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Long-term safety and efficacy of recombinant factor VIII Fc fusion protein (rFVIIIFc) in subjects with haemophilia A

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Introduction: The safety, efficacy and prolonged half-life of recombinant factor VIII Fc fusion protein (rFVIIIFc) in previously treated patients with severe haemophilia A was demonstrated in the phase 3 A-LONG and Kids A-LONG studies. Here, we report interim safety and efficacy data from the rFVIIIFc extension study, ASPIRE (ClinicalTrials.gov #NCT01454739). **Methods:** Eligible subjects could enrol in ASPIRE upon completing A-LONG or Kids A-LONG. There were four treatment groups: individualized prophylaxis; weekly prophylaxis; modified prophylaxis (for subjects in whom optimal treatment could not be achieved with individualized or weekly prophylaxis); and episodic treatment. The primary endpoint was development of inhibitors. **Results:** A total of 150 A-LONG subjects and 61 Kids A-LONG subjects enrolled in ASPIRE. As of the interim data cut (6 January 2014), the median time on study was 80.9 (A-LONG) and 23.9 (Kids A-LONG) weeks. The majority of subjects (A-LONG, 92.0%; Kids A-LONG, 57.4%) had ≥100 cumulative rFVIIIFc exposure days. No inhibitors were observed. Adverse events were generally consistent with those expected in the general haemophilia A population. Median annualized bleeding rates (ABRs) were low with individualized [A-LONG: 0.66; Kids A-LONG: 0.00 (<6 years old), 1.54 (6 to <12 years old)], weekly (A-LONG: 2.03) and modified (A-LONG: 1.97) prophylaxis. There was no change in prophylactic infusion frequency or total weekly prophylactic dose in the majority of subjects from A-LONG and Kids A-LONG. **Conclusion:** Interim data from ASPIRE confirm the long-term safety of rFVIIIFc and the maintenance of a low ABR with extended-interval prophylactic dosing in patients with severe haemophilia A.

Keywords: factor VIII, haemophilia A, phase 3, prophylaxis, recombinant fusion proteins

Introduction

Patients with haemophilia A are at risk for serious complications, including life-threatening spontaneous and traumatic bleeding and recurrent haemarthroses [1]. Prophylactic treatment with coagulation factor VIII (FVIII) is the standard of care to prevent bleeding in patients with haemophilia A. Optimal prophylaxis with conventional FVIII products, which have half-lives of approximately 12 h, often requires three to four intravenous infusions weekly [2,3]; more frequent administration may be necessary in children, who generally have a shorter FVIII half-life compared with adults [4]. Such frequent infusions can deter adherence to prophylaxis [5–7].

Recombinant FVIII Fc fusion protein (rFVIIIFc) was developed to prolong the half-life of FVIII [8–11]. The Fc portion of rFVIIIFc binds to the neonatal Fc receptor and utilizes the IgG recycling pathway to extend the plasma half-life of the molecule [12]. The safety, efficacy and prolonged half-life of rFVIIIFc were demonstrated in previously treated adults, adolescents and

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children with severe haemophilia A in the phase 3 A-LONG and Kids A-LONG studies [13,14]. Here, we report interim data from subjects enrolled in the rFVIIIFc extension study, ASPIRE (ClinicalTrials.gov identifier, NCT01454739), the aim of which was to evaluate the long-term safety of rFVIIIFc and its efficacy in the prevention and treatment of bleeding episodes in subjects with haemophilia A.

Materials and methods

Study design

Subjects completing the A-LONG [13] or Kids A-LONG [14] studies were eligible for enrolment in ASPIRE. The data cut-off date for this interim analysis was 6 January 2014; the estimated study completion date is December 2018. This open-label, non-randomized study had an episodic (on-demand) treatment group and three prophylactic treatment groups: individualized, weekly and modified prophylaxis. In the episodic group, dosing was based on the type and severity of bleeding episodes. Subjects in the individualized prophylaxis group were treated with 25–65 IU kg^{-1} rFVIIIFc every 3–5 days, or twice-weekly rFVIIIFc (20–65 IU kg^{-1} on Day 1, 40–65 IU kg^{-1} on Day 4). In subjects <12 years of age, the investigator could make dose adjustments up to a maximum of 80 IU kg^{-1}, with an administration frequency of up to every 2 days, if necessary, to maintain adequate FVIII activity trough levels and prevent spontaneous bleeding episodes. The weekly prophylaxis group received 65 IU kg^{-1} rFVIIIFc every 7 days. Subjects in whom optimal treatment could not be achieved using either the individualized or weekly prophylaxis dosing guidelines could participate in the modified prophylaxis group (Data S1).

Subjects were permitted to change their treatment group at the time of enrolment or at any time during the extension study. Subjects <12 years of age were allowed to participate only in the individualized and modified prophylaxis groups; however, a Kids A-LONG subject who reached 12 years of age during the study could choose to participate in any of the four treatment groups.

Outcome measures

The primary endpoint was development of inhibitors (anti-FVIII neutralizing antibodies). Subjects were tested for inhibitor formation at each clinic visit (approximately every 6 months). A positive inhibitor test result was defined as a neutralizing antibody value ≥0.6 BU mL^{-1} (by Nijmegen-modified Bethesda assay) and confirmed on retesting within 2–4 weeks. Secondary endpoints included the annualized number of bleeding episodes per subject, rFVIIIFc exposure days (EDs), and subject's assessment of response to treatment of a bleeding episode (Data S1). Additional outcomes included the incidence of adverse events (AEs), the number of infusions and dose per infusion required to control a bleeding episode and the assessment of haemostatic response in subjects undergoing major surgery.

Analytical methods

Exposure and efficacy analyses were performed separately for subjects from A-LONG and Kids A-LONG. Results were analysed by treatment group for all subjects; Kids A-LONG subjects were also analysed by age cohort (<6 years of age; 6 to <12 years of age) at the time of entry into the parent study. Subjects who changed treatment groups were included in the summary analyses of any group in which they participated for the period of time that they were in the given group.

Safety analyses were performed on data from subjects who received at least one dose of rFVIIIFc. Efficacy analyses were performed on data from subjects who participated in the episodic group at any time, or who had ≥2 prophylactic infusions of rFVIIIFc (exclusive of perioperative management periods).
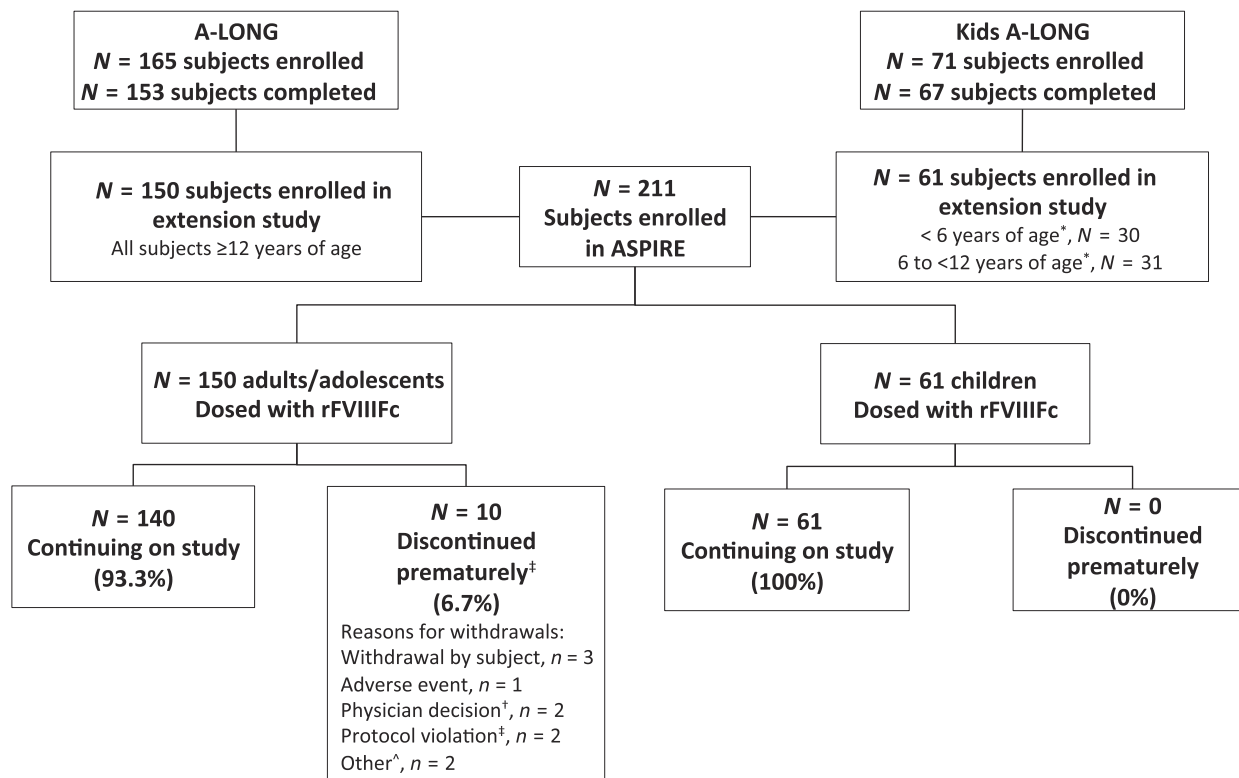
Results

Study population

The study enrolled 211 male subjects: 150/153 subjects (98.0%) who completed A-LONG and 61/67 subjects (91.0%) who completed Kids A-LONG (<6 years of age, *n* = 30; 6 to <12 years of age, *n* = 31; Fig. 1, Table S1). As of the interim data cut, 10 subjects from A-LONG and no subjects from Kids A-LONG had discontinued the extension study (Fig. 1).

At the time of the interim data cut, the median time on ASPIRE among subjects from A-LONG was 80.9 weeks; 121 subjects (80.7%) had completed an 18-month study visit. From the start of A-LONG to the ASPIRE interim data cut, subjects had a median of 111.7 cumulative weeks of rFVIIIFc treatment [137 subjects (91.3%) had received rFVIIIFc for ≥2 years], and a median 193.5 cumulative rFVIIIFc EDs [138 subjects (92.0%) had ≥100 EDs] (Figure S1).

Among Kids A-LONG subjects, the median time on ASPIRE was 23.9 weeks (<6 years cohort, 10.6 weeks; 6 to <12 years cohort, 28.7 weeks). At the time of the interim data cut, 22 subjects (36.1%) had completed the 6-month study visit. From the start of Kids A-LONG to the ASPIRE interim data cut, subjects had a median of 51.1 cumulative weeks of rFVIIIFc treatment [23 subjects (37.7%) had received rFVIIIFc for ≥1 year], and a median 103.0 cumulative rFVIIIFc EDs [35 subjects (57.4%) had ≥100 EDs] (Figure S1).

Fig. 1. Subject disposition. Subjects who completed the phase 3 A-LONG and Kids A-LONG studies were eligible for enrolment in the ASPIRE extension study. Of the subjects completing the phase 3 studies, 150/153 A-LONG subjects (98.0%) and 61/67 (91.0%) Kids A-LONG subjects respectively enrolled in ASPIRE. Ten subjects from A-LONG discontinued the extension study early; no subjects from Kids A-LONG discontinued the study as of the interim data cut.

Safety summary

No subjects developed an inhibitor to FVIII during the ASPIRE study as of the interim data cut. AEs were generally consistent with those expected in the general haemophilia population (Table 1). The majority of AEs were judged by the investigator to be unrelated to rFVIIIFc treatment.

Three adult subjects (1.4%) experienced a total of four non-serious, mild AEs that were assessed by the investigator as related to rFVIIIFc treatment. One subject retrospectively reported chromaturia (intermittent dark urine) with the first morning void 24 h after a dose of rFVIIIFc, occurring three times over ~1.5 years, and also noted after taking other medications. One subject reported headache and hot flush [hot flashes] occurring on a single day only. The events of chromaturia, headache and hot flush each resolved spontaneously without treatment, and did not recur despite continued rFVIIIFc treatment in the study. One additional subject receiving episodic treatment was reported to have elevated blood creatinine (128 μmol L^{-1} at final study visit; reference range: 67–112 μmol L^{-1}) observed 12 days after receiving his most recent dose of rFVIIIFc. The event of increased blood creatinine was reported to result in discontinuation of rFVIIIFc treatment and withdrawal from the study. The subject had multiple factors that may have contributed to the event, including medical history of kidney stones, hypertension, and HIV, and concomitant medications known to be associated with renal impairment (hydrochlorothiazide, Lisinopril, and tenofovir disoproxil fumarate).

A total of 29 serious AEs (SAEs) were reported on study, excluding perioperative management periods (Table S2), with 23 subjects (10.9%) experiencing at least one SAE (four subjects experienced two SAEs each, and one subject experienced three SAEs). All of the SAEs were assessed by the investigator as unrelated to rFVIIIFc treatment, all had resolved by the time of the interim data cut, and none led to study discontinuation. There were no reports of serious

Table 1. AE summary (≥3% in either study population).

	Parent study		
	A-LONG N = 150	Kids A-LONG N = 61	Overall N = 211
Subjects with at least one AE, n (%)*,†	111 (74.0)	27 (44.3)	138 (65.4)
Nasopharyngitis	24 (16.0)	3 (4.9)	27 (12.8)
Upper respiratory tract infection	13 (8.7)	3 (4.9)	16 (7.6)
Arthralgia	11 (7.3)	0	11 (5.2)
Fall	7 (4.7)	3 (4.9)	10 (4.7)
Laceration	8 (5.3)	0	8 (3.8)
Diarrhoea	7 (4.7)	1 (1.6)	8 (3.8)
Headache	7 (4.7)	0	7 (3.3)
Cough	6 (4.0)	1 (1.6)	7 (3.3)
Influenza	6 (4.0)	1 (1.6)	7 (3.3)
Contusion	5 (3.3)	0	5 (2.4)
Dental caries	5 (3.3)	0	5 (2.4)
Haemophilic arthropathy	5 (3.3)	0	5 (2.4)
Viral infection	2 (1.3)	3 (4.9)	5 (2.4)
Vomiting	2 (1.3)	3 (4.9)	5 (2.4)
Head injury	2 (1.3)	2 (3.3)	4 (1.9)
Central venous catheter removal	0	2 (3.3)	2 (0.9)
Viral upper respiratory tract	0	2 (3.3)	2 (0.9)
Tooth socket haemorrhage	0	2 (3.3)	2 (0.9)
Number of subjects who experienced at least one SAE, n (%)	17 (11.3)	6 (9.8)	23 (10.9)
Total number of SAE, n	22	7	29

AE, adverse event; SAE, serious AE; rFVIIIFc, recombinant factor VIII Fc fusion protein.

*Excludes AEs occurring during the perioperative management period; percentages are based on the number of subjects treated with rFVIIIFc. All but four AEs occurring in three adult subjects were judged by the investigator to be unrelated to rFVIIIFc treatment. Among 15 subjects in the surgical subgroup, 7 subjects (46.7%) experienced at least one AE during the perioperative management period with a total of 14 AEs reported (13 non-serious AEs; 1 SAE); all 14 AEs were assessed by investigators as unrelated to rFVIIIFc.

†Ten subjects experienced at least one AE (14 total AEs) that had an event onset prior to Day 1 of the extension study; these AEs were reported in the clinical database for ASPIRE instead of the clinical databases for A-LONG or Kids A-LONG; this had no impact on the overall safety profile of rFVIIIFc.

allergic reactions or anaphylaxis to rFVIIIFc, no serious vascular thrombotic events, and no deaths.

Changes to prophylactic dosing regimen

The protocol permitted subjects to change treatment groups at any time during the extension study. Of the 150 A-LONG subjects enrolled in ASPIRE, 25 (16.7%) changed treatment groups at the time of enrolment and 17 (11.3%) made one change to their treatment group during ASPIRE; no subjects changed treatment groups more than once (Fig. 2). Nearly all Kids A-LONG subjects (59/61 subjects; 96.7%) continued on individualized prophylaxis; two subjects switched to the modified prophylaxis group upon enrolment into ASPIRE. No Kids A-LONG subjects changed their treatment group during ASPIRE. A summary of subjects in the modified prophylaxis group is provided in Data S1.
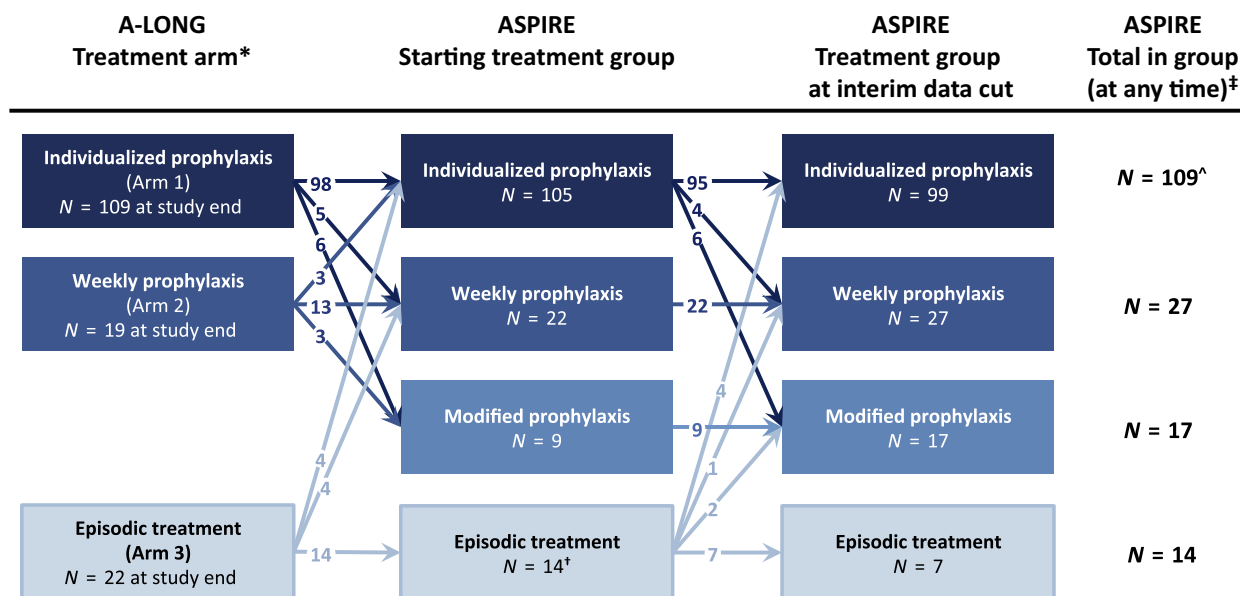
The majority of subjects previously on a prophylactic regimen in A-LONG had either no change to their infusion interval (92/128 subjects; 71.9%) or had a longer infusion interval (28/128 subjects; 21.9%) during ASPIRE (Fig. 3). Of the 19 subjects randomized to the once-weekly treatment arm of A-LONG (who had been previously treated episodically with FVIII), only three subjects changed to a shorter prophylactic infusion interval (twice-weekly) during ASPIRE. The proportion of A-LONG subjects with a prophylactic infusion interval of 5 days or longer remained consistent in the extension study (at the end of A-LONG, 43.8%; during ASPIRE, 43.3%). No A-LONG subjects switched from prophylactic to episodic treatment in ASPIRE. However, 15/22 subjects (68.2%) from the episodic arm of A-LONG switched to a prophylaxis group in ASPIRE (individualized, n = 8; weekly, n = 5; modified, n = 2). The majority of Kids A-LONG subjects (58/61 subjects; 95.1%) had no change to their prophylactic infusion interval on ASPIRE (Figure S2). Among subjects infusing twice-weekly in Kids A-LONG, 53/56 subjects (94.6%) remained on a twice-weekly dosing schedule in ASPIRE; two subjects lengthened their prophylactic infusion interval to either every 4 or every 5 days.

rFVIIIFc total weekly prophylactic dose

The total weekly prophylactic dose remained generally consistent among A-LONG and Kids A-LONG subjects during the extension study. For A-LONG subjects, the median [interquartile range (IQR)] average total weekly prophylactic dose in the individualized, weekly and modified prophylaxis groups was 79.6 (74.5, 97.1) IU kg^{-1}, 65.4 (62.8, 67.4) IU kg^{-1} and 69.5 (64.3, 89.3) IU kg^{-1} respectively. Median annualized rFVIIIFc consumption was 4181.3, 3500.6 and 3724.6 IU kg^{-1}, for the respective prophylactic groups. Among A-LONG subjects previously treated prophylactically (n = 128), 64.1% had no change to, 20.3% reduced, and 15.6% increased their total weekly prophylactic dose (Fig. 4a). The median (IQR) average weekly prophylactic dose in Kids A-LONG subjects receiving individualized prophylaxis was 99.9 (88.6, 114.2) IU kg^{-1} for subjects <6 years of age (median annualized consumption = 5133.1 IU kg^{-1}), and 91.2 (81.0, 107.9) IU kg^{-1} for subjects 6 to <12 years of age (median annualized consumption = 4819.8 IU kg^{-1}). Compared with their previous total weekly prophylactic dose, 78.7% had no change to, 11.5% reduced, and 9.8% increased their total weekly prophylactic dose (Fig. 4b).

Annualized bleeding rate

In the individualized, weekly and modified prophylaxis groups in ASPIRE, 38.9%, 22.2% and 23.5% of

*Subjects enrolled in ASPIRE included 109 of the 112 subjects who completed A-LONG in the individualized prophylaxis arm, and 19/19 and 22/22 subjects completing A-LONG in the weekly prophylaxis and episodic treatment arms, respectively.

†Five subjects who continued episodic treatment from the end of A-LONG to the beginning of ASPIRE moved into a different treatment group within the first week of the study (individualized prophylaxis, *n* = 3; modified prophylaxis, *n* = 2). The 2 subjects who moved from the episodic group into the modified prophylaxis group did not have a defined routine prophylaxis regimen in the modified prophylaxis group.

‡Protocol permitted subjects to change treatment groups over the course of this extension study; therefore, subjects may be represented in more than 1 group. "Total" indicates the number of subjects in the given group at any time from the beginning of ASPIRE to the interim data cut.

^One subject from A-LONG was not assessed for efficacy because he had surgery prior to the extension study and was in his surgical period from the time of enrolment until after the interim data cut.

Fig. 2. Change in treatment group among adults and adolescents (end of A-LONG to ASPIRE interim data cut). Subjects' treatment groups at the end of A-LONG (leftmost boxes), at the start of ASPIRE (middle boxes), and at the interim data cut for ASPIRE (rightmost boxes) are shown. Subjects in the individualized prophylaxis group were treated with 25–65 IU kg^{-1} recombinant factor VIII Fc fusion protein (rFVIIIFc) every 3–5 days, or twice-weekly rFVIIIFc (20–65 IU kg^{-1} on Day 1, 40–65 IU kg^{-1} on Day 4). Subjects in the weekly prophylaxis group received 65 IU kg^{-1} at weekly intervals. In the modified prophylaxis group, dosing could be adjusted to meet the needs of individual subjects; this included, but was not limited to, less frequent dosing, addition of 'prevention' doses prior to strenuous activity, or targeting a FVIII trough level of >3% (if the bleeding history and/or activity level required). Of the 150 A-LONG subjects enrolled in ASPIRE, 42 (28.0%) changed treatment groups upon enrolment into or during ASPIRE, including 15/22 subjects treated episodically in A-LONG who changed to a prophylactic regimen in ASPIRE; no subjects changed treatment groups more than once. Subjects who changed groups during the study were included in the safety and efficacy analyses for any treatment group in which they participated, for the period of time they participated in that group, as indicated at the right of the figure.

A-LONG subjects, respectively, experienced zero bleeding episodes on study. Median (IQR) bleeding rates in ASPIRE were low in subjects in the rFVIIIFc prophylaxis groups compared with subjects in the episodic group (Table 2). Annualized bleeding rates (ABRs) in subjects with an efficacy period of ≥6 months in a given treatment group were consistent with ABRs in the overall population. In all A-LONG subjects treated with rFVIIIFc prophylaxis during ASPIRE, the median ABR for spontaneous joint bleeding episodes was 0.0, compared with 11.2 for subjects treated episodically. In subjects with ≥1 target joint present at baseline, the median (IQR) ABR was 0.7 (0.0, 3.0) in the individualized prophylaxis group (*n* = 72), 2.5 (0.6, 4.5) in the weekly prophylaxis group (*n* = 16), 4.4 (1.3, 9.6) in the modified prophylaxis group (*n* = 12) and 15.2 (5.2, 33.2) in the episodic treatment group (*n* = 12).

Among Kids A-LONG subjects in the individualized and modified prophylaxis groups during ASPIRE, 59.3% and 50.0% of subjects respectively experienced zero bleeding episodes on study. The median (IQR) ABR in Kids A-LONG subjects is presented in Table 3. The median ABR for spontaneous joint bleeding episodes was 0.0 in both age cohorts. Among Kids A-LONG subjects in the individualized prophylaxis group who had ≥1 target joint present at baseline, the median (IQR) ABR was 4.4 (0.0, 8.8) for those <6 years of age (*n* = 2) and 1.8 (0.0, 3.4) for those 6 to <12 years of age (*n* = 5).

Treatment of a bleeding episode

A total of 566 bleeding episodes occurred among A-LONG subjects who were treated prophylactically on ASPIRE; subjects treated episodically experienced a total of 262 bleeding episodes (Table 4, Table S3). Overall, 90.8% of bleeding episodes were controlled with one infusion; 96.9% with one or two infusions. Among first infusions evaluated by subjects for a response, 83.8% overall were rated as excellent or good (individualized prophylaxis, 77.6%; weekly prophylaxis, 80.9%; modi-

ASPIRE infusion frequency (interim data cut)

A-LONG infusion frequency (end of study)	Every 3 days N = 28 (18.7%)	Twice weekly N = 43 (28.7%)	Every 4 days N = 9 (6.0%)	Every 5 days N = 26 (17.3%)	Every 6 days N = 2 (1.3%)	Once Weekly N = 33 (22%)
Every 3 days N = 35 (23.3%)	26	6	3	0	0	0
Twice weekly N = 33 (22.0%)	0	26	2	3	0	2
Every 4 days N = 4 (2.7%)	1	1	2	0	0	0
Every 5 days N = 37 (24.7%)	0	1	2	22	2	10
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Once weekly* N = 19 (12.7%)	0	3	0	0	0	16

Change in infusion interval
Lengthened (n = 28, 21.9%)
No change (n = 92, 71.9%)
Shortened (n = 8, 6.3%)

	Every 3 days	Twice weekly	Every 4 days	Every 5 days	Every 6 days	Once Weekly	Other N = 2 (1.3%)	Episodic N = 7 (4.7%)
Episodic treatment N = 22 (14.7%)	1	6	0	1	0	5	2†	7

*Subjects in the weekly prophylaxis group of A-LONG were previously on FVIII episodic treatment and were randomised into this group vs. the episodic treatment group.
†These 2 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.

Fig. 3. Change in infusion frequency among adult and adolescent subjects (end of A-LONG to ASPIRE interim data cut). Changes in prophylactic infusion frequency from the end of A-LONG to the time of the ASPIRE interim data cut are shown for individual A-LONG subjects (n = 128). The majority of these subjects had either no change to (white boxes) or lengthened (dark grey boxes) their infusion interval during ASPIRE. The infusion frequency at the time of the ASPIRE interim data cut is also shown for subjects previously in the episodic arm of A-LONG (n = 22).
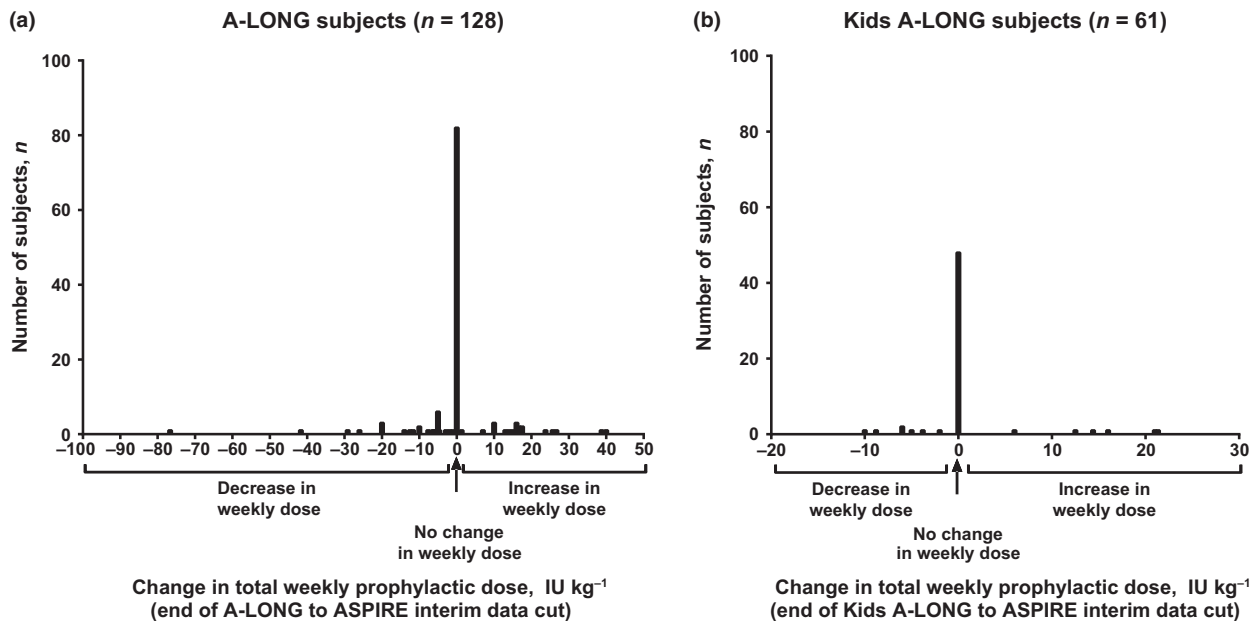

(a) A-LONG subjects (n = 128)
Number of subjects, n
Decrease in weekly dose — No change in weekly dose — Increase in weekly dose
Change in total weekly prophylactic dose, IU kg⁻¹ (end of A-LONG to ASPIRE interim data cut)

(b) Kids A-LONG subjects (n = 61)
Number of subjects, n
Decrease in weekly dose — No change in weekly dose — Increase in weekly dose
Change in total weekly prophylactic dose, IU kg⁻¹ (end of Kids A-LONG to ASPIRE interim data cut)

Fig. 4. Change in total weekly prophylactic dose during ASPIRE among subjects treated prophylactically in A-LONG and Kids A-LONG. Overall, the majority of A-LONG (64.1%) and Kids A-LONG (78.7%) subjects had no change in their total weekly prophylactic dose during the extension study relative to their total weekly prophylactic dose at the end of the parent study. The median change in weekly prophylactic dose was 0.0 IU kg⁻¹ week⁻¹. Among A-LONG subjects, 20.3% reduced and 15.6% increased their total weekly prophylactic dose on ASPIRE. Among Kids A-LONG subjects, 11.5% reduced and 9.8% increased their total weekly prophylactic dose on ASPIRE.

Table 2. Summary of annualized bleeding rate [median (IQR)] during ASPIRE among A-LONG subjects with an efficacy period.*

Treatment group	
Individualized prophylaxis, n	108
Overall ABR	0.66 (0.00, 2.63)
Spontaneous ABR	0.00 (0.00, 1.23)
Spontaneous joint ABR	0.00 (0.00, 0.64)
Traumatic ABR	0.00 (0.00, 1.28)
Subjects in group ≥6 months, *n*	98
ABR	0.67 (0.00, 2.59)
Weekly prophylaxis, n	27
Overall ABR	2.03 (0.60, 4.39)
Spontaneous ABR	0.76 (0.00, 2.66)
Spontaneous joint ABR	0.00 (0.00, 2.66)
Traumatic ABR	0.66 (0.00, 1.94)
Subjects in group ≥6 months, *n*	27
ABR	2.03 (0.60, 4.39)
Modified prophylaxis, n[†]	17
Overall ABR	1.97 (0.96, 7.03)
Spontaneous ABR	0.96 (0.00, 5.51)
Spontaneous joint ABR	0.00 (0.00, 3.84)
Traumatic ABR	0.65 (0.00, 2.51)
Subjects in group ≥6 months, *n*	17
ABR	1.97 (0.96, 7.03)
Episodic, n	14
Overall ABR	18.36 (10.45, 30.46)
Spontaneous ABR	13.27 (1.39, 16.60)
Spontaneous joint ABR	11.15 (1.39, 15.11)
Traumatic ABR	2.36 (0.00, 9.05)
Subjects in group ≥6 months, *n*	8
ABR	18.36 (13.41, 26.29)

ABR, annualized bleeding rate; IQR, interquartile range; rFVIIIFc, recombinant factor VIII Fc fusion protein.
*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 perioperative management periods. One subject from A-LONG was not assessed for efficacy because he had surgery prior to the study and was in his surgical period from the time of enrolment until after the interim data cut-off date.
[†]Two subjects in the modified prophylaxis group were treated episodically during A-LONG, and did not have a defined routine prophylaxis regimen during ASPIRE.

fied prophylaxis, 87.6%; episodic treatment, 90.8%). Among Kids A-LONG subjects, there were a total of 23 bleeding episodes in the <6 years of age cohort and 28 bleeding episodes in the 6 to <12 years of age cohort. Of these bleeding episodes, 82.6% (<6 years cohort) and 82.1% (6 to <12 years cohort) were controlled with one infusion; 95.7% and 89.3%, respectively, with one or two infusions. Among first infusions evaluated by subjects for a response, 91.3% (<6 years cohort) and 92.6% (6 to <12 years cohort) were rated as excellent or good.

Perioperative management

During ASPIRE, a total of 15 major surgeries were performed in 13 subjects from A-LONG (Data S1); no major surgeries were performed on study in subjects from Kids A-LONG. No unique safety concerns emerged during the perioperative period. Thirteen major surgeries in 11 A-LONG subjects were assessed for response; haemostasis was rated by the investigator/surgeon as excellent or good for all 13 major

Table 3. Summary of annualized bleeding rate [median (IQR)] during ASPIRE among Kids A-LONG subjects with an efficacy period.*

Treatment group	<6 years cohort	6 to <12 years cohort
Individualized prophylaxis, n	29	30
Overall ABR	0.00 (0.00, 2.00)	1.54 (0.00, 3.41)
Spontaneous ABR	0.00 (0.00, 0.00)	0.00 (0.00, 1.75)
Spontaneous joint ABR	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)
Traumatic ABR	0.00 (0.00, 0.00)	0.00 (0.00, 1.82)
Subjects in group ≥6 months, *n*	4	17
ABR	2.37 (0.00, 9.21)	1.51 (0.00, 1.82)
Modified prophylaxis, n	1	1
Overall ABR	6.55[†]	0.00
Spontaneous ABR	6.55	0.00
Spontaneous joint ABR	6.55	0.00
Traumatic ABR	0.00	0.00
Subjects in group ≥6 months, *n*	0	0

ABR, annualized bleeding rates; IQR, interquartile range; rFVIIIFc, recombinant factor VIII Fc fusion protein.
*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 perioperative management periods.
[†]Subject was on-study for 0.31 years, and experienced two spontaneous joint bleeding episodes during that time.

Table 4. Dose of rFVIIIFc required to control a bleeding episode during ASPIRE.

	Number of subjects who experienced a bleeding episode, n	Number of bleeding episodes, n*	Average dose per infusion, IU kg^{-1}, median (IQR)
A-LONG (N = 150)			
Individualized prophylaxis	66	301	46.88 (26.94, 51.49)
Weekly prophylaxis	21	143	33.19 (26.67, 50.85)
Modified prophylaxis	13	122	34.19 (29.47, 38.96)
Episodic	11	262	26.88 (25.00, 31.25)
Kids A-LONG (N = 61)			
Individualized prophylaxis			
<6 years	8	21	43.86 (28.57, 72.82)
6 to <12 years	16	28	49.27 (37.49, 58.24)
Modified prophylaxis			
<6 years	1	2	57.47 (NA)
6 to <12 years	0	0	NA

rFVIIIFc, recombinant factor VIII Fc fusion protein; IQR, interquartile range; NA, not applicable.
*This includes all bleeding episodes reported during the study. Average dose per infusion could not be evaluated for three A-LONG subjects (individualized prophylaxis, *n* = 2; modified prophylaxis, *n* = 1) for whom information on the dose(s) administered to treat a bleeding episode was incomplete.

surgeries, with intraoperative and postoperative blood loss comparable to what would be expected for a subject who did not have haemophilia.

Discussion and conclusions

These interim data from ASPIRE confirm the long-term safety and efficacy of rFVIIIFc for the prevention

and treatment of bleeding in previously treated adults, adolescents and children with severe haemophilia A. This study represents the most extensive exposure to a long-acting factor to date – the majority of subjects had ≥100 EDs from the start of the parent study to the ASPIRE interim data cut. As of the interim data cut, no subjects developed an inhibitor during this study, and the AEs observed were generally consistent with those expected in the general haemophilia population.

Although subjects were allowed to change treatment groups during ASPIRE, only 28.0% and 3.3% of the A-LONG and Kids A-LONG subjects, respectively, switched groups upon enrolment or during the extension study; no one switched groups more than once. In ASPIRE, the majority of subjects on rFVIIIFc prophylaxis in the parent studies were able to maintain or lengthen their infusion interval. For example, among subjects who were infusing twice weekly at the end of A-LONG, 79% stayed on a twice-weekly regimen in ASPIRE, while the remaining 21% extended their dosing interval. Among subjects on weekly prophylaxis in A-LONG (all of whom were treated episodically prior to A-LONG), 84% chose to remain on this regimen in ASPIRE, suggesting weekly rFVIIIFc dosing is a viable therapeutic option for a number of subjects. While the median ABR in the weekly prophylaxis group was higher than that of the individualized prophylaxis group in ASPIRE (2.03 vs. 0.66), it was lower than that observed in the weekly prophylaxis arm during A-LONG (3.59) [13]. Many subjects previously treated episodically with rFVIIIFc switched to a prophylactic regimen in the extension study, suggesting that the prophylactic dosing options in ASPIRE were suitable for patients who may have previously been unwilling or unable to commit to a prophylactic regimen.

In the A-LONG and Kids A-LONG studies, the median total weekly rFVIIIFc prophylactic dose was comparable to the median prestudy total weekly FVIII prophylactic dose, but with a reduced number of infusions required per week [14,15]. In ASPIRE, subjects' total weekly rFVIIIFc prophylactic dose generally did not change or decreased relative to that at the end of the parent study, and the majority of subjects maintained or further increased their dosing interval compared with the parent study. These data suggest that rFVIIIFc prophylaxis has the potential to offer greater treatment flexibility than a conventional FVIII product; rFVIIIFc might be administered more frequently to maintain higher FVIII trough levels, if desired, or with an extended dosing interval to reduce infusion burden.

The efficacy of rFVIIIFc for the prevention and control of bleeding was maintained during the extension study, with subjects in the prophylaxis groups exhibiting low ABRs and the majority of subjects in all treatment groups reporting high satisfaction with resolution of bleeding episodes, consistent with what was observed in A-LONG [13] and Kids A-LONG [14]. In some cases, the bleeding rates observed in ASPIRE, particularly for spontaneous joint bleeds, were lower than those observed in the parent studies, even when infusion intervals were lengthened. Additionally, in subjects entering the parent studies with target joints, bleeding rates were low with rFVIIIFc prophylaxis. These data suggest that rFVIIIFc prophylaxis is highly efficacious for the long-term treatment of haemophilia A, including in patients with target joints.

The ASPIRE protocol allowed for a high degree of dosing flexibility across all treatment groups, and the individualization of dosing regimens was designed to create a setting that was generally reflective of real-world practices. However, the allowance for subjects to change treatment groups during the study made direct comparisons between treatment groups difficult. Other study limitations include the small number of subjects in the weekly prophylaxis group, and in particular the lack of paediatric subjects in this group (as dictated by the protocol). As there were no major surgeries in Kids A-LONG subjects during ASPIRE, data on the use of rFVIIIFc in a surgical setting in subjects aged <12 years are lacking. Analyses were limited to the data available as of the interim data cut, and many of the paediatric subjects had participated in ASPIRE for <6 months. Although subjects >12 years of age had significant exposure to rFVIIIFc in the parent studies, longer term follow-up is needed in patients ≤12 years of age. Additionally, exclusion of subjects with history of an inhibitor makes it difficult to determine if the lack of inhibitors observed in ASPIRE would be applicable in a patient population at high risk for inhibitor development; further study is needed to characterize the immunogenicity of rFVIIIFc in such patients.

In summary, the ASPIRE extension study represents the first longer term clinical experience to date with a prolonged half-life rFVIII therapy. Interim data from the study provide further confirmation of the safety and efficacy of rFVIIIFc prophylaxis in paediatric, adolescent, and adult patients with severe haemophilia A, and demonstrate maintenance of a low ABR with extended prophylactic dosing intervals.

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Author contributions

GA and GFP contributed to the design and conceptualization of the research, design of data analyses, interpretation of data and drafting and revising the manuscript. BN, JM, DP, GY, RL, BK, SR, SB, HH, KJP, IP-F and SJ contributed to the data collection, interpretation of data and drafting and revising of the manuscript. LMC contributed to the design of data analyses, data collection, interpretation of data and drafting and revising of the manuscript. XL contributed to the design of data analyses, performed the statistical analyses and contributed to the interpretation of data and revising of the manuscript. The authors had full editorial control of the paper, and provided their final approval of all content.

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Supporting Information

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

Figure S1. Cumulative rFVIIIFc EDs among A-LONG (*n* = 150) and Kids A-LONG (*n* = 61) subjects continuing into ASPIRE.

Figure S2. Change in infusion frequency among paediatric subjects (end of Kids A-LONG to ASPIRE interim data cut).

Table S1. Subject demographics and clinical characteristics.

Table S2. Serious adverse events (SAE) occurring in ASPIRE subjects, by system organ class.

Table S3. Dose of rFVIIIFc required to control a bleeding episode, by type of bleeding episode.

Data S1. Prophylactic treatment; treatment of bleeding episodes; perioperative management and major surgeries.