OBJECTIVE

- To report changes in dosing regimens from pre–A-LONG to the second interim data cut of ASPIRE (December 8, 2014)

METHODS

Study Design

- Eligible subjects aged ≥12 years with severe hemophilia A (<1 IU/dL endogenous factor VIII [FVIII] activity) who completed the Phase 3 A-LONG study (ClinicalTrials.gov Identifier: NCT01181128) could enroll in 1 of 4 treatment groups in ASPIRE (NCT01454739; Table 1)
  - Subjects could change treatment groups at any point in ASPIRE

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 – For example, less frequent dosing or targeting a FVIII trough level >3 IU/dL
Episodic treatment	• rFVIIIFc dosing based on type and severity of bleeding episode

Analyses

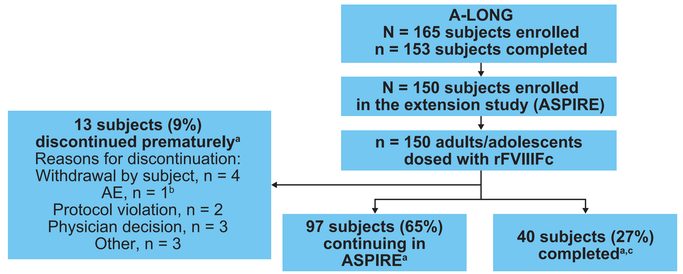
- In this post hoc analysis, subjects with available prestudy (pre–A-LONG) FVIII and on-study rFVIIIFc dosing data at the second ASPIRE interim data cut (December 8, 2014) were evaluated for:
  - Change in dosing interval
  - Change in prescribed total weekly prophylactic consumption (IU/kg/week)

RESULTS

Study Population

- Subject disposition is summarized in Figure 1
- From the first dose of rFVIIIFc in A-LONG to the second ASPIRE interim data cut:
  - Median (range) cumulative duration of treatment was 1,107.6 (252.6–1,371.6) days (~3.0 years)
  - Median cumulative rFVIIIFc exposure was 264 days

Figure 1. Subject disposition



AE = adverse event; HIV = human immunodeficiency virus.
[a]As of the second ASPIRE interim data cut on December 8, 2014.
[b]AE was blood creatinine increase, which was assessed by the investigator as mild and related to rFVIIIFc; this subject had several comorbidities, including HIV, hypertension, and concomitant medications associated with elevated creatinine and renal impairment.
[c]Completed: ended participation in the study without premature discontinuation. All subjects had the opportunity to continue in the study for up to 4 years or until rFVIIIFc became commercially available in the applicable participating country.

Annualized Bleeding Rates

- Median annualized bleeding rates (ABRs) were low with rFVIIIFc prophylaxis (Table 2)
  - Estimated median (interquartile range [IQR]) bleeding events in the 12 months prior to A-LONG[1] were the following:
    - Subjects receiving prior prophylaxis = 6.0 (2–15)
    - Subjects receiving prior episodic treatment = 27.0 (18–40)

Table 2. Summary of ABRs during ASPIRE among subjects with an efficacy period[a]

Treatment group[b]	Individualized prophylaxis (n = 108)	Weekly prophylaxis (n = 28)	Modified prophylaxis (n = 19)	Episodic treatment (n = 13)
ABR, median (IQR)				
Overall	0.8 (0.0–2.7)[c]	2.1 (0.5–4.8)[c]	3.6 (1.2–8.1)[d]	19.1 (12.4–30.5)
Spontaneous	0.0 (0.0–0.8)	1.2 (0.0–2.4)	1.6 (0.0–4.7)	14.6 (10.9–16.4)
Traumatic	0.2 (0.0–1.3)	0.4 (0.0–1.3)	0.6 (0.0–3.0)	1.4 (0.0–5.0)
Joint	0.4 (0.0–1.7)	1.6 (0.4–3.3)	1.6 (0.0–6.9)	13.1 (5.0–27.0)

[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.
[b]Subjects could change treatment groups at any point in ASPIRE; thus, subjects could be represented in >1 treatment group.
[c]The median overall ABRs in the individualized and weekly prophylaxis groups were 1.6 and 3.6, respectively, at the end of A-LONG.[1]
[d]The median overall ABR increased in the modified prophylaxis group from the first to the second ASPIRE interim data cut (2.0 and 3.6, respectively); however, the mean overall ABR remained similar (5.1 vs 5.4, respectively). This discrepancy may be due to the small number of subjects in the modified prophylaxis group as of the first (n = 17) and second (n = 19) interim data cuts.

Changes to Prophylactic Dosing Regimens

- Among subjects treated prophylactically with FVIII prestudy (n = 79), the dosing interval with rFVIIIFc was lengthened in 76 (96.2%) subjects, shortened in 2 (2.5%) subjects, and unchanged in 1 (1.3%) subject, relative to their prestudy dosing interval, as of the second ASPIRE interim data cut (Figure 2)

Figure 2. Change in prophylactic dosing interval from pre–A-LONG to the second ASPIRE interim data cut

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

Pre–A-LONG dosing interval	Every 3 days n = 28 (18.7%)	Twice weekly n = 42 (28.0%)	Every 4 days n = 10 (6.7%)	Every 5 days n = 24 (16.0%)	Every 6 days n = 1 (0.7%)	Once weekly n = 36 (24.0%)
5 times weekly n = 1 (0.7%)	–	–	–	1	–	–
4 times weekly n = 5 (3.3%)	3	1	1	–	–	–
3 times weekly n = 62 (41.3%)	17	22	6	11	1	5
Twice weekly n = 10 (6.7%)	1	1	1	1	–	6
Once weekly[a] n = 1 (0.7%)	–	–	–	1	–	–

Change in dosing interval
- Lengthened (n = 76; 96.2%)
- No change (n = 1; 1.3%)
- Shortened (n = 2; 2.5%)

	Every 3 days	Twice weekly	Every 4 days	Every 5 days	Every 6 days	Once weekly	Other n = 3 (2.0%)	Episodic n = 6 (4.0%)
Episodic treatment n = 71 (47.3%)	7	18	2	10	–	25	3[b]	6

[a]Subjects in the weekly prophylaxis group of A-LONG were previously on FVIII episodic treatment and were randomized into this group versus the episodic treatment group.
[b]These 3 subjects were treated episodically during A-LONG and moved to the modified prophylaxis group during ASPIRE; they did not have a defined routine prophylaxis regimen during ASPIRE.

- Median (IQR) change in total weekly prophylactic factor consumption from prestudy to the second ASPIRE interim data cut was 0.0 (−17.0 to 26.7) IU/kg/week

CONCLUSIONS

- Updated interim data from ASPIRE show that adults/adolescents with severe hemophilia A achieved and preserved lengthened prophylactic dosing intervals while overall maintaining similar weekly factor consumption with rFVIIIFc compared with their prestudy FVIII regimens
- Median overall ABRs in the individualized and weekly prophylaxis groups were lower as of the second ASPIRE interim data cut (0.8 and 2.1, respectively) compared with those at the end of A-LONG (1.6 and 3.6, respectively).[1] These results suggest that the long-term efficacy of rFVIIIFc is consistent with that observed in A-LONG, and that individuals with severe hemophilia A may have the ability to reduce bleeding rates with rFVIIIFc treatment over an extended duration of use

References

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