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Long-lasting recombinant factor VIII Fc fusion (rFVIIIFc) for perioperative management of subjects with haemophilia A in the phase 3 A-LONG study

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Background: To improve the pharmacokinetics (PK) of factor VIII (FVIII), Fc technology was used to develop a monomeric recombinant FVIII Fc fusion protein (rFVIIIFc), with an extended half-life compared with currently available recombinant factor VIII (rFVIII) products. rFVIIIFc comprises a rFVIII molecule genetically linked to the Fc domain of immunoglobulin G_1, with no intervening sequence. The recently completed A-LONG phase 3 study evaluated safety, efficacy, and PK of rFVIIIFc for prophylaxis, treatment of acute bleeds, and perioperative control of bleeding in previously treated subjects with severe haemophilia A and demonstrated a 1.5-fold increase in half-life for rFVIIIFc vs. rFVIII (Advate®).

Aims: To evaluate the efficacy of rFVIIIFc for haemostatic control in the setting of major surgery.

Methods: Eligible male subjects ≥ 12 years old, with severe haemophilia A (< 1 IU/dL [1%] endogenous FVIII), a history of ≥ 150 prior exposure days (ED) to FVIII, and no current/prior FVIII inhibitors, received either individualised prophylaxis (25–65 IU/kg every 3–5 days; Arm 1), weekly prophylaxis (65 IU/kg; Arm 2), or episodic (on-demand; Arm 3) treatment. Subjects from each arm were eligible to enter the surgery subgroup for assessment of rFVIIIFc in perioperative management if they required major surgery, had ≥ 12 EDs to rFVIIIFc and negative inhibitor titres following this period and within 4 weeks prior to surgery. Dosing for subjects in this subgroup was determined by the investigator based on the subject's rFVIIIFc PK profile, dose regimen of FVIII generally required for the planned surgery, and bleeding status.

Results: Overall, nine major surgeries were performed in nine subjects (eight subjects from Arm; 1 subject from Arm 2), including knee arthroplasty (n = 5), laparoscopic inguinal hernia repair (n = 2), appendectomy (n = 1), and arthroscopy (n = 1). Haemostatic response with rFVIIIFc was rated by investigators/surgeons as excellent (8/9) or good (1/9) for all nine surgeries. Median (range) estimated blood loss, available for 7/9 surgeries, was 15.0 (0, 600) mL during surgery and 0.0 (0, 1100) mL post-operatively (post-surgical drainage). A single injection of rFVIIIFc was sufficient to maintain haemostasis to the end date/time of all major surgeries, at a median (range) dose of 51.4 (50, 77) IU/kg. Median (range) rFVIIIFc consumption (summarized over all injections during each referenced time period) was 80.6 (65.8, 115.4) IU/kg on the day of major surgery, 161.3 (45.8, 237.3) IU/kg for Days 1–3 days following surgery, and 387.1 (28.1, 728.8) IU/kg for Days 4–14 following surgery. No subjects reported a bleeding episode during the postoperative or rehabilitation periods. Overall, seven adverse events (AEs) were reported in 4 (44.4%) subjects in the surgery subgroup, of which six AEs were of mild or moderate severity, and one AE was considered severe. Two serious AEs (inguinal hernia and appendicitis) were reported in two subjects. All AEs during the perioperative period were assessed by the investigators as unrelated to rFVIIIFc treatment.

Summary/Conclusions: The results from this surgery study showed that rFVIIIFc effectively maintained haemostasis in all major surgeries, and suggest that perioperative haemostasis achieved after infusion of rFVIIIFc was comparable to that expected for similar surgeries in subjects without haemophilia.

PA 4.07-3

The importance of biomarkers of joint damage in monitoring the efficacy of different prophylaxis regimens for severe haemophilia A

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Background: Haemophilic arthropathy, with characteristic joint damage, is the main cause of morbidity in individuals with severe haemophilia A. The most important clinical strategy for management of these patients is treatment by continous prophylaxis with intravenously applied factor (F) VIII. Recently, it was shown that serum and/or urine biomarkers of cartilage turnover in joints reflected the degree of total joint degradation in haemophilia patients.

Aims: The aims of this study were to detect correlations between serum and urine concentrations of biomarkers of joint cartilage degradation and the radiological score for haemophilic arthropathy, as well as to estimate whether measurement of these biomarkers could be useful in monitoring the efficacy of different (secondary) prophylaxis regimens for severe haemophilia A.

Methods: This single-center study included 20 adult males with severe haemophilia A manifested by plasma FVIII < 1% of normal, without inhibitor. The first group involved five patients treated with full-dose prophylaxis: 20 U/kg three times per week. The second group included five patients given intermediate-dose prophylaxis: 10–15 U/kg three times per week. The third group consisted of 10 patients treated on demand (i.e. only in acute bleeding episodes). The following joint cartilage degradation products were measured: serum cartilage oligomeric matrix protein (COMP) and urinary C-terminal telopeptide of type II collagen (CTX-II). Blood and urine samples were collected initially, before the start of treatment (marked as COMP-1 and CTX-II-1) and after 3 months follow-up (marked as COMP-2 and CTX-II-2). Radiological evaluation of haemophilic arthropathy was estimated initially according to the Pettersson score. Approval from the local Ethics Committee and informed written consent were obtained from each subject.

Results: The mean age of the patients was 32 years (range 19–55). The results showed significant positive correlations between the number of points in the Pettersson score and both COMP level (r = 0.602, P = 0.006) and CTX-II level (r = 0.580, P = 0.009). In the group of patients given full-dose prophylaxis, the mean value for COMP-2 was significantly lower than that for COMP-1 (P = 0.043), while in the group of patients receiving intermediate-dose prophylaxis and in those treated on demand the mean values of COMP-2 were not significantly changed when compared to those for COMP-1. Likewise, in the group of patients treated with full-dose prophylaxis, the mean value for CTX-II-2 was significantly lower than that for CTX-II-1 (P = 0.014). Moreover, the mean value of CTX-II-2 was also significantly decreased compared to that for CTX-II-1 (P = 0.028) in the group

receiving intermediate-dose prophylaxis. The mean values of CTX-II in the group of patients treated on demand showed no change.
Conclusions: Joint cartilage degradation products, such as the biomarkers: serum COMP and urinary CTX-II, can provide an estimation of the amount of joint damage in patients with haemophilia A. Measurement of serum/urinary biomarker levels is useful for monitoring the efficacy of the applied doses of FVIII in different treatment approaches towards these patients.

PA 4.07-4

Factor VIII genotype and correlation with the hemophilia severity score

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Background: Hemophilia A is classified into mild (> 5–40%), moderate (2–5%) and severe (≤ 1%) disease based upon plasma factor activity levels. Severity of bleeding is commensurate with the baseline factor levels in general; however heterogeneity of bleeding patterns in patients with severe disease is well described. The Hemophilia Severity Score (HSS) is a validated measure of phenotypic severity that takes into account the annual incidence of joint bleeds, the World Federation of Hemophilia Orthopedic joint score and annual factor consumption. The joint score and factor consumption are adjusted for age at the start of prophylaxis and body weight. Multiple factor VIII (F8) mutations have been described.
Aim: We examined the relationship between genotype and phenotypic severity in a cohort of patients with severe hemophilia A.
Methods: After informed consent was obtained, patients with severe hemophilia A (≤ 1%) were recruited from The Emory Hemophilia Treatment Center during routine clinic visits. Patients with concomitant bleeding disorders or thrombocytopenia (< 100,000/μL) were excluded. Each patient received a HSS score. In addition, genotype data was recorded if known or performed if unknown. Mutation analysis was performed by sequencing, multiplex ligation-dependent probe amplification, and polymerase chain reaction for inversions in F8 introns 22 and 1. The F8 genotype was classified as large deletions (single exon or multiple exons), nonsense mutations, intron 1 and 22 inversions, small deletions/insertions/combined deletions and insertions, missense mutations, frameshifts and splice sites. We considered severe molecular defects to include intron 1 and 22 inversions, nonsense mutations and large deletions, while less severe molecular gene defects included missense, splice site, small deletions and frameshift mutations. Associations between genotype and HSS phenotype were examined via one-way ANOVA. Association between severity of mutation and HSS phenotype was determined via t-test.
Results: To date, 71 patients with severe hemophilia A enrolled on the study. The patients ranged in age from 3 to 61 years. Full HSS and genetic data were available on 48 patients. Four (8%) patients manifested large deletions, 18 (38%) had inversion 22, 4 (8%) exhibited intron 1 inversion, 3 (6%) had nonsense mutations, 7 (15%) demonstrated frameshifts, 10 (21%) with missense mutations and 2 (4%) had splice site changes. The mean HSS differed significantly among the mutation types $P = 0.032$. The patients that manifested severe mutations had a significantly higher mean HSS (1.05 vs. 0.54) than those with less severe mutations, $P = 0.0045$.
Summary/Conclusion: We have demonstrated that bleeding severity as scored by the HSS correlates with the type and severity of genetic mutations. We surmise that patients with less severe mutations may produce small amounts of F8 and this may correlate with a less severe bleeding phenotype. These results suggest that assessment of F8 genotype, above and beyond F8 activity, may provide useful information regarding phenotypic severity in patients with severe hemophilia.

PA 4.07-5

A new treatment concept for haemophilia: safety, pharmacokinetics and pharmacodynamics of single i.v. and s.c. doses of a monoclonal anti-TFPI antibody in healthy males and haemophilia subjects

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Background: Regular prophylaxis with either factor VIII or IX is the current gold standard of care for patients with severe haemophilia to prevent joint damage. Frequency of the injections, poor venous access, cost, compliance and time commitment continue to be barriers for widespread use across the world. Novo Nordisk has developed a monoclonal antibody (mAb 2021) targeting tissue factor pathway inhibitor (TFPI). If successful, mAb 2021 has the potential to alter current concepts of prophylaxis in all types of haemophilia, including convenient subcutaneous (s.c.) administration with potential for improved compliance.
Aims: Safety was the primary objective. Secondary objectives were pharmacokinetics (PK) and pharmacodynamics (PD) of mAb 2021 after single i.v. and s.c. doses in healthy subjects (HS) and subjects with haemophilia A or B (patients).
Methods: This was a phase 1, multi-centre, placebo-controlled, double-blind trial. Escalating single i.v. and s.c. doses were administered to healthy subjects ($N = 28$) and patients with haemophilia ($N = 24$). Informed consent was obtained from all participating trial subjects. The trial was approved by the relevant ethical committees. I.v. dose cohorts for HS: 0.5, 5, 50 and 250 μg/kg; and for patients: 250, 1000, 3000 and 9000 μg/kg. S.c. dose cohorts for HS: 50, 250 and 1000 μg/kg; and for patients: 1000 and 3000 μg/kg. Four subjects were included in each dose cohort of which one received placebo.
We registered all Adverse Events (AEs), including Serious Adverse Events (SAEs), local tolerability, laboratory assessments, anti-drug antibodies, vital signs and ECG. A mAb 2021 ELISA was used for PK, and a residual TFPI functionality assay based on FXa generation for PD. An ELISA measured plasma TFPI.
Results: There were no SAEs and no anti-drug antibodies. Fifty-seven of 76 AEs were mild, 17 were moderate and two were graded as severe (one endodontic procedure, and one sciatica, both unlikely related to mAB 2021). Nineteen AEs occurred after placebo. Five AEs were judged by investigators as related, of which three occurred after administration of mAb 2021. Two of these were graded as mild and one as moderate severity, the latter a small superficial thrombophlebitis in a HS in the 1000 μg/kg s.c cohort, manifesting only as local skin tenderness and diagnosed with ultrasound. The symptom disappeared spontaneously, without treatment, the day after diagnosis. Injection site reactions were few, all mild except for one moderate.
There were no clinically relevant changes in Platelets, AT, APTT and PT. As expected a dose dependent procoagulant effect of mAb 2021 was seen as increased levels of D-dimers and prothrombin fragments 1 + 2.
Non-linear PK of mAb 2021 was observed due to target mediated clearance. A maximum AUC of 33.960.278 h*ng/mL and a maximum concentration of 247.104 ng/mL was measured at the highest dose, 9000 μg/kg i.v. Residual TFPI functionality and Total free plasma TFPI levels decreased in a mAb 2021 concentration dependent manner.
Conclusions: mAb 2021 was found to be safe after i.v. and s.c. administration. PK was influenced by target mediated clearance. A mAb 2021 concentration dependent effect was observed on plasma TFPI functionality and levels.