Highlights of the WFH 2018 World Congress

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SUMMARY

From the 20th till the 24th of May 2018, Glasgow formed the background for the annual meeting of the World Federation of Hemophilia (WFH), the largest international meeting for the bleeding disorders community. The therapeutic options for people with haemophilia (PWH) have rapidly evolved in the last five years. Moving on from conventional plasma-derived and recombinant clotting concentrates (CFC), there are now extended half-life CFCs as well as several novel haemostasis agents (e.g. emicizumab). In addition, gene transfer proved to be successful for both haemophilia A and B patients. It has been demonstrated that all these products provide better haemostasis and convenience than conventional CFCs. This summary will focus on new data presented with some of these novel therapeutic options during WFH 2018. For a complete overview of abstracts presented during the meeting we would like to refer to the official congress website *(https://www.wfh.org/congress/en/home)*.

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NEWS ON EXTENDED HALF-LIFE CONCENTRATES

HEAD-TO-HEAD PHARMACOKINETIC COMPARISON OF N9-GP AND RFIXFC IN HAEMOPHILIA B PATIENTS

N9-GP and rFIXFc are extended half-life (EHL) products that maintain higher FIX activity levels with fewer injections and reduce the number of bleeding episodes with prophylaxis in patients with haemophilia B. In the Paradigm-7 trial, the PK profiles of N9-GP and rFIXFc (Alprolix) were compared. Fifteen previously treated adult males with congenital haemophilia B (factor IX activity ≤2%) received single injections (50 IU/kg) of N9-GP and rFIXFc with at least 21 days between doses. The primary endpoint was dose-normalised area under the factor IX activity-time curve from 0 to infinity ($AUC_{0\text{-inf,norm}}$). The estimated $AUC_{0\text{-inf,norm}}$ (N=12) was significantly higher for N9-GP than rFIXFc—9656 IU*h/dL and 2199 IU*h/dL, respectively (ratio=4.39, p<0.0001). The maximum factor IX activity dose-normalized to 50 IU/kg (N=14) was 91 IU/dL with N9-GP and 45 IU/dL with rFIXFc (ratio=2.02, p<0.001). Looking at the terminal half-life (N=12), the researchers reported 103.2 hours with N9-GP *vs.* 84.9 hours with rFIXFc (ratio=1.22, p<0.001). No new safety concerns were observed.[1]

PRELIMINARY PHASE 1/2A DATA WITH BIVV001 IN HAEMOPHILIA A

For decades, scientists have been trying to overcome the von Willebrand factor (VWF) ceiling, which imposes a limit on the half-life of FVIII. BIVV001 (rFVIIIFc-VWF-XTEN) is a recombinant FVIII therapy that builds on Fc fusion technology by adding a region of VWF and XTEN polypeptides to potentially extend its time in circulation.

In the phase 1/2a EXTEN-A trial, researchers are evaluating the safety and PK of BIVV001 in a low- and high-dose cohort of severe haemophilia A patients aged 18 to 65. Four adult males received a single dose of recombinant FVIII therapy (25 IU/kg) followed, after a washout period, by a single, low dose of BIVV001 (25 IU/kg). No inhibitors have been detected, and BIVV001 was generally well tolerated. BIVV001 extended the half-life of FVIII to 37 hours, which is a substantial increase on the thirteen hours seen with recombinant FVIII. The average FVIII activity for the four subjects was 13.0% at five days and 5.6% at seven days post-infusion.[2]

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Endpoint	Arm D: Emicizumab 1.5 mg/kg QW n=48*	NIS: FVIII prophylaxis n=48
Duration of efficacy period, median (min-max), weeks	33.7 (20.1–48.6)	30.1 (5.0–45.1)
ABR, model based (95% CI)†	1.5 (1.0; 2.3)	4.8 (3.2; 7.1)
Reduction vs NIS FVIII RR, P-value	**68% reduction** 0.32, P<0.0001	—
Median ABR, calculated (IQR)	0.0 (0.0–2.1)	1.8 (0.0–7.6)
Patients with zero bleeds, % (95% CI)	54.2 (39.2; 68.6)	39.6 (25.8; 54.7)
Patients with 0–3 bleeds, % (95% CI)	91.7 (80.0; 97.7)	72.9 (58.2; 84.7)

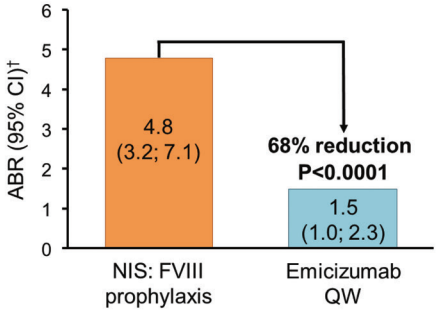

FIGURE 1. Intra-individual comparison of treated bleeds between emicizumab and prior FVIII prophylaxis.[3]

LATE BREAKING DATA WITH EMICIZUMAB IN THE TREATMENT OF HAEMOPHILIA A PATIENTS WITHOUT INHIBITORS

Emicizumab is a humanised bispecific monoclonal antibody that bridges activated FIX and FX to restore function of missing FVIIIa. As there is no structural homology to FVIII, emicizumab is not expected to induce FVIII inhibitors nor is it likely that its function will be affected by the presence of inhibitors. The drug is administered subcutaneously and has a long half-life of approximately 30 days. The late breaking abstract session at WFH 2018 featured both the presentation of the full results of the phase III HAVEN 3 study, evaluating emicizumab prophylaxis every one or two weeks in patients with haemophilia A without factor VIII inhibitors, and of the Phase III HAVEN 4 study, assessing emicizumab prophylaxis every four weeks in haemophilia A patients with or without factor VIII inhibitors.[3,4]

In the Phase III HAVEN 3 study, adults and adolescents aged twelve years or older without factor VIII inhibitors who received emicizumab prophylaxis every week (N=36) or every two weeks (N=35) showed a 96% (p<0.0001) and 97% (p<0.0001) reduction in treated bleeds, respectively, compared to those who received no prophylaxis (N=18). Interestingly, 55.6% and 60% of patients treated with emicizumab every one or two weeks, respectively, experienced zero treated bleeds. In contrast, none of the patients receiving no prophylaxis remained free of bleeds.[3] Importantly, in an intra-patient comparison, once-weekly emicizumab prophylaxis showed superior efficacy compared to prior factor VIII prophylaxis, the standard of care for people with haemophilia A without factor VIII inhibitors. This is reflected by a 68% reduction (p<0.0001) in the number of treated bleeds (*Figure 1*). With emicizumab prophylaxis, the percentage of patients with zero bleeds was 54.2% *vs.* 39.6% with standard FVIII prophylaxis.[3]

Moreover, 93.7% (N=89/95) of all participants who completed a treatment preference survey preferred emicizumab to their previous haemophilia treatment, with 97.8% (N=45/46) of those in the intra-patient comparison preferring emicizumab to their prior factor VIII prophylaxis. There were no unexpected or serious adverse events (AEs) related to emicizumab. The most common AEs occurring in 5% or more of people in the HAVEN 3 trial were injection site reactions, joint pain (arthralgia), common cold symptoms (nasopharyngitis), headache, upper respiratory tract infection and influenza.[3]

HAVEN 4 is a single-arm phase III trial evaluating 4-weekly emicizumab prophylaxis in adults and adolescents (twelve years or older). The study included 41 patients in total, of whom 38 were eighteen years or older and 40 had severe haemophilia A. In five patients there were FVIII inhibitors present at study entry, 68.3% had less than nine bleeds in the 24 weeks prior to study entry and 61% had target joints.[4] The reported median annualised bleeding rate (ABR) for treated bleeds was zero, with 56.1% of persons experiencing zero treated bleeds. In total, 90.2% of study participants experiencing three or fewer treated bleeds during the study follow-up. As was seen in HAVEN-3, emicizumab was also the preferred treatment option for patients enrolled in HAVEN-4. In fact, all participants (N=41/41; 100%) who responded to a patient preference survey preferred emicizumab to their previous haemophilia treatment. There were no serious AEs related to emicizumab, and the most common AEs were consistent with previous studies (injection site reactions were the most common AE, seen in 22% of patients).[4]

In summary, both HAVEN-3 and HAVEN-4 show that subcutaneous emicizumab prophylaxis can provide a highly efficacious and flexible treatment option, with reduced burden for persons with haemophilia A. In fact, emicizumab is

the first medicine to show superior efficacy to prior factor VIII prophylaxis, demonstrated by a statistically significant reduction in treated bleeds in the HAVEN 3 study intra-patient comparison.

UPDATES ON GENE TRANSFER FOR HAEMOPHILIA A AND B

Adeno-associated viral vectors (AAV) and lentiviral vectors represent some of the most promising gene delivery technologies that allow for a relatively efficient delivery of the therapeutic FVIII and FIX transgenes into the relevant target cells. During WFH 2018, results of two early-stage studies demonstrated that gene therapies could potentially serve as eventual treatment options for both haemophilia A and B patients.[5,6]

In a first study, Pasi *et al.* presented long-term efficacy and safety results of a phase I/II trial evaluating gene transfer with valoctocogene roxaparvovec (BMN 270), an AAV5 vector containing a B-domain-deleted FVIII gene, in patients with severe haemophilia A. In total, thirteen patients received a single intravenous dose of valoctocogene roxaparvovec, seven at a dose of 6e13 vg/kg and six at a lower 3e13 vg/kg dose. The data presented at WFH 2018 included 104 weeks of data for the 6e13 vg/kg cohort and 52 weeks of data for the 4e13 vg/kg cohort.[5] In the 6e13 vg/kg cohort, the data showed continued and substantial reductions in bleeding requiring Factor VIII infusions. Overall, a 97% reduction in mean ABR was reported with no spontaneous bleeds and elimination of all bleeds in target joints in the second year. In total, 71% and 86% of participants had zero bleeds requiring Factor VIII infusions in years one and two, respectively (14%, had zero bleeds requiring Factor VIII infusions for a year at baseline). There was a 96% reduction in mean FVIII usage through week 104. The 4e13 vg/kg cohort also showed a substantial reduction in bleeding requiring Factor VIII infusions with a 92% reduction in ABR. With this dose, 83% of participants had zero bleeds requiring Factor VIII infusions following treatment for a year (17%, had zero bleeds requiring Factor VIII infusions for a year at baseline). Mean Factor VIII usage decreased by 98%. At 104 weeks post-infusion, the mean Factor VIII activity level of the 6e13 vg/kg cohort was within the normal range at 59%, and the median is near normal at 46%. For the 4e13 vg/kg cohort, mean Factor VIII activity levels from week 20 through 52 have been consistently within the mild range. At 52 weeks post-infusion, mean and median Factor VIII activity levels of the 4e13 vg/kg cohort were reported at 32%. Overall, valoctogogene roxaparvovec has been well-tolerated by participants across all doses.[5]

A second gene transfer abstract that caught the eye discussed phase I/II data with SPK-9001 in haemophilia B patients.[6] SPK-9001 is an investigational vector that contains a bio-engineered AAV capsid and a codon-optimized, high-activity human factor IX gene enabling endogenous production of factor IX. Sullivan *et al.* reported results with SPK-9001 in fifteen patients with severe or moderately severe haemophilia B.[6] Thirteen patients had at least twelve weeks of follow-up after SPK-9001 infusion, which is the length of time required to achieve steady-state factor IX activity levels. All thirteen patients reached stable factor IX levels of more than 12%. The range of steady-state factor IX activity level, beginning at twelve weeks through 52 weeks of follow-up for the first ten patients infused, was 14.3% to 76.8%. The next three patients were infused with SPK-9001 manufactured using an enhanced process and reached twelve or more weeks of follow-up. For these patients, the range of steady-state factor IX activity level was 38.1% to 54.5%. Based on individual participant history for the year prior to the study, the overall ABR for all fifteen patients was reduced by 98% four weeks after SPK-9001 treatment. One patient experienced a bleeding event 4 or more weeks after SPK-9001 infusion. The overall annualised infusion rate (AIR) was reduced by 99% (based on data after week four) for all fifteen patients (AIR: 0.9 infusions per patient after SPK-9001 *vs.* 57.2 before SPK-9001). No serious AEs or factor IX inhibitors were reported.[6] As such; a single administration of SPK-9001 resulted in dramatic reductions in bleeding and factor IX infusions, with no serious adverse events.[6]

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