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Dosing Regimens Before and Following Long-term Treatment With Recombinant Factor VIII Fc Fusion Protein (rFVIIIFc) in Children 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–Kids A-LONG to the second interim data cut of ASPIRE (December 8, 2014)

METHODS

Study Design

- Eligible subjects <12 years of age with severe hemophilia A (<1 IU/dL endogenous factor VIII [FVIII] activity) who completed Kids A-LONG (ClinicalTrials.gov Identifier: NCT01458106) could enroll in 1 of 2 treatment groups in ASPIRE (NCT01454739; Table 1)
  - Subjects could switch to any treatment group in ASPIRE once they reached 12 years of age

Table 1. ASPIRE treatment groups

Treatment group	Dosing guidance per protocol
Subjects of any age	
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) • Pediatric subjects could receive a maximum dose of 80 IU/kg every 2–5 days
Modified prophylaxis	• Investigators could personalize dosing for subjects in whom optimal prophylaxis could not be achieved with individualized or weekly dosing – For example, less frequent dosing or targeting a FVIII trough level >3 IU/dL
Subjects ≥12 years of age only	
Weekly prophylaxis	• rFVIIIFc 65 IU/kg every 7 days
Episodic treatment	• rFVIIIFc dosing based on type and severity of bleeding episode

Analyses

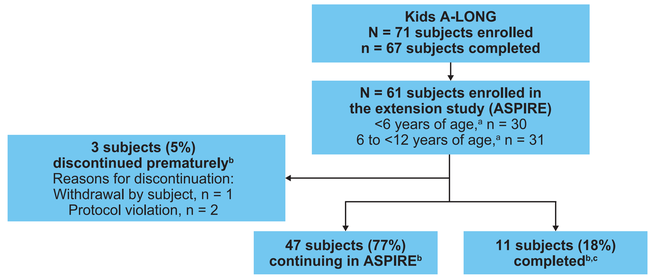
- In this post hoc analysis, subjects with available prestudy (pre–Kids A-LONG) FVIII and on-study rFVIIIFc dosing data at the second ASPIRE interim data cut (December 8, 2014) were evaluated for:
  - Change in dosing interval
  - Change in prescribed total weekly prophylactic consumption (IU/kg/week)

RESULTS

Study Population

- Subject disposition is summarized in Figure 1
- From the first dose of rFVIIIFc in Kids A-LONG to the second ASPIRE interim data cut:
  - Median (range) cumulative duration of treatment was 666.5 (172.6–768.6) days (~1.8 years)
  - Median cumulative rFVIIIFc exposure was 198 days

Figure 1. Subject disposition



[a]Subjects from Kids A-LONG remained in their parent study–assigned age cohort throughout the extension study; no subjects changed treatment groups during ASPIRE.
[b]As of the second ASPIRE interim data cut on December 8, 2014.
[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. Subjects who were first dosed with rFVIIIFc when they were <12 years of age were followed to ≥100 exposure days, even if rFVIIIFc became commercially available.

Annualized Bleeding Rates

- Median annualized bleeding rates (ABRs) were low with rFVIIIFc prophylaxis (Table 2)
  - Estimated median (range) total bleeding events in the 12 months prior to Kids A-LONG[2] were the following:
    - Subjects <6 years of age (n = 36): 2 (0–16)
    - Subjects 6 to <12 years of age (n = 35): 4 (0–36)
    - Overall (n = 71): 2 (0–36)

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

Treatment group	n	ABR, median (IQR) Overall	Spontaneous	Traumatic
Individualized prophylaxis				
<6 years cohort	29	1.46 (0.00–2.41)	0.95 (0.00–1.46)	0.00 (0.00–0.98)
6 to <12 years cohort	30	1.34 (0.66–3.57)	0.00 (0.00–0.72)	0.80 (0.00–2.68)

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.
[b]For the 2 pediatric subjects in the modified prophylaxis group, the overall, spontaneous, and traumatic ABRs were 4.09, 3.07, and 1.02, respectively (<6 years cohort; n = 1), and 1.01, 0.00, and 1.01, respectively (6 to <12 years cohort; n = 1).

Changes to Prophylactic Dosing Regimens

- Among subjects treated prophylactically with FVIII prestudy (n = 54), the dosing interval with rFVIIIFc was lengthened in 42 (77.8%) subjects, shortened in 2 (3.7%) subjects, and unchanged in 10 (18.5%) subjects, 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–Kids A-LONG to the second ASPIRE interim data cut

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

Pre–Kids A-LONG dosing interval	3 times weekly n = 1 (1.6%)	Every 3 days n = 5 (8.2%)	Twice weekly n = 53 (86.9%)	Every 4 days n = 1 (1.6%)	Every 5 days n = 1 (1.6%)
Every other day n = 14 (23.0%)	1	2	11	–	–
3 times weekly n = 27 (44.3%)	–	3	23	1	–
Twice weekly n = 11 (18.0%)	–	–	10	–	1
Once weekly n = 2 (3.3%)	–	–	2	–	–
Episodic treatment n = 7 (11.5%)	–	–	7	–	–

Change in dosing interval
- Lengthened (n = 42; 77.8%)
- No change (n = 10; 18.5%)
- Shortened (n = 2; 3.7%)

- Median (IQR) change in total weekly prophylactic factor consumption from prestudy to the second ASPIRE interim data cut was 0.5 (−16.0 to 25.0) IU/kg/week

CONCLUSIONS

- Based on these updated interim data from ASPIRE, children with severe hemophilia A lengthened their prophylactic dosing interval (77.8% lengthened, 18.5% no change) and maintained similar weekly factor consumption (median change in consumption, 0.5 IU/kg/week) with low bleeding rates (overall ABR, 1.3–1.5) on rFVIIIFc compared with their prestudy FVIII regimens
- As of the second ASPIRE interim data cut, median overall ABRs among subjects aged <6 years and 6 to <12 years (1.5 and 1.3, respectively) were comparable to those at the end of Kids A-LONG (0.0 and 2.0, respectively).[2] These results suggest that long-term efficacy with rFVIIIFc was consistent with that observed in Kids A-LONG

References

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