Biomedical/Coagulation Research:

Use of platelet microcapsule hybrids loaded with factor VIII to treat hemophilia A mice

Shannon Meeks, MD, Caroline Hansen, PhD, Hunter Baldwin, Wilbur Lam, MD, PhD

Background: Hemophilia A (factor VIII deficiency) is an X-linked disorder that is treated with intravenous infusions of factor VIII. The development of an antibody response to factor VIII is the most significant complication of treatment with factor VIII. We have designed a small polyelectrolyte multilayer (PEM) capsule that can be loaded with factor VIII. The surface of the capsule is coated with fibrinogen allowing it to bind to quiescent platelets in circulation. When the platelets are activated at the site of a growing hemostatic plug they contract and rupture the PEM capsule resulting in factor VIII release. Methods: The PEM capsules will be loaded with varying amounts of factor VIII. They will be injected into hemophilia A mice and the ability to stop bleeding following a tail-snip will be assessed following our standard laboratory protocol for the tail-snip assay. The control groups will consist of hemophilia A mice treated with factor VIII at standard doses as well as mice treated with saline. Results: Capsules loaded with 0.83 and 0.55 nM factor VIII resulted in minimal bleeding that was no different than the hemophilia mice treated with our standard 2.5 nM dose of factor VIII and significantly less bleeding than hemophilia A mice treated only with saline. Conclusions: Lower doses of factor VIII are needed when it is delivered to the site of bleeding by our novel PEM capsule system.

Ultrasound-mediated Therapeutic Gene Transfer for Hemophilia

Cynthia Anderson, PhD, MA, BS

Objective: Hemophilia B is an X-linked blood coagulation disease that results from mutations in factor IX (FIX), which is normally produced and secreted by liver cells. Gene-based therapies directed at Hemophilia B might be particularly feasible because restoration of modest levels of FIX activity can have substantial therapeutic benefits, particularly for severe forms of the coagulopathy (<1% normal plasma FIX activity). We are investigating a preclinical gene transfer approach known as Ultrasound Targeted Microbubble Destruction (UTMD) to direct the delivery of plasmid DNA vectors encoding human FIX to the livers of Hemophilia B (FIX-/-) mice. Methods: In UTMD, gene-expression vectors are bound to the shells of lipid microbubbles, administered intravenously, and deposited at the liver by acoustic cavitation of the microbubbles. Ultrasound parameters were identified that produced site-specific transfection of hepatocytes in vivo without substantial damage or bleeding in the livers of FIX-/- mice. Exogenous hFIX levels were evaluated in the
plasma and livers of FIX-/- treated mice at multiple time points after UTMD. Western blotting and immunofluorescence imaging were used to evaluate hFIX in treated plasma and livers. Activated partial thromboplastin time (APTT) assays were used to measure coagulation and alanine transaminase assays and H&E staining were performed to assess hepatic toxicity in plasma and livers. Summary: Reductions in clotting time and improvements in FIX activity were observed in treated FIX-/- mice 4-5 days after UTMD compared with untreated FIX-/- control mice (P=0.001 and P=0.012 for conventional and transposon plasmids, respectively). Reduced clotting times persisted for both plasmids 12 days after treatment (reflecting percentage FIX activity of 3.12±1.56%, P=0.02 and 3.08±0.10%, P=0.001, respectively). Clotting times from an additional set of treated mice were evaluated for long-lasting effects and demonstrated a persistent reduction in average clotting time 160 days after a single treatment (P=0.044).

Conclusions: To advance these studies, we are evaluating high intensity focused ultrasound (HIFU) as an approach for improving gene transfer efficiency. HIFU uses an acoustic lens to focus multiple beams of ultrasound at a single point and can be modulated to target different anatomical depths. We hypothesize that HIFU-based gene transfer may enhance vascular permeability in the liver permitting the delivery of a more concentrated dose of hFIX which may increase transfection and the therapeutic benefit of this approach. We are currently evaluating the bioeffects of varying HIFU parameters on reporter gene transfer in the livers of wildtype mice. This new optimized HIFU-based approach will be used to direct the delivery of hFIX to the livers of FIX-/- mice and these findings will be compared to our previous unfocused UTMD gene therapy studies. The goal of this work is to advance the development of an anatomically targeted, minimally invasive gene therapy strategy for treating Hemophilia.

**PiggyBac mediated gene transfer for prevention of anti-factor VIII antibodies in hemophilia A**

**BCR 053**

Janice Staber, MD, Blake Johnson, BS, Molly Pollpeter, BS, Chandler Tinsman, BA

Objective: Hemophilia A, caused by a deficiency of factor VIII (FVIII), is the most severe inherited bleeding disorder; those affected suffer disabling joint and muscle hemorrhages. Approximately 30% of persons treated with FVIII replacement develop neutralizing antibodies (“inhibitors”). These patients not only have higher health care costs compared to non-inhibitor patients, but they also have increased mortality. A decrease in the rate of inhibitor formation would dramatically improve the outcomes for patients with hemophilia. It is speculated that plasma-derived FVIII products containing von Willebrand Factor (vWF) reduce the risk of inhibitor development compared to recombinant FVIII products which have no vWF. vWF is a carrier protein for FVIII and provides protection while FVIII is in the blood stream. Previous in vitro studies suggest that vWF may protect from inhibitor development by epitope masking and decreasing endocytosis by dendritic cells. Therefore, we hypothesized that in vivo co-expression of vWF and FVIII would stabilize FVIII expression and decrease inhibitor development.

Methods: We utilize a non–viral gene transfer approach called piggyBac, a DNA transposon, containing the human FVIII gene (PB-FVIII). We previously demonstrated long-term correction of the bleeding phenotype with this liver-directed gene therapy strategy in a mouse model of hemophilia A. As we previously published, PB-FVIII conferred wild-type FVIII levels when given to hemophilia A mice. To answer the question regarding the importance of vWF, we initiated studies in a hemophilia A mouse model to co-express FVIII and vWF. We delivered the PB-FVIII + piggyBac containing vWF (PB-vWF) and compared them to animals injected with PB-FVIII alone. We investigated abundance and persistence of FVIII activity, anti-FVIII antibodies, and vWF levels over time.
Summary: All piggyBac-treated FVIII null animals demonstrated FVIII levels similar to wild type animals. However, after 20 weeks, mice receiving PB-FVIII without PB-vWF demonstrated decreased FVIII activity while mice receiving PB-FVIII + PB-vWF demonstrated stable, wild-type FVIII levels until the end of the study. To determine vWF effects on anti-FVIII antibodies levels in vivo, we injected hemophilia A mice with PB-FVIII with or without PB-vWF (PB-FVIII alone, PB-FVIII + PB-vWF or PB-FVIII-vWF). In preliminary studies, we found that total IgG anti-FVIII antibodies are decreased in animals receiving PB-FVIII-vWF or PB-FVIII + PB-vWF compared to PB-FVIII alone (p <0.01). In addition, fewer FVIII null animals develop anti-FVIII antibodies when vWF is co-expressed in the piggyBac vector.

Conclusions: In a liver-directed gene therapy strategy, anti-FVIII antibodies are decreased in animals receiving vectors containing FVIII and vWF compared to animals receiving FVIII alone. This supports a role for vWF in providing protection from FVIII inhibitors.

Effects of Factor VIII Prophylaxis on Vascular Remodeling and Synovial Gene Expression Changes Associated with Hemarthrosis in FVIII-Deficient Mice

BCR 064


Objective

Repeated joint bleeding in patients with hemophilia leads to hemophilic arthropathy (HA), which cannot be entirely prevented by clotting factor replacement. Vascular remodeling and permeability are associated with hemarthrosis and may contribute to HA progression; however, the underlying mechanisms and effects of FVIII replacement are poorly understood. Here, we explored vascular changes and synovial gene expression profiles in FVIII-deficient mice after induced hemarthrosis +/- FVIII replacement.

Methods

Hemarthrosis was induced in FVIII-deficient mice by sub-patellar needle puncture +/- 100-200 IU/kg recombinant human FVIII (rhFVIII) intravenously 2 hours before and 6 hours after injury. Vascularity and gene expression were analyzed at baseline and 2 weeks post-injury. Vascularity was assessed by histology with Safranin-O-Fast Green and α-smooth muscle actin (αSMA) staining, and by musculoskeletal ultrasound with Power Doppler to detect microvascular flow. The permeability of synovial vessels was determined by quantification of extravasated albumin-bound Evans blue dye in knee joints at near-infrared fluorescence. For gene expression studies, RNA was extracted from synovial tissue and cDNA libraries were prepared using the NEBNext Ultra II DNA Library Prep Kit and sequenced on an Illumina NextSeq500 platform (single-end; 75bp reads). The R BioConductor packages tximport, edgeR and limma were used to read Salmon transcript files and implement the limma-voom method for differential expression analyses. Functional enrichment was performed using Signaling Pathway Impact Analysis.

Results
Knee injury caused profound hemarthrosis in vehicle-treated mice that was largely prevented with rhFVIII prophylaxis (day 2 hematocrit: 26.4% and 46.3%, respectively). Soft tissue proliferation increased to a similar extent in both groups, as did various vascular parameters: microvascular flow (vehicle: 1.8-fold; rhFVIII: 1.5-fold), vessel number (vehicle: 2.2-fold, p=0.0005; rhFVIII: 2.0-fold, p=0.004), vessels with diameter ≥ 20 µm (vehicle: 2.9-fold, p=0.02; rhFVIII: 2.7-fold, p=0.02), and αSMA area per vessel (vehicle: 2.3-fold, p>0.05; rhFVIII: 3.6-fold, p=0.0006). Vascular permeability also increased significantly after joint bleeding (1.7-fold, p=0.0007) and was only partially rescued by rhFVIII prophylaxis (1.3-fold, p>0.05). RNA sequencing revealed a strong transcriptional response (1527 differentially expressed genes (DEG), 13 perturbed pathways), that was not substantially dampened in rhFVIII-treated mice (891 DEG, 20 perturbed pathways). Notably, perturbation of extracellular matrix (ECM)-receptor interactions was highly significant with vehicle (pGFWER=1.7x10^{-11}) and rhFVIII prophylaxis (pGFWER=1.4x10^{-10}). STRING analysis of the top 20 DEG revealed enrichment of ECM components and organization, and numerous genes encoding ECM constituents, including collagens and MMPs, were significantly upregulated. Changes in ECM gene expression may facilitate the observed synovial tissue and vascular remodeling after hemarthrosis.

Conclusions

Hemarthrosis in FVIII-deficient mice triggers profound changes in synovial gene expression that may drive associated tissue and vascular remodeling processes. These changes are incompletely mitigated by rhFVIII prophylaxis. Further exploration will enable identification of disease markers and targeted drug discovery to intercept the progression of HA.
Clinical Research/Available Clinical Trials:

BAY 94-9027 Maintains Hemostasis During Major Surgery in Adults and Adolescents With Severe Hemophilia A: PROTECT VIII Results

CRA 026

Shadan Lalezari, Elena Santagostino, Jonathan Ducore, Lisa A. Michaels, Kapil Saxena, Camila Linardi

Objective: BAY 94-9027 is an extended–half-life recombinant factor VIII (FVIII) product. Efficacy in maintaining hemostasis during major surgery was evaluated in a subset of patients with severe hemophilia A in the phase 2/3 PROTECT VIII study.

Methods: Patients aged 12–65 years requiring major surgery during PROTECT VIII or its ongoing extension were included in the analysis. Patients with severe hemophilia A undergoing major surgery who were not enrolled in PROTECT VIII but met all study inclusion and exclusion criteria also were eligible to participate. BAY 94-9027 dosing during the perioperative period was based on preoperative pharmacokinetic measurements and adjusted at the physician’s discretion. Types of procedures and duration of surgeries, BAY 94-9027 consumption on the day of surgery, intraoperative blood loss, surgeon assessment of hemostasis during surgery, and need for blood transfusion were evaluated.

Summary: 17 patients (median [range] age, 37 [13–61] years) underwent 20 major surgeries, including 15 orthopedic surgeries (9 joint replacements [hip, n=1; knee, n=6; ankle, n=2], 2 open synovectomies, 3 arthroscopies, and 1 thigh hematoma evacuation), 3 complex dental extractions, 1 penile prosthesis, and 1 inguinal hernia repair at data cutoff (January 2015). Median (range) surgical duration was 102 (17–217) minutes, and median (range) total dose used on day of surgery, including preoperative, intraoperative, and postoperative infusions on that day, was 72.4 (43–136) IU/kg. Median (range) number of FVIII infusions on the day of surgery was 2 (1–3), with 40% of procedures requiring only 1 infusion (preoperative) on that day. Following a median (range) presurgical dose of 52.1 (41–64) IU/kg, the median (range) FVIII level (chromogenic assay; measured in a central laboratory) immediately before the second infusion was 71.6 (44–140) IU/dL; median (range) time between the presurgical and second infusions was 12.3 (3.6–50.0) hours. Hemostasis during surgery was good (13/20; 65%) or excellent (7/20; 35%) for all procedures. Intraoperative blood loss was within expected ranges for all surgeries (median [range], 50 [0–1000] mL), and blood transfusions were required in 4 patients undergoing knee surgeries.

Conclusions: BAY 94-9027 is efficacious in maintaining hemostasis during major surgeries in adolescents and adults with severe hemophilia A. Excellent or good hemostasis with blood loss as expected was achieved in all surgical procedures, which included major orthopedic surgeries (75% of all procedures), with 40% of patients requiring only a single infusion of BAY 94-9027 on the day of surgery.

Effective Protection for >5 Years with BAY 94-9027 Prophylaxis: PROTECT VIII Extension Trial Interim Results

CRA 028

Prasad Mathew, Graeme Thomson, Pål Andrè Holme, Maria Wang, Monika Maas Enriquez
Objective: In the PROTECT VIII phase 2/3 trial, the extended-half-life recombinant factor VIII product BAY 94-9027 provided effective bleed protection with twice-weekly, every-5th-day, and every-7th-day prophylaxis for 36 weeks. Herein, we report interim efficacy data from the PROTECT VIII extension study in patients receiving BAY 94-9027 prophylaxis for up to 5.4 years.

Methods: In the PROTECT VIII trial, previously treated males aged 12 to 65 years with severe hemophilia A received BAY 94-9027 for 36 weeks on demand or for prophylaxis either twice weekly (30–40 IU/kg), every 5 days (45–60 IU/kg), or every 7 days (60 IU/kg). Patients could continue in the extension study using the same or a different regimen. Bleeds were recorded in electronic patient diaries, and annualized bleeding rates (ABRs) were calculated.

Summary: Of 134 patients enrolled in PROTECT VIII, 121 patients aged 15 to 67 years (median age, 40 years) at the data cutoff (January 2018) continued in the extension with either on-demand treatment (n=14) or prophylaxis (n=107). At the time of analysis, patients had spent a median of 3.9 years (range, 297–1965 days) in the study since enrollment, with a median of 223 (range, 23–563) exposure days. Median (quartile [Q] 1; Q3) ABR for total bleeds during the extension study was 34.1 (20.3; 36.6) for on-demand patients and 1.6 (0.3; 4.6) for prophylaxis patients. Median (Q1; Q3) ABR for joint bleeds was 0.9 (0; 3.3) for prophylaxis patients during the extension. Median (Q1; Q3) ABR for total bleeds during the extension was similar for patients receiving prophylaxis twice weekly (1.7 [0.8; 3.6]; n=23), every 5 days (1.2 [0; 4.6]; n=33), and every 7 days (0.7 [0; 1.6]; n=23); among patients who switched prophylaxis frequency during the extension (n=28), total ABR was 3.1 (1.2; 6.2). Compared with the main study, ABR during the extension was further reduced in patients who remained in their treatment arm, including patients receiving prophylaxis every 7 days (median [Q1; Q3] main study ABR for total bleeds, 0.96 [0; 4.3]). Of patients receiving prophylaxis, 20.6% had zero bleeds during the extension. No safety issues were identified.

Conclusions: Good bleeding control was maintained with BAY 94-9027 prophylaxis with extended intervals of every 5 days and every 7 days throughout the PROTECT VIII extension study for up to >5 years.

Annual Bleed Rates Compared Before and After Changing to Extended Half Life Products in Home Infusion Patients with Severe Hemophilia

CRA 032

Kirstin Schmidt, RN, Kim Milenski, RPh, Donna Haffler, RN, BSN, Elizabeth Hanlon, RN, BSN, Betsy Benny, PharmD, RPH

Objective: The purpose is to determine if EHL factor products have an effect on bleed rates in patients with severe hemophilia A and B. Hemophilia may lead to uncontrolled bleeding into soft tissues, muscles, and weight bearing joints. Bleeding may begin spontaneously or following trauma. Over time, irreversible joint, muscle, and organ damage may occur and progress to disability or shortened life span. Prophylactic factor replacement infusions are the standard of care in the management of patients with severe hemophilia A and B, reducing the risk of spontaneous bleeding episodes and joint damage. The traditional shorter half-life factor VIII (~12 hours) and factor IX (~20 hours) replacement products requires dosing on a schedule of two to three times per week or more. However, frequent intravenous administration may lead to patient dissatisfaction and/or non-adherence. The extended half-life (EHL) factor products may allow for less frequent dosing, consistent factor levels, and decreased bleed rates when compliance is maintained.
Methods: A retrospective chart review of electronic medical records examined data collected from September 2015 to September 2017. The inclusion criteria comprised of patients with a diagnosis of severe hemophilia who were prescribed an EHL factor product, comparing bleed records six months preceding and six months following the transition. Data was gathered using the Hemophilia Health Assessment (HHA) form, an internal form used to record patient bleeding episodes on a monthly basis. Exclusion criteria included one or more incomplete/missing HHA forms during the review period, presence or history of an inhibitor, diagnosis of mild/moderate hemophilia, and surgery/procedures during period of data collection.

Summary: Forty-six patients were identified with eighteen patients meeting all the inclusion criteria; 6 six factor IX patients and 12 factor VIII patients with a mean age of 23.5. The annual bleed rate (ABR) for patients on traditional factor products was 3.5 during the 6-month period prior to transitioning to the EHL product. The ABR dropped to 0.77 in the 6-month period following transition. Six patients reported zero bleeds while using the traditional factor products and 11 patients reported zero bleeds on EHL products. Ankle bleeds were the most common type of bleed, with 27 of 63 bleeds identified in this joint. Four of the 18 patients have documented target joints. Patients with severe hemophilia have frequent spontaneous bleeding episodes in their joints and muscles. EHL factor products require less frequent dosing which may sustain circulating factor levels and reduce the number of infusions.

Conclusion: Although the sample size was not large enough to determine statistical significance, bleed rates were lower in patients transitioned to extended half-life factor products. These results suggest that EHL factor products may be an effective treatment option to reduce the bleed rates in patients with severe hemophilia.

HOPE-B: Study design of a Phase III trial of an investigational gene therapy AMT-061 in subjects with severe or moderately severe hemophilia B

CRA 035

Steven Pipe, Giancarlo Castaman, Nigel S. Key, Susan Lattimore, Frank W. G. Leebeek, Wolfgang Miesbach, Steven Zelenkofske, Michael Recht

Objective: Somatic gene therapy for hemophilia B offers the potential to ameliorate the disease severity through continuous endogenous production of FIX protein with a single treatment. Robust preliminary efficacy and safety results have been obtained in ten subjects with hemophilia B after treatment with AMT-060, an adeno-associated virus (AAV) serotype 5 vector containing a wildtype factor (F) IX gene, in an ongoing Phase I/II trial (CT-AMT-060-01). Following a single dose of 2x1013 gc/kg, stable FIX activity at a mean of 7.2% was observed in patients (n=5) after 1.5 years follow-up, without evidence of capsid-directed T-cell activation in two patients experiencing transient transaminitis, or immune-mediated loss of FIX activity, or inhibitor development in any patient. AMT-060 was modified to encode the highly active Padua variant of FIX, which is expected to result in an increased FIX activity-to-protein ratio of approximately 7-9 fold. The purpose of this Phase III trial is to demonstrate the efficacy of AMT-061 in
terms of endogenous FIX activity and annualized bleeding rate, and to further describe its safety profile in patients with hemophilia B.

Methods: This is an open-label, single-dose, multi-center, multinational trial, with over 15 sites planned in the United States, as well as sites in the Netherlands, Germany, Denmark, Italy, Ireland, and other European countries. The trial will consist of screening, lead-in, treatment + post-treatment follow-up phases (1 year), and a long-term follow-up (4 years), for a total of 5 years post-treatment. Participants will be adult males with severe or moderately severe congenital hemophilia B (FIX ≤ 2%), utilizing continuous routine FIX prophylaxis, with no history of FIX inhibitors, no active hepatitis B or C, nor uncontrolled HIV. Eligible patients will enter a prospective lead-in phase, during which FIX use and bleeding episodes will be documented. Patient reported outcome (PRO) questionnaires and joint status will also periodically be determined. Pre-existing AAV5 neutralizing antibodies will be assessed but not used as an exclusion criterion. At the completion of the lead-in phase, patient eligibility will be re-confirmed and participants re-consented prior to receiving the single dose of AMT-061. Assessments during the post-treatment follow-up phases will include FIX activity, bleeds, use of FIX replacement, routine laboratory parameters, adverse events, transaminases, and AAV5 antibodies.

Summary and Conclusions:
Based on the available clinical and non-clinical data, the modification of AMT-060 to AMT-061 with a highly active FIX (‘Padua’) variant is anticipated to achieve comparable levels of FIX protein but result in higher FIX activity, while preserving the safety profile and absence of T-cell activation observed with AMT-060. By not excluding patients from participating based on neutralizing antibody status, safety and efficacy can be evaluated in a broader population of patients.

**Efficacy of on-demand treatment of bleeding episodes in hemophilia B patients with extended half-life N9-GP in pivotal trials: an in-depth analysis of treatment**

CRA 036

Miguel Escobar, Christopher Walsh, David Cooper, Guy Young

Objective: N9-GP is a glycoPEGylated recombinant factor-IX (rFIX) product that provides approximately two times incremental recovery, five times half-life, and 10 times area under the plasma concentration-time curve compared with standard rFIX. Phase 3 single-dose (40 IU/kg) in adults showed incremental recovery 2.34 %/IU/kg and 17% mean FIX activity at 7 days. This analysis investigates N9-GP 40 IU/kg as a single-dose on-demand (OD) treatment for hemophilia B, focusing on predictors of a second dose.

Methods: In the paradigm™2 pivotal trial of previously treated adult/adolescent patients (≤2% FIX), the FDA requested that a group receive OD treatment prior to US enrollment into prophylaxis. This case-by-case analysis evaluated OD treatment in relationship to bleed type/pattern and prestudy treatment regimen. Hemostatic efficacy was reported by patients on a 4-point scale.

Summary: Fifteen patients were enrolled for OD treatment (13 severe, two moderate); 13 were previously treated OD and two with prophylaxis. Overall, 14/15 patients experienced 143 bleeds during 26 weeks, of which 120 (84%) in 13 patients were treated with one dose. Seven patients (five severe, two moderate) treated all bleeds (62) with one dose (36 ‘excellent’ and 26 ‘good’ response). The other seven patients, described below, experienced 58 bleeds (72%) treated with one dose (seven ‘excellent’, 49 ‘good’, one ‘moderate’, one not reported); their other 23 bleeds (28%) required ≥2 doses (17 ‘good’, six ‘moderate’).
Two of these seven had 4/11 (36%) recurrent target joints (TJ) bleeds/rebleeds treated with additional doses. An 18-year-old previously treating with plasma-derived FIX (pdFIX), 76 IU/kg/bleed, had three right elbow TJ bleeds in two months treated with one, five, and two doses. A 27-year-old previously on prophylaxis (pdFIX 100 IU/kg every 3 days and 100 IU/kg/bleed) had two bleeds in a right ankle TJ in 2 weeks treated with two doses (including one for early rebleeding) and six doses prior to withdrawing from the study. Another four patients with bleeds requiring multiple doses had been historically treated with multiple high FIX doses (IU/kg x doses per bleed: 60×2, 80×2, 80×2, and 81×3) with prescribed dosing of 120, 160, 160, and 243 IU/kg/bleed; they reported 63 bleeds, of which 45 (71%) were treated with a single 40-IU/kg dose, 17 with two, and one with four doses. Average N9-GP dosing was 44.0, 74.7, 97.9, and 52.8 IU/kg/bleed (63%, 53%, 39%, and 78% reduction in FIX use per episode). The last patient was treated prestudy with 10 IU/kg/bleed had seven bleeds (six treated with one dose, mean 46.8 IU/kg/bleed).

Conclusions: N9-GP 40 IU/kg was effective as a single-dose OD bleed treatment (84%). Additional dose(s) for some bleeds were associated with recurrent TJ bleeds in patients not on prophylaxis or patients previously taking multiple high doses for bleeding.

Long-term Benefit of BAY 81-8973 Prophylaxis in Children With Severe Hemophilia A: Interim Analysis of the LEOPOLD Kids Extension Study

CRA 037

Gili Kenet, Valentina Uscatescu, Bryce A. Kerlin, Despina Tseneklidou-Stoeter, Nikki Church

Objective: BAY 81-8973 (Kovaltry®) is a full-length, unmodified recombinant human factor VIII (FVIII) for prophylaxis and treatment of bleeds in patients with hemophilia A. Safety and efficacy of BAY 81-8973 in children, adolescents, and adults were established in the LEOPOLD clinical trials. This analysis reports interim data from the LEOPOLD Kids extension study for patients with ≥100 exposure days (EDs) to BAY 81-8973 in the main study plus extension study.

Methods: In LEOPOLD Kids, boys aged ≤12 years with severe hemophilia A and ≥50 EDs to FVIII received BAY 81-8973 (25–50 IU/kg) ≥2 times/wk for ≥50 EDs. Patients completing the main study could enroll in an ongoing extension study for ≥100 EDs.

Summary: Of 51 patients who completed the main study, 46 (90.2%) entered the extension study (aged <6 years, n=22; aged 6–12 years, n=24). Patients were treated for a median (range) of 1494 (175–1989) days and accumulated 546 (67–1011) EDs in the extension study. Median (quartile [Q]1; Q3) dose per prophylaxis infusion was 37.7 (33.1; 41.8) and 30.9 (29.1; 34.9) IU/kg for younger and older patients, respectively; annual prophylaxis dose was 4984 (3679; 6529) and 4089 (3283; 5555) IU/kg. Median (Q1; Q3) annualized number of total bleeds was 2.0 (0.2; 4.2) and 1.8 (0.5; 3.0) for younger and older patients, respectively; annualized total bleed rate was 3.0 (0; 6.0) and 0 (0; 6.4) for these patients in the main study. Median (Q1; Q3) annualized total bleeds within 48 hours of prophylaxis infusion was 0.8 (0; 1.7) and 1.0 (0.1; 1.6) in younger and older patients in the extension study. Response was excellent/good in 337/405 bleeds (83.2%); data were missing for 22 (5.4%) bleeds. Most bleeds (93.5%) were mild/moderate and were spontaneous (42.4%) or trauma related (53.6%). One patient experienced a mild treatment-related serious adverse event (transient very low FVIII inhibitor titer concurrent with acute infection and positive immunoglobulin G anticardiolipin) and remained in the extension study. No change in treatment was required, and the patient was clinically well.

Conclusions: Data from the LEOPOLD Kids extension study show that BAY 81-8973 provides safe and effective long-term prophylaxis in children with severe hemophilia A treated for a median of 4.1 years, confirming safety results observed in the main study.
**Integrated efficacy and safety analysis of Phase 2 and 3 studies with glecaprevir/pibrentasvir in patients with a history of bleeding disorders and chronic hepatitis C virus genotype 1–6-infection**

CRA 038

Frederik Nevens, MD, PhD, Jihad Slim, Yves Horsmans, Edward Gane, Mark Sulkowski, Armen Asatryan, Neddie Zadeikis, Stanley Wang, Yao Yu, Federico Mensa, Fred Poordad

**Objective**

Hepatitis C virus (HCV) infection is a significant health problem for patients with bleeding disorders due to the absence of highly effective HCV screening of blood products prior to the early 1990s. The aim of this analysis was to evaluate the safety and efficacy of the ribavirin-free regimen of glecaprevir/pibrentasvir (G/P) among patients with a history of bleeding disorders.

**Methods**

Data from 11 Phase 2 and 3 registrational studies conducted across 18 countries worldwide were included. HCV genotype (GT) 1–6-infected patients with compensated liver disease received G/P for 8, 12 or 16 weeks. The sustained virologic response 12 weeks after end of treatment (SVR12) rate and safety are reported.

**Results**

Sixty-two patients with history of bleeding disorders were identified, the most common disorder being hemophilia (37%, [23/62]). The remaining 63% (39/62) of patients had other disorders, including Von Willebrand disease. The cohort was 76% (47/62) male and 89% (54/62) white race with a mean age of 50.5 years (standard deviation ± 12.1). Additionally, 23% (14/62) had compensated cirrhosis. The HCV genotype breakdown among the patients was: GT1, 39%; GT2, 18%; GT3, 21%; GT4, 13%, GT5, 8%; GT6, 2%. In addition to bleeding disorders, a medical history of anemia was reported in 16% (10/62) of patients. SVR12 was achieved in 100% (62/62) of patients.

Adverse events (AEs) were reported in 68% (42/62) of patients, and 37% (23/62) of patients experienced an AE assessed as possibly related to study drugs. Serious AEs (SAE) were reported in 3 (5%) patients, none being assessed as related to the study drugs; 2 of these SAEs (1 per patient) were associated with the underlying bleeding disorder. There was 1 (2%) AE leading to discontinuation of study drug (dyspepsia); the patient went on to achieve SVR12. There was 1 (2%) non-treatment emergent death reported, occurring 60 days after the last dose of study drug.

Post-baseline grade ≥3 laboratory abnormalities occurred in 3 patients: one each in hemoglobin, aspartate aminotransferase and bilirubin (all n = 1; 2%), without concurrent elevations in alanine aminotransferase.

**Conclusions**

G/P achieved a 100% SVR12 rate in patients with a history of bleeding disorders and demonstrated a favorable safety profile, thus providing support for treatment of chronic HCV infection with the G/P regimen in this patient population.
Effective Long-term Prophylaxis with BAY 94-9027 in Previously Treated Children: Interim Results of the PROTECT VIII Kids Extension Study

CRA 039

Gili Kenet, Tina Biss, MacGregor Steele, Camila Linardi, Despina Tseneklidou-Stoeter, Kapil Saxena

Objective: BAY 94-9027 is an extended–half-life recombinant factor VIII (FVIII) product. In the PROTECT VIII Kids trial, BAY 94-9027 was efficacious for the prevention and treatment of bleeding episodes in previously treated children with severe hemophilia A. We report interim long-term efficacy and safety data from the PROTECT VIII Kids extension study.

Methods: In PROTECT VIII Kids, previously treated patients (PTPs) aged <12 years with severe hemophilia A received BAY 94-9027 prophylaxis twice weekly (25–60 IU/kg), every 5 days (45–60 IU/kg), or every 7 days (60 IU/kg). Patients completing ≥50 exposure days (EDs) and ≥6 months in the main study or a 12-week safety substudy (part 2) that enrolled PTPs aged <6 years could continue in the optional extension for an additional ≥50 EDs.

Summary: Fifty-nine of 73 patients treated with BAY 94-9027 in PROTECT VIII Kids (main study or part 2) continued in the extension (median [range] age at enrollment in the main study, 5.0 [2–11] years). At data cutoff (January 2018), patients had a median (range) of 1456 (351–1665) days in the trial (main study or part 2 plus extension). Patients in the extension received prophylaxis twice weekly (n=20), every 5 days (n=20), every 7 days (n=8), or switched prophylaxis frequency during the extension (variable frequency; n=11). Median (range) dose/infusion was 52.1 (19–62) IU/kg. Median annualized bleeding rate (ABR) for total bleeds was 1.8 for all patients and 0.8, 1.1, 2.1, and 3.2 for those treated twice weekly, every 5 days, every 7 days, or with varying frequency, respectively. Median ABR for joint bleeds in all patients was 0.7. During the extension, 3 patients (5.1%) experienced treatment-related adverse events (AEs) classified as mild (n=1), moderate (n=1), or severe (n=1). One patient discontinued because of a serious AE that was not related to treatment. No confirmed FVIII inhibitors or anti-PEG antibodies were observed; no patients had sustained levels of detectable PEG in plasma.

Conclusions: Long-term treatment (up to ~4.5 years) with BAY 94-9027 prophylaxis was efficacious and well tolerated in previously treated pediatric patients with severe hemophilia A.

PROTECT VIII Extension Trial Interim Data: Safety of >5 Years of Treatment With BAY 94-9027

CRA 040

Shadan Lalezari, Mark T. Reding, Heng Joo Ng, Despina Tseneklidou-Stoeter, Camila Linardi

Objective: BAY 94-9027 is an extended–half-life recombinant factor VIII (FVIII) product. In the PROTECT VIII study, BAY 94-9027 provided effective protection against bleeds and was well tolerated with twice-weekly, every-5-day, and every-7-day prophylaxis in patients with severe hemophilia A. We report interim safety data from the PROTECT VIII extension study evaluating long-term outcomes in patients using BAY 94-9027 prophylaxis for >5 years.

Methods: Previously treated patients aged 12 to 65 years with severe hemophilia A were enrolled in PROTECT VIII, in which they received BAY 94-9027 for 36 weeks on demand or as twice-weekly (30–40 IU/kg), every-5-day (45–60 IU/kg), or every-7-day (60 IU/kg) prophylaxis. Patients could subsequently participate in an extension study with the same or a different regimen. Adverse events
(AEs), anti-PEG antibodies, inhibitor development, renal safety, and plasma PEG levels were evaluated during the extension phase.

Summary: One hundred twenty-one of 134 patients from PROTECT VIII continued in the extension study receiving BAY 94-9027 either on demand (n=14) or as prophylaxis (n=107). At data cutoff (January 2018), patients aged 15 to 67 years at time of analysis (median age, 40 y) had a median (range) of 1420 (297–1965) days in the trial since enrollment and a median (range) of 223 (23–563) exposure days. Prophylaxis patients were treated either twice weekly (n=23), every 5 days (n=33), every 7 days (n=23), or switched frequency during the extension (n=28). Overall, 9 patients (7.4%) experienced treatment-related AEs during the extension classified as either mild (n=4), moderate (n=4), or severe (n=1). Two patients (1.7%) experienced 3 SAEs considered to be treatment-related (elevated liver function tests in a patient with hepatitis C; 2 incidences of back pain); these 2 patients discontinued the study. Transient low-titer anti-PEG antibodies were detected at a single visit in 8 patients but were not associated with clinical events. No patients developed FVIII inhibitors or had sustained levels of detectable PEG in plasma. No specific changes in renal parameters were observed.

Conclusions: During the ongoing PROTECT VIII extension, BAY 94-9027 prophylaxis was well tolerated for >5 years, and no patients developed FVIII inhibitors.

**Discrepant Hemophilia A: Single Institution Experience**

CRA 041

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Objective: Discrepant hemophilia is considered when there is discrepancy between factor VIII (FVIII) activity measurements and clinical bleeding phenotype. Diagnosis and management of discrepant hemophilia is challenging. Baseline FVIII activity level is crucial in determining the severity of hemophilia. Factor VIII activity can be measured by one stage assay (OSA), two stage assay, and two stage chromogenic substrate assay (CSA). One stage assay is currently the standard of care in US. Approximately 1/3 of non-severe hemophilia A patients demonstrate discrepancy of FVIII level between different assays. The criterion for discrepant hemophilia is defined as two fold difference between OSA and CSA. Discrepant hemophilia can lead to underestimation/overestimation of true factor activity and hence can affect clinical management. Appropriate diagnosis is crucial in non-severe hemophilia patients so appropriate treatment can be administered to control hemostasis. The aim of our study was to evaluate institutional experience with discrepant hemophilia A.

Methods: This case series included a retrospective chart review of patients with hemophilia A. The data collection involved: patient demography, disease characteristics, and laboratory testing and management. OSA was performed in local laboratory while CSA was performed at send out reference laboratory.

Results: We identified 4 cases of discrepant hemophilia A based on clinical phenotype. Following is the brief description of our cases: Case#1: Thirteen years old with history of T&A hemorrhage who later developed iliopsoas bleed. OSA showed normal FVIII activity but CSA confirmed the clinical diagnosis of mild hemophilia A. Complete resolution of hematoma achieved after FVIII treatment. Case #2: Seventeen years old with mild hemophilia A, multiple hemarthroses, and target joints. Bleeding phenotype was consistent with moderate hemophilia A which was later confirmed by CSA. He responded to FVIII prophylaxis therapy. Case #3: Thirty years old with extensive joint bleed post-surgery and normal FVIII activity by OSA. CSA confirmed diagnosis of mild hemophilia A. He responded to Stimate. Case #4: Fifty-three years old male whose diagnosis of mild hemophilia A was in question. Since his FVIII activity was normal by OSA, the treatment with FVIII concentrates was deferred prior to surgery.
He experienced post-operative bleeding which responded to FVIII concentrates. In our patients, OSA overestimated FVIII activity. Factor VIII activity by CSA confirmed the severity of hemophilia A which was consistent with patient’s bleeding phenotype. The revised diagnosis had direct impact on clinical decision making.

Conclusions: Our experience suggests that discrepant hemophilia is under-recognized in hemophilia population. It should be considered in differential diagnosis when there is discrepancy between bleeding phenotype and baseline FVIII activity. Lack of accessibility of CSA may have limited the awareness and ability to diagnose discrepant hemophilia in US. National efforts need to be invested to get CSA approved for clinical practice in US.

**Long-term clinical outcomes of rFVIIIIFc prophylaxis in adults 50 years of age or older with severe hemophilia A**

CRA 042

Doris Quon, MD, Shannon Jackson, Jing Feng, Nisha Jain

Objective: Recombinant factor VIII Fc fusion protein (rFVIIIIFc) is an extended half-life FVIII therapy approved for treatment of adults and children with hemophilia A. A-LONG parent (NCT01181128) and ASPIRE extension (NCT01454739) Phase 3 studies evaluated safety and efficacy of rFVIIIIFc for prevention and treatment of bleeding episodes for previously treated subjects with severe hemophilia A. A subgroup analysis was performed using A-LONG and ASPIRE interim data cut 3 and including subjects ≥50 years of age.

Methods: Subjects were assigned to one of the following treatment regimens: individualized prophylaxis (IP; 25–65 IU/kg rFVIIIIFc every 3–5 days), weekly prophylaxis (WP; 65 IU/kg every 7 days), modified prophylaxis (MP; tailored dosing if IP and WP were suboptimal), and episodic treatment (ET; on-demand dosage dependent on type and severity of bleeding episode). Subjects could change treatment groups at any time in ASPIRE and may appear in more than one treatment regimen. For this subgroup analysis outcomes included inhibitor development, the annualized bleeding rate (ABR), ABRs for subjects with target joints and target joint resolution, hemophilia quality of life questionnaire for adults (Hem-A-QoL), modified hemophilia joint health score (mHJHS), and cumulative exposure.

Summary: Twenty-one subjects ≥50 years of age (median [range] age, 57 [50–65] years) in A-LONG and/or ASPIRE received rFVIIIIFc (IP, n = 14; WP, n = 7; MP, n = 3; ET, n = 3). Baseline median (interquartile range [IQR]) ABR was 13 (6–22) for subjects who received pre-study prophylaxis and 27 (19–43) for subjects who received pre-study ET. No subjects developed inhibitors. Median (IQR) ABRs on treatment (with n ≥5) were 1.77 (0.35–5.26; IP) and 2.01 (0.25–4.76; WP). On-treatment ABRs (median [IQR]) for subjects with target joints (with n ≥5) were 1.39 (0.00–5.26; IP) and 2.01 (0.25–4.76; WP). All 49 evaluable target joints were resolved during prophylactic treatment. Mean (standard deviation) change from baseline in total Hem-A-QoL score and mHJHS was –1.9 (10.9) and –9.2 (11.43), respectively, for subjects who were always on prophylactic rFVIIIIFc treatment. Subjects had a median (IQR) of 4.05 (3.04–4.26) years of treatment with rFVIIIIFc and 293 (227–364) cumulative rFVIIIIFc exposure days. There was no increase in weekly factor consumption.

Conclusions: For previously treated subjects ≥50 years of age with severe hemophilia A, rFVIIIIFc prophylaxis for approximately 4 years resulted in low ABRs and improved/sustained joint health without inhibitor development and without increase in factor consumption, suggesting that rFVIIIIFc prophylaxis...
in adults ≥50 years of age has overall clinical benefits irrespective of baseline status. These data were similar to the overall study population.

### Long-term clinical outcomes of rFIXFc prophylaxis in adults 50 years of age or older with severe hemophilia B

CRA 043

Margaret Ragni, Jing Feng, Nisha Jain

Objective: Recombinant factor IX Fc fusion protein (rFIXFc) is an extended half-life therapy approved for the treatment of children and adults with hemophilia B. B-LONG parent (NCT01027364) and B-YOND extension (NCT01425723) Phase 3 studies evaluated the safety and efficacy of rFIXFc in prevention and treatment of bleeding in previously treated subjects with severe hemophilia B. This analysis evaluated clinical outcomes for over 3 years in a subgroup aged ≥50 years using B-LONG and B-YOND interim data cut 2.

Methods: Subjects were assigned to one of the following treatment regimens: weekly prophylaxis (WP; 20–100 IU/kg every 7 days), individualized interval prophylaxis (IP; 100 IU/kg every 8–16 days), modified prophylaxis (MP-tailored dosing if IP and WP were suboptimal), and episodic treatment (ET; on-demand dosage dependent on type and severity of bleeding episode). In B-YOND, subjects could change treatment groups at any time and may appear in more than one treatment regimen. For this subgroup analysis outcomes included inhibitor development, the annualized bleeding rate (ABR), ABRs for subjects with target joints and target joint resolution, hemophilia quality of life questionnaire for adults (Hem-A-QoL), cumulative exposure, and factor consumption.

Summary: Overall, 26 subjects ≥50 years of age (median [range], 56 [50–71] years) in B-LONG and/or B-YOND received rFIXFc (WP, n = 13; IP, n = 7; MP, n = 3; ET, n = 8). Baseline median (interquartile range [IQR]) ABR was 1 (0–5) and 20 (12–27) for subjects who received prophylaxis and on-demand treatment regimens, respectively. No subjects developed inhibitors. On-treatment overall ABRs (median [IQR]; with n ≥5) were 2.13 (1.16–4.35; WP), 1.14 (0.48–2.64; IP), and 12.83 (8.96–20.59; ET). On-treatment target joint ABR (median [IQR]; with n ≥5) was 3.17 (1.16–4.35; WP, n=9). All 19 target joints resolved with prophylactic treatment. Mean (standard deviation) total Hem-A-QoL score changed by −3.9 (10) points from baseline to last visit for 9 subjects always on prophylactic treatment during the parent and extension studies. Subjects had a median (IQR) of 3.42 (0.98–4.31) years of treatment with rFIXFc and 90 (44.0–198) cumulative rFIXFc exposure days. Factor consumption remained stable.

Conclusions: In subjects ≥50 years of age with severe hemophilia B, these data from over 3 years of rFIXFc prophylaxis demonstrated sustained bleed control and target joint resolution while maintaining consistent factor consumption. Results are consistent with the overall study population, suggesting that rFIXFc treatment provides long-term clinical benefits for individuals with severe hemophilia B, irrespective of age and presence of target joints.

### A Multicenter, Retrospective Data Collection Study on the Compassionate Use of a Plasma-Derived Factor X Concentrate to Treat Patients with Hereditary Factor X Deficiency

CRA 046
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Objective: Report results of an open-label international study that collected retrospective data on compassionate use of high-purity plasma-derived FX concentrate (pdFX) in subjects with hereditary factor X (FX) deficiency (FXD).

Methods: This study included subjects with hereditary FXD (irrespective of severity) who received compassionate use pdFX as routine prophylaxis (RP), on-demand (OD) treatment, short-term prevention, and/or perisurgical hemostatic cover. Dosing was at the investigator’s discretion and tailored to each patient. Data from date of first compassionate use dose until data cutoff (31 December 2015) were collected retrospectively.

Summary: All 15 enrolled subjects from 12 study centers received ≥1 pdFX dose for compassionate use. Of these, 13 subjects were aged ≥12 years (mean, 22.8 years) and 2 were aged <12 years, 8 (53.3%) were female, 12 (80.0%) were white, 3 (20.0%) were Asian. All subjects had moderate or severe FXD (FX activity [FX:C] <5 IU/dL).

Of the 15 patients, 7 received only RP, 7 received only OD, and 1 alternated between OD and RP. The 8 subjects on RP received a total of 1239 RP infusions (mean, 154.9 infusions/subject, range 39–492), with a mean dose/infusion/subject of 32.5 IU/kg. The 2 subjects aged <12 years received larger RP doses than the 6 older subjects (mean doses/infusion/subject of 51.1 vs 26.3 IU/kg).

Twelve subjects (8 OD, 4 RP; all aged ≥12 years) reported 88 bleeds (34 minor, 7 major, and 47 not rated); 37 bleeds were menorrhagic, 28 were traumatic, 17 were spontaneous, 4 were other, and 2 had unknown cause. pdFX efficacy was rated as effective for the 79 bleeds (including 1 subdural hematoma) treated with OD pdFX. Mean pdFX dose was 22.2 IU/kg/infusion/subject, with a mean of 9.5 infusions/subject to treat a bleed. More bleeds occurred in the OD than in the RP population.

Two subjects underwent 1 dental procedure each, with only 1 presurgical pdFX dose required per patient; a third surgery, a portacath insertion, required 6 infusions to prevent postoperative bleeding. Two successful pregnancies/childbirths were also reported, with no abnormal bleeding complications or efficacy/safety concerns reported.

The mean duration of compassionate use was 87.6 weeks for the 15 subjects, with a range of 15–211 weeks (0.3–4.0 years). Over the 1373 infusions administered across 25.2 subject-years, investigators rated overall pdFX efficacy as excellent in 14 (93.3%) subjects and good in 1 (6.7%) subject. No adverse drug reactions, safety concerns, infusion site reactions, tolerability issues, or inhibitor development were reported during pdFX compassionate use.

Conclusions: The higher bleed rate in OD versus RP use and the treatment duration (up to 4 years) support the efficacy and safety of pdFX demonstrated in prospective clinical studies and its continued use in the treatment of subjects with hereditary FXD.

BIVV001 – a novel, weekly dosing, VWF-independent, extended half-life FVIII therapy: first-in-human safety, tolerability, and pharmacokinetics

CRA 047
Objective: Prophylactic dosing with replacement factor products is the standard treatment for patients with severe hemophilia. Weekly dosing remains elusive for most patients with hemophilia A, owing to the short half-life that von Willebrand factor (VWF) imposes on FVIII. BIVV001 (recombinant factor VIII Fc fusion protein [rFVIIIFc]-VWF-XTEN) is a novel investigational FVIII therapy that is engineered to function independently of VWF. It leverages the Fc technology of rFVIIIFc and the addition of XTEN polypeptides with the goal of achieving once-weekly, or less frequent, dosing.

Methods: EXTEN-A (NCT03205163) is a phase 1/2a clinical study. Each patient received one dose of full-length rFVIII followed by one dose of BIVV001.

In the low-dose cohort, adult males aged 18–65 years with severe hemophilia A (defined as <1 IU/dL [<1%] endogenous FVIII) initially received a single intravenous (IV) dose of rFVIII. After a washout period, patients subsequently received a single dose of BIVV001 (25 IU/kg). FVIII activity was measured at various time points after both treatments. Patients underwent safety observation for 28 days following BIVV001 administration, which included inhibitor assessments 14 and 28 days post BIVV001 dosing. The low dose cohort is complete and a minimum of eight evaluable patients are planned to complete the high dose cohort. Primary endpoints are safety and tolerability of a single IV dose of BIVV001. Secondary analyses include assessment of pharmacokinetic (PK) parameters.

Summary: Preliminary PK and safety data of the EXTEN-A study representing the low-dose cohort will be presented. These will be the first clinical data reported for a novel approach to overcome the VWF-mediated FVIII activities in patients with hemophilia A.

Conclusions: Once-weekly, extended-dosing prophylaxis has not been achieved thus far for most patients with severe hemophilia A. BIVV001 is a novel extended half-life FVIII replacement therapy that is independent of the half-life ceiling imposed by VWF binding. It may enable weekly, or less frequent, dosing regimens. This study will provide the first BIVV001 safety and PK data in patients with hemophilia A.

Disclosures:
AS: Nothing to disclose
DVQ: Fees: Bayer, CSL Behring, Grifols, HEMA Biologics, Novo Nordisk, Pfizer, Shire. Fees for non-CME/CE services: Shire, Bioverativ, Grifols, Novo Nordisk, Shire
JMS: Fees: Emergent BioSolutions, UniQure, HEMA Biologics
SP, KR, NW, DR: Employee of Bioverativ

Pharmacokinetics, Efficacy, and Safety of High-Purity Factor X for Prophylactic Treatment of Hereditary Factor X Deficiency

CRA 048

Ri Liesner, James N. Huang, Kaan Kavakli, Steven K. Austin, Jeanette Payne, Kim Clark, Clive Dash, Chioma Akanezi, Nuria Bermejo, Martina Buehrlen
Objective: Hereditary factor X (FX) deficiency (FXD) is a rare autosomal recessive bleeding disorder characterized by mild-to-severe bleeding into mucous membranes, muscles, or joints. Plasma-derived FX (pdFX) is a high-purity FX concentrate approved in the US for on-demand treatment of hereditary FXD and in Europe for prophylactic and/or on-demand treatment of hereditary FXD. The objective of this work was to evaluate pharmacokinetic, efficacy, and safety data on pdFX for prophylactic treatment of hereditary FXD.

Methods: Results from 3 studies of patients with hereditary FXD are included. TEN01 was an efficacy/safety study in which pdFX pharmacokinetic data were obtained in subjects aged ≥12 years with moderate/severe FXD. Prophylactic efficacy/safety was evaluated using data from 2 studies: TEN02, a prospective, open-label, multicenter, nonrandomized study in pediatric patients [aged <12 years] with moderate/severe FXD, and TEN05, a retrospective, multicenter data-collection study in subjects who received pdFX on a compassionate-use basis. In TEN02, a 40–50 IU/kg twice-weekly pdFX dosing regimen was recommended, with dose and frequency adjusted over 6 weeks to maintain FX:C (clotting) levels ≥5 IU/dL; in TEN05, pdFX dosing was at the investigator’s discretion.

Summary: In TEN01 (N=16), mean terminal half-life and incremental recovery of pdFX were 29.4 h and 2.00 IU/dL per IU/kg, respectively. In a pharmacokinetic model of twice-weekly pdFX dosing, trough plasma FX:C ≥5 IU/dL was achieved (concentration <120 IU/dL) at a geometric mean dose of 24.5 IU/kg (95% CI, 19.8–30.4 IU/kg). In TEN02 and TEN05, 1776 prophylactic pdFX infusions (2,033,039 IU; 68,603 IU/kg) were administered to 17 subjects (9 in TEN02, 8 in TEN05). For the 9 TEN02 subjects (aged <12 years), there were 59.7 mean exposure days (EDs) per subject, with 9.3 infusions/month and a mean dose of 38.8 IU/kg per child. For the 8 TEN05 subjects (aged 1–32 years), there were 154.9 mean EDs per subject, with a mean dose of 32.5 IU/kg per subject. For all subjects, investigators rated pdFX prophylactic efficacy as excellent. In TEN02, 3 of 9 subjects experienced 10 bleeds (4 pdFX-treated). In TEN05, 4 of 8 subjects experienced 17 bleeds (10 pdFX-treated). In TEN02, 28 adverse events were reported in 8 children, none considered pdFX-related. In TEN05, no safety concerns were reported. No evidence of inhibitor development was seen in either study.

Conclusions: pdFX administered as routine prophylaxis was effective in preventing bleeds and was well tolerated in pediatric and adolescent/adult subjects at the doses and dose frequencies used in the above clinical trials.

An update on cognitive and behavior function in children and young adults with hemophilia: a 25-year journey from the Hemophilia Growth and Development Study to the current eTHINK study

CRA 051

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Objective: The Evolving Treatment of Hemophilia’s Impact on Neurodevelopment, Intelligence and Other Cognitive Functions (eTHINK) study aims to evaluate the impact of hemophilia on neurodevelopment and cognitive function through the use of validated instruments and to identify covariates that drive differences in neuropsychological performance.

Methods: A sample of at least 510 males aged 1-21 years (~25 per age) with hemophilia A or B (any severity, with or without inhibitors) will be enrolled in a cross-sectional, non-interventional study.
Following ethics review and informed consent, data collected will include a structured developmental and hemophilia history interview, a standardized neurologic examination, and a comprehensive neuropsychological assessment of cognitive/motor development (Bayley-III), intelligence (WPPSI-IV/WASI-II), attention/processing speed (CogState™), executive function (BRIEF-P/BRIEF2/BRIEF-A), mood and behavior (BASC-3), and adaptive behavior (ABAS-3). Assessments will include objective tests as well as parent and patient self-report rating scales. Z scores will be derived from published general population norms for each instrument and analyzed to develop hemophilia population specific norms. Secondary analysis for predictors of outcome will include regression modeling and chi-square tests of top vs bottom quartile responses.

Summary: Initiated in the early 1990s under Centers for Disease Control, Maternal and Child Health Bureau, and National Institutes of Health, the Hemophilia Growth and Development Study (HGDS) evaluated the impact of hemophilia on neurodevelopment, executive function, and intelligence. The 4-year observational study enrolled 333 patients from 14 US centers, aged 6-18 years at baseline (62% HIV+), who underwent annual/semi-annual comprehensive assessments including neurologic examination, neuroimaging (MRI), and neuropsychological assessment. Results suggested that hemophilia and HIV had independent effects at baseline and follow-up. Baseline neurologic examination findings were common, as were progressive abnormalities of gait/coordination. Imaging showed baseline CNS bleeds in 12% of patients and new CNS bleeds (2% per year), which often occurred in the absence of reported head trauma. HIV+ children were more likely to show lower scores on neuropsychological assessments. Academic/adaptive skills were lower than expected based on mean IQ, and more behavioral/emotional problems were seen, including attention abnormalities related to known/silent CNS bleeds. There was a large shift in mean scores in IQ and achievement for the children with more severe hemophilia. Six small studies published between 1996 and 2009 reported impacts on academic achievement, attention, and behavior.

Conclusions: HGDS established 25 years ago that hemophilia and HIV have independent effects on cognitive and behavioral function in children with hemophilia. Since then, standards of care in hemophilia treatment have changed significantly, but no follow-up studies have investigated whether these changes have affected the profile of neurocognitive outcomes in hemophilia. We therefore designed the eTHINK study to provide valuable insights into whether subgroups of children and young adults with hemophilia remain at risk for impaired neuropsychological outcomes.

Head-to-head pharmacokinetic comparisons of N9-GP with standard FIX and rFIXFc in patients with hemophilia B

CRA 054

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Objective: Nonacog beta pegol (N9-GP) and recombinant factor IX-Fc fusion protein (rFIXFc) are two modified rFIX compounds with extended half-lives compared with standard FIX products. We report results from two head-to-head, single-dose pharmacokinetic (PK) trials comparing N9-GP with standard FIX and rFIXFc in previously-treated patients (PTPs) with congenital hemophilia B (≤2% FIX).

Methods: paradigm™1 (NCT00956345) was a first human-dose trial in PTPs investigating the safety and PK of a single N9-GP dose. Sixteen PTPs (21-55 years) received one dose of their previous FIX product, followed by one dose of N9-GP at the same dose level (25, 50, or 100 IU/kg) with ≥7 days between doses. FIX activity was assessed up to 48 hours (standard FIX) or 168 hours (N9-GP) with additional samples at 2 and 4 weeks analyzed by one-stage clotting assay (TriniCLOT™) with product-specific
standard as calibrator. paradigm™7 (NCT00956345) was a multicenter, randomized, head-to-head trial where 15 patients (21-65 years) received single injections (50 IU/kg) of N9-GP and rFIXFc with ≥21 days between doses. FIX activity was assessed for up to 240 hours using a one-stage clotting assay (SynthAFax or Actin FSL) and a chromogenic assay (ROX factor IX) with normal human plasma as calibrator. The primary endpoint was area under the FIX activity–time curve from 0 to infinity, dose normalized to 50 IU/kg (AUC0-inf,norm).

Summary: In paradigm™1, the estimated terminal half-life of N9-GP was 93 hours, 4.8 times longer than for patients’ previous product. For N9-GP, estimated incremental recovery at 30 minutes (IR30min) (1.33 IU/dL per IU/kg) was 94% and 20% higher compared with rFIX and plasma-derived FIX (pdFIX), respectively. AUC0-inf,norm with N9-GP was 10.1 times and 7.7 times higher compared with rFIX and pdFIX, respectively. Time to 3% and 1% FIX activities was 16.2 and 22.5 days, respectively. In paradigm™7, the estimated AUC0-inf,norm measured with one-stage clotting assay was 4.4 times higher for N9-GP compared with rFIXFc (9656 versus 2199 IU*h/dL). IR30min was 2.2 times higher (1.7 versus 0.8 IU/dL per IU/kg), maximum activity, dose normalized to 50 IU/kg, was 2 times higher (91% versus 45%), and FIX activity at 168 hours was 5.8 times higher (19% versus 3%). N9-GP had a longer terminal half-life (103.2 versus 84.9 hours; ratio: 1.22). Results were similar when measuring FIX activity with chromogenic assay. One patient in paradigm™1 developed transient hypersensitivity symptoms during administration of N9-GP and was excluded from PK analyses. No patient developed inhibitors in either trial, and no unexpected safety concerns were identified.

Conclusion: These two single-dose PK trials show that N9-GP achieves higher FIX activity levels and greater AUC than pdFIX, rFIX, and rFIXFc through higher recovery and longer terminal half-life. These findings will support clinicians’ understanding of differences in PK between specific FIX products.

Congenital afibrinogenemia: a case report of perioperative hematological management during difficult orthopedic surgery

CRA 055

Tomas Simurda, MD

Background: Congenital afibrinogenemia is an autosomal recessive bleeding disorder referring to the total absence of fibrinogen measured by an antigenic assay. The commonest manifestation of the disease is bleeding from mucosal surfaces, however musculoskeletal bleeding, gynecologic and obstetric complications, spontaneous bleeding, bleeding after minor trauma and during interventional procedures or thromboembolic episodes.

Objective: We hereby report the only case of this disorder in Slovakia with a successful perioperative management of hemostasis during revision total hip arthroplasty.

Method and results: Preoperatively, the patient received fibrinogen concentrate in the dose of 75mg/kg, this dose increased the level of fibrinogen after 2 hours to corresponding 170mg/dL. During surgery, the patient received fibrinogen concentrate in the dose of 25mg/kg. The patient was administered an intraoperative transfusions because of blood loss. Twenty-four hours after surgery, the fibrinogen concentrate was applied in the patient at the dose 37.5 mg/kg every 8 hours. One day after surgery, we administered fibrinogen concentrate at the dose of 37.5 mg/kg every 12 hours with a targeted level of fibrinogen in the interval of 130-150mg/dL. We continued to reduce the dose of fibrinogen concentrate. The patient was discharged safely at 12th day after surgery with level of fibrinogen above 50mg/dL. The administration of fibrinogen concentrate was combined with low molecular weight heparin.

Conclusion: Our results in this patient with congenital afibrinogenemia who underwent the successful
repeated total left hip arthroplasty reaffirm the recommendation to tailor treatment to ensure a hemostasis balance between the replacement of clotting factor (fibrinogen concentrate) and thromboprophylaxis.

Change in cost and units consumed by people with factor VIII and factor IX deficiency after switching from a standard half-life product to an extended half-life product

CRA 057

Crystal Blankenship, PharmD, Mark Jacob, RN

Objective: To examine whether a difference exists in factor consumption and cost after a person with factor VIII or factor IX switches from a standard half-life (SHL) factor product to an extended half-life (EHL) factor product managed by a single specialty pharmacy.

Methods: All electronic medical records of patients with factor VIII or IX deficiencies who filled factor prescriptions with a single specialty pharmacy were reviewed. Data, including regimen, dosing and label instructions for fills of all recombinant and plasma-derived factor VIII and factor IX products between September 2013 and December 2017 were examined retrospectively. Adult patients (age ≥ 18 years) who switched from an SHL to an EHL product with 6 months of fill data available, for both periods before and after the initial EHL prescription was dispensed, were eligible for inclusion. Total cost was calculated using average wholesale price (AWP) using MediSpan (accessed June 1, 2018).

Summary: Sixty-three (63) people with factor VIII deficiency and 29 people with factor IX deficiency met study criteria by having a prescription for factor and switching from an SHL product to an EHL product, as well as 6 months of dispensing prior to and after the change. The mean cost of therapy with an SHL factor VIII product for 6 months was $272,192 versus $455,260 for 6 months after switching to an EHL factor VIII product, an increase of 67%. The mean number of units of an SHL factor VIII product dispensed was 141,934 units compared to 181,688 units of an EHL factor VIII product per person, which is an increase of 28%. The mean cost of therapy with an SHL factor IX product for 6 months was $234,146 versus $474,858 for the 6 months after switching to an EHL factor IX product, an increase of 100%. The mean number of units of an EHL factor IX product dispensed was 147,730 units compared to 124,509 of an EHL factor IX product, a decrease of 16%.

Conclusion: EHL products have several reported advantages over SHL products including longer interval between infusions, less frequent troughs (that may lead to decreased risk of bleeding episodes) and improved adherence. This analysis of dispensing data from a single specialty pharmacy indicates that change of prescription from SHL products to EHL products is associated with a higher cost of treatment. There are many more elements in factor prescribing that could contribute to future discussion.

Bypassing agent (BPA) use for the treatment of bleeds in persons with Hemophilia A (PwHA) with inhibitors before and after emicizumab prophylaxis in the HAVEN 1 study

CRA 058

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Background
Emicizumab was approved by the FDA in 2017 for routine prophylaxis in PwHA with inhibitors.
HAVEN 1, a phase III study in adolescent and adult PwHA with inhibitors, demonstrated that emicizumab prophylaxis significantly reduced annualized treated bleed rate by 87% (P<0.001) vs no prophylaxis. In this retrospective, post-hoc analysis, we examined the use of BPAs to treat breakthrough bleeds before and after emicizumab initiation in HAVEN 1.

Methods
HAVEN 1 patients were included from emicizumab-treated Arms A (previously treated with only episodic BPA) and C (previously treated with prophylactic BPA) and who had participated in the non-interventional study (NIS). In both studies, bleed and treatment data collection were comparable. In the study protocol, no guidance for the treatment of bleeds was provided; and hemostatic efficacy was not measured, thus optimal treatment of bleeds cannot be accurately assessed. Additionally, only data before October 7th, 2016 are included in this analysis to better represent treatment patterns before amended BPA guidance was provided. We describe the total number of patients and bleeds, number of infusions per bleed, and the cumulative dose/kg per bleed before and after emicizumab initiation.

Results
This analysis (48 total patients) included 24 patients each from Arm A and Arm C who participated in the NIS prior to enrollment in the HAVEN 1 trial. On average, patients received numerically fewer activated prothrombin complex concentration (aPCC) infusions with lower cumulative doses while on emicizumab as compared to prior to emicizumab administration. In Arm A, 11 bleeds were treated with aPCC resulting in an average of 1.2 aPCC infusions/bleed and an average cumulative aPCC dose/bleed of 95.9 U/kg while on emicizumab as compared to 136 bleeds resulting in an average of 1.7 infusions/bleed and cumulative dose 134 U/kg prior to emicizumab. Similar findings were seen in Arm C (bleeds, aPCC infusion/cumulative dose numbers: 14,2.3/166.6 U/kg on emicizumab compared to 205, 2.6/189 U/kg prior to emicizumab.) Fewer bleeds were treated with rFVIIa and no clear trend was seen regarding how rFVIIa was used to treat bleeds. In Arm A, 11 bleeds were treated with rFVIIa resulting in an average of 1.5 infusions/bleed and cumulative dose 212.2 µg/kg on emicizumab, vs 97 bleeds, 1.4 infusions/bleed and cumulative dose 181.6 µg/kg prior. In Arm C, 14 bleeds were treated with rFVIIa resulting in 4.4 infusions/bleed and cumulative dose 555.6 µg/kg on emicizumab vs 58 bleeds, 8.6 infusions/bleed and cumulative dose 1829 µg/kg prior.

Conclusions
Treatment of bleeds with aPCC in HAVEN 1 resulted in numerically fewer infusions and lower cumulative doses of aPCC per bleed while on emicizumab when compared to bleeds treated prior to emicizumab initiation. Treatment of bleeds with rFVIIa showed no clear trend.

Surgical Experience in Two Multicenter, Open-label Phase 3 Studies of Emicizumab in Persons with Hemophilia A with Inhibitors (HAVEN 1 and HAVEN 2)

CRA 062

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Objective
The HAVEN 1 and HAVEN 2 multi-center, open-label phase 3 studies investigated subcutaneous administration of emicizumab, a therapeutic bispecific antibody, in adults/adolescents and children with...
hemophilia A and inhibitors, respectively. Patients with planned surgeries, except for minor procedures, were excluded from both studies. However, unplanned emergency surgeries and minor procedures were permitted while receiving emicizumab. The objective of this report is to describe the hemostatic experience during surgeries that occurred in these studies.

Methods
We describe the combined surgical experiences from HAVEN 1 and HAVEN 2 (interim analysis), specifically the frequency of peri-operative bypassing agent (BPA) use and post-operative bleeding events in patients receiving emicizumab. Peri-operative management was at the investigators’ discretion; no specific guidance (per protocol) on surgical management was provided by the sponsor. Additionally, the type/frequency of surgical procedures and numbers of procedures associated with/without use of prophylactic BPAs are summarized. Frequency of post-operative bleeding, reported as bleeding events resulting from a surgery or procedure, as well as the doses of peri-operative BPAs are also described. Bleeding events were defined as in HAVEN 1 (Oldenburg et al. NEJM 2017).

Summary
Overall, 22 patients underwent 29 surgical procedures (24 procedures in 17 patients in HAVEN 1; 5 procedures in 5 patients in HAVEN 2). Twenty procedures (69%) were managed without prophylactic BPAs; 9 (31%) with prophylactic BPAs. Among the 29 surgeries, 6 were tooth extractions and 9 were central venous access device (CVAD)-related procedures (insertion/replacement/removal). Of the remaining 14 procedures, there was a right knee arthroscopy, synovectomy, debridement of arthrofibrosis, and chondroplasty in HAVEN 1 and a laparoscopic appendectomy in HAVEN 2.

Among the 20 surgeries not managed with prophylactic BPAs, 14 (70%) had no post-operative bleed(s), and 6 (30%) had post-operative bleeds (2 treated with BPAs; 4 not treated with BPAs). The two treated post-operative bleeds occurred with a tooth extraction and with the right knee arthroscopy, synovectomy, debridement of arthrofibrosis, and chondroplasty.

Among the 9 surgeries managed with prophylactic BPAs, 8 were managed with rFVIIa (mean dose [range]: 152.81 µg/kg [86.54–254.72 µg/kg]; median no. of injections, 1); 1 used prophylactic aPCC (single dose of 49.78 U/kg). Eight (89%) of these surgeries did not result in post-operative bleeding; 1 (11%) was a tooth extraction resulting in a single treated post-operative bleed.

Anti-fibrinolytics were used in 4/29 surgical procedures: 3 tooth extractions and 1 CVAD removal. Among the 7 surgeries that resulted in post-operative bleeding, 3 were managed with rFVIIa and none with aPCC.

Conclusions
In this analysis of patients with hemophilia A with inhibitors who underwent surgical procedures while receiving emicizumab prophylaxis, the majority of patients did not receive pre-operative BPA treatment. Post-operative bleeding requiring additional BPA treatment was only required in ~10% of patients.

Achievement of therapeutic levels of factor VIII activity following gene transfer with valoctocogene roxaparvovec (BMN 270): Long-term efficacy and safety results in patients with severe hemophilia A

CRA 063
Objective: As a single gene disorder of Factor VIII (FVIII), hemophilia A (HA) is an ideal candidate for gene therapy. We present results from an ongoing Phase 1/2 study of valoctocogene roxaparvovec (BMN 270; AAV5-FVIII-SQ) gene transfer in patients with severe HA.

Methods: As of 16 April 2018, 13 subjects (6E13 vg/kg, n=7; 4E13 vg/kg, n=6) received a single intravenous dose of valoctocogene roxaparvovec, an AAV5 vector containing a B-domain-deleted FVIII gene. Safety, efficacy, immunogenicity, and other endpoints are being evaluated.

Summary: FVIII activity is presented as median levels over 4-week intervals. In the 6E13 cohort, FVIII activity plateaued by Week 20 post-valoctocogene roxaparvovec, with median levels between Weeks 20-104 in the non-hemophilic range ([range] 46-122 IU/dL); Week 104 median FVIII activity was 46 IU/dL ([range] 6-145 IU/dL). In the 4E13 cohort, median [range] FVIII activity increased to just below the normal range (NR) at Week 52 [n=6]: 32 [3-59] IU/dL. Prior FVIII prophylaxis subjects had median [interquartile range, IQR] annualized FVIII infusions decline from 139 [122-157] (6E13) and 156 [126-183] (4E13) to 0 [0-0.4] and 0 [0-1] 4 weeks post-infusion through last follow-up; median [IQR] annualized bleeding rates post-infusion were 0 [0-0] in both cohorts (no bleeding episodes in 5 subjects in each cohort). Mild, grade 1, asymptomatic alanine aminotransferase (ALT) increases were reported in six of seven 6E13 and four of six 4E13 subjects; one 4E13 subject had a grade 2 ALT increase. Peak ALT levels ranged from 44-141 U/L (upper limit of normal=43 U/L). All subjects had a normal ALT level at last follow-up and all subjects were off of corticosteroid therapy. No subjects developed inhibitors to FVIII.

Conclusions: Gene transfer with valoctocogene roxaparvovec in subjects with severe HA resulted in sustained, clinically relevant FVIII activity that reduced self-reported bleeding and exogenous FVIII use 2 years post-infusion in the 6E13 cohort. FVIII activity in the 4E13 cohort was maintained at the upper range of mild HA 1 year post-infusion. Both doses enabled achievement of long-term therapeutic levels of FVIII activity and prevention of hemophilia-related bleeding with a favorable safety profile.
Psychosocial Issues:

Gender Differences in Parenting Stress and Social Support in Hemophilia Families

PI 029

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Objective
This research study examined gender differences in parenting stress and social support perceptions in families of children with hemophilia. This study sought to raise awareness of gender differences related to hemophilia parents’ stress and impact how they can better utilize social support networks as they raise their chronically ill child. Understanding the link among gender, stress, and perceptions of social support is important to help parents develop coping strategies to meet the unique challenges of caring for their child with hemophilia.

Methods
A quantitative, online survey design was used for this study. Two instruments measured the data: the Parenting Stress Index-Short Form (PSI-SF) measured parenting stress, and the Medical Outcome Study Social Support Survey (MOS-SSS) measured social support. A demographic questionnaire developed by the researcher was also used. Using a purposive sampling technique, mothers and fathers, over the age of 18, who have children with hemophilia, and reside in Maryland, Washington, DC, or northern Virginia were recruited for the study. Two research questions and related hypotheses were developed for the study. MANOVA was used to determine whether mothers and fathers of children with hemophilia differ with regard to level of perceived parenting stress and level of perceived social support.

Summary
The study revealed that mothers expressed significantly higher levels of parenting stress than did fathers. The findings also indicated that mothers’ perception of social support was significantly higher than that of fathers. No significant difference in parenting stress in the severity of the child’s hemophilia was found. The total sample consisted of 62 participants; 59.7% (n = 37) were mothers and 40.3% (n=25) fathers. Univariate testing found that mothers (M = 140.05) had a significantly higher level of perceived parenting stress than fathers (M = 121.08). Univariate testing found that mothers (M = 68.46) had a significantly higher level of perceived social support than fathers (M = 56.32). Parenting stress did not significantly differ for parents with children with mild to moderate hemophilia (M = 134) and parents with children with severe hemophilia (M = 131.64).

Conclusion
The findings from this study support the need for hemophilia advocates to have a more in-depth dialogue about parenting stress. No matter the severity of the child’s hemophilia, all hemophilia parents experience stress and are in need of gender-specific social support. Study results should equip hemophilia advocates with information that will add clarity to the implications of gender differences and how to relate these differences to understanding stress and providing gender-specific social support. The information from this study can be used to engage parents through programs and services that would help decrease stress and increase social support use to improve the health, wellness, and overall quality of life of the hemophilia family.
Empowering the Future of Hemophilia Through Swimming

PI 065

Annie Phillips, MSW

Swimming is an important life skill that benefits hemophilia patients medically and psychosocially. As a recipient of the NHF "Social work Excellence Grant" our HTC has implemented a swim program for patients with hemophilia and other bleeding disorders. We currently have 17 children enrolled and are also monitoring these children by conducting before and after physical therapy and QOL examinations.

The Relationship of Hope and Self-Compassion with Quality of Life among Individuals with Bleeding Disorders

PI 077

Darci Klein, MS, Sunnye Mayes, PhD, Carrick Carter, PsyD, Osman Khan, MD

Objective: The purpose of this study is to explore the bivariate and linear relationships between and among self-compassion, hope, and quality of life (QOL) among individuals with bleeding disorders. It is expected that these findings will guide the development of positive psychological interventions for this population.

Methods: The final sample included 86 participants (61.6% male) with a mean age of 29.7 years (SD = 14.42). The majority of participants were diagnosed with hemophilia A (44.2%) or von Willebrand disease (44.2%). Participants completed a demographic questionnaire, and 3 self-report measures: the Self-Compassion Scale (SCS; Neff, 2003), the Adult Hope Scale (AHS; Snyder et al., 1991), and the PedsQL Inventory – Core Generic (Varni et al., 1999). The SCS is a 26-item scale with 6 subscales. Three subcales assess positive components (self-kindness, common humanity, and mindfulness) and three subcales assess negative components (self-judgment, isolation, and over-identification). The AHS is a 12 item instrument comprised of two scales: agency (the ability to identify goals for the future) and pathways (the ability to identify means to achieve those identified goals). The PedsQL assesses physical, mental, social, and school/work domains of QOL, in addition to total QOL, assessing all subscales.

Summary: There was a significant and positive relationship between overall Quality of Life (QOL) and Overall Self-Compassion (r = .39, p < .001). There were significant and inverse bivariate relationships between Overall Quality of Life and each of the negative Self-Compassion components including Self-Judgement (r = -.44, p < .001), Isolation (r = -.35, p < .001), and Over-Identification (r = -.45, p < .001). A multiple regression analysis was conducted to explore the linear relationship of self-compassion and hope with QOL. Self-Compassion and hope were found to be significant concurrent predictors of QOL, F (2, 83) = 11.45, p < .001. Examination of the standardized beta weights revealed that hope (β = .31, t = 2.54, p < .05) was the only significant individual contributor to QOL.

Conclusions: Hope and self-compassion were identified as variables that contribute to QOL among individuals with bleeding disorders. Hope, defined as the ability to identify and work toward identified goals, was the strongest predictor of QOL in the model. These findings provide implications for the use of hope-increasing interventions as a means to improve QOL. These findings provide further evidence for the use of strengths-based strategies to enhance well-being within the bleeding disorder population.
Future studies could evaluate the effectiveness of specific interventions to improve hope and QOL among various subsets of the bleeding disorder community.
Inhibitors:

rFVIIIIFc for immune tolerance induction in severe hemophilia A subjects with inhibitors: a follow-up retrospective analysis

I 033

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Objective: We previously reported the outcome of a retrospective review of 19 subjects undergoing immune tolerance induction (ITI) with recombinant factor VIII Fc fusion protein (rFVIIIIFc) in subjects with severe hemophilia A with inhibitors. We showed that immune tolerance with rFVIIIIFc is possible and potentially faster in high-risk subjects undergoing first-time ITI, and in some subjects undergoing rescue ITI. A follow-up study continues monitoring the previous 19 subjects, as well as identifying new subjects, for a total of 25–30 subjects to be enrolled. Herein, we report interim results by monitoring the longer-term outcomes of the original 19 subjects, as well as 1 new subject.

Methods: Retrospective chart review at approximately 15 sites (US and Canada) in males with severe hemophilia A and high-titer inhibitors treated with rFVIIIIFc for ITI.

Summary: Of 20 subjects treated, 7 and 13 underwent first-time ITI and rescue ITI, respectively. Median peak historical Bethesda titer (BT) was 130.5 (range, 3–1126). At start of treatment, 6 of 7 first-time ITI subjects had BT >10, with 4 having BT >50. In total, 19 of 20 subjects represented a high-risk group for ITI failure.

Five of 7 first-time ITI subjects were tolerized, with faster tolerization in those treated with daily doses. The remaining 2 of 7 subjects had a decrease in BT and continue receiving rFVIIIIFc ITI.

For rescue ITI, the average number of prior ITI courses was 2.8 (range, 1–7). Regarding inhibitor titer, 7 of 13 subjects became BT-negative (1 of these subsequently became tolerized), 3 of 13 had a decrease in BT and continue receiving rFVIIIIFc ITI, and 3 of 13 have not yet had a decrease in BT (2 continue receiving rFVIIIIFc ITI, and 1 was deemed an ITI failure and switched to bypass therapy alone).

The trend towards rapid BT negativity with higher doses given daily continued in this follow-up study. Almost all, 6 of 7 subjects (2 first-time ITI and 4 rescue ITI) who received ≥130 U/kg/day achieved a negative BT. No adverse events related to rFVIIIIFc were reported.

Conclusions: This is a follow-up to a previously published study on the use of an extended half-life factor for ITI. In these subjects with high-risk features for ITI failure, a trend towards a rapid decrease of BT in first-time ITI continued, with 5 of 7 subjects tolerized. For rescue ITI, rFVIIIIFc showed therapeutic benefit in the subject population, including 1 subject who was successfully tolerized. Two prospective trials using rFVIIIIFc for ITI are ongoing.

Conflict of Interest: This study was sponsored by Bioverativ, a Sanofi company. E Tsao, J Dumont, N Jain, J Feng: Employee of and holds equity in Bioverativ, a Sanofi company. Z Alkhateeb: Employee of Trinity Partners. S Pipe: Consultant to Bioverativ, a Sanofi company. The views expressed in this abstract are those of the authors and do not reflect the official policy of the Department of Defense or U.S. Government.

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New Products:

Retrospective review of unplanned hospitalizations and perceived pain in children and adults with a diagnosis of factor ten deficiency receiving home infusions of commercially available factor ten

NP 022

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TITLE: Retrospective review of unplanned hospitalizations and perceived pain in children and adults with a diagnosis of factor ten deficiency receiving home infusions of commercially available factor ten.

AUTHORS: Randy Broyles, Peg Gruenemeier, Sandy Puckett and Julie Winton

BACKGROUND: Inherited factor X deficiency is an autosomal recessive bleeding disorder with an estimated occurrence rate of 1:1,000,000\(^1\). Historically, bleeding symptoms have been treated with topical therapies, antifibrinolytic agents, fresh frozen plasma (FFP) or plasma-derived FIX concentrates (PCCs). In 2015, the first factor X (FX) concentrate was approved in the U.S.

OBJECTIVE: This organization was interested in reviewing clinical outcomes such as perceived pain and unplanned hospitalizations of adults and children with FX disease currently being treated in the home with Coagadex®.

METHODS: This organization conducted a retrospective review of a population of seven adult and pediatric patients. Patients were surveyed for pain, bleeding episodes, hospitalizations/ER visits, dosing parameters and administration methods pre/post initiation of FX therapy. There were 3 children, 12 years old and under and four adults. Ages ranged from 5-60 years old with the average age of 27.9. There were five males and two females. The average length of treatment was 6.4 months. One patient was naïve, six converted from other therapies. Dose ranges administered by caregivers or self-infusion were 750 - 2800 IU (26-61 IU/Kg). One patient was on-demand and six were administering prophylaxis therapy.

RESULTS: There were two converted prophylaxis patients reported pain with PCC’s and none with FX; one on-demand naïve patient stated his pain was markedly improved with prn administration of FX; four converted prophylaxis patients with no prior pain history reported no changes in pain on FX therapy. For on-demand patients treating bleeding episodes, three reported a decrease in the number of bleeding episodes, three were unchanged and one reported one additional bleeding episode. A total of ten hospitalizations or emergency room visits were reported during the six months prior to initiation of FX treatment and only one in the six months following initiation of treatment.

CONCLUSION: Early recognition and home treatment with FX concentrate allows for prompt resolution of bleeding symptoms, decreased pain and decreased hospitalization or emergency room visits. Further investigation is needed to determine cost-savings for decreased hospitalization/ER visits.

References:
Real-world bleeding outcomes and adherence metrics among persons with hemophilia A and B receiving standard or extended half-life factor replacement products

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OBJECTIVE: We sought to explore real-world outcomes, such as annualized bleeding rate (ABR) and markers of adherence, in persons with hemophilia A (PwHA) or with hemophilia B (PwHB) who receive standard half-life (SHL) or extended half-life (EHL) factor VIII (FVIII) or factor IX (FIX) replacement products.

METHODS: We analyzed de-identified data from the Adelphi Disease Specific Programme (DSP) database, a patient health record–based survey of hematologists in the US and 5 European countries (France, Germany, Italy, Spain and the UK). Data were collected from May–November 2017 for male patients with moderate or severe HA or HB. Outcomes in the two groups of patients (SHL vs EHL) were compared and descriptive statistics were used to summarize results.

SUMMARY: A sample of 595 patients with HA or HB met the inclusion criteria (US, n=123; Europe, n=472). Age, weight, and body mass index (BMI) were similar between SHL and EHL groups for PwHA and PwHB on both continents. Higher ABR was noted consistently in Europe vs the US. Hemophilia A: Analysis included 101 patients from the US (SHL, n=64; EHL, n=37) and 360 patients from Europe (SHL, n=340; EHL, n=20). The ABR was similar between both groups on both continents (median: US, 1.0 SHL and 1.0 EHL; Europe, 1.0 SHL and 1.5 EHL; mean: US, 1.3 SHL and 1.2 EHL, P=0.68; Europe, 1.8 SHL and 1.7 EHL, P=0.76). The mean of the physician-reported ‘number of doses missed of the last 10 doses’ appeared to be numerically higher in the EHL vs the SHL group in the US (mean: 0.4 SHL and 1.6 EHL, P=0.13), whereas in Europe, the trend was reversed (mean: 0.7 SHL and 0.0 EHL, P=0.29). Hemophilia B: Analysis included 22 patients from the US (10 SHL; 12 EHL) and 112 patients from Europe (91 SHL; 21 EHL). The median ABR for PwHA and PwHB in the US was 1.0 (SHL) and 1.0 (EHL), and the mean was 1.6 SHL and 0.8 EHL (P=0.25); in Europe, the median ABR was 2.0 SHL and 1.0 EHL, and the mean was 2.2 SHL and 1.6 EHL, P=0.25. The mean of the physician-reported ‘number of doses missed of the last 10 doses’ was 0.8 SHL and 0.5 EHL (P=0.63) in the US and 0.6 SHL and 0.1 EHL (P=0.33) in Europe.

CONCLUSIONS: These preliminary real-world data, unadjusted for treatment regimen and inclusive of US and ex-US sampling, showed no clinically meaningful difference in ABR or adherence markers in PwHA or PwHB who received SHL versus EHL FVIII or FIX products. These observations may challenge assumptions regarding adherence and or clinical outcomes associated with SHL/EHL product selection among PwHA and PwHB. Further analyses should be explored.
Quality of Life/Outcomes Research:

Identification of Challenges and Coping Strategies in the Management of Bleeding Disorders, From the Patient Perspective

QLO 044

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Objective
We conducted a pilot study using a single open-ended question to elicit patient-perceived challenges and management strategies in individuals with bleeding disorders. The de-identified responses and themes expressed in this study were analyzed. The identification of perceived challenges and management strategies in individuals with bleeding disorders offers the opportunity to improve value based care.

Methods
This retrospective, cross-sectional cohort study used a sample of convenience at The Hemophilia Center at OHSU. Study population included 20 participants. Inclusion criteria included: ages seven to eighty nine, diagnosed with a bleeding disorder and seen during any outpatient Hemophilia Center clinic visit between March 1, 2017 and April 30, 2018. Participants were included if, during the course of their clinical care, they answered the question, “What is the most significant (or greatest) challenge you have in managing your bleeding disorder and what do you do about it?” Data extracted included question response, age, type and severity of bleeding disorder. Responses were analyzed for themes by the investigators and using qualitative data analysis software. Coded demographic data was correlated.

Summary
Seven challenge themes were identified: activity restrictions, infusions, emotion/stress, pain, future plans, education and access. Management themes included: self-advocacy, parent directed, activity modification or avoidance, acceptance, inquiry, asking for assistance, planning ahead, resiliency, and peer supports. Younger participants’ (9-17 years) challenges included activity restriction and infusions with management strategies of self-advocacy, activity avoidance and modification. Participants aged 18-57 years highlighted challenges with access to care, infusions, emotion/stress, pain, education and future planning. Management strategies in this group were focused on acceptance, planning ahead, peer support and resiliency. Analysis based on severity of bleeding disorder revealed that subjects with severe hemophilia reported infusions and activity restriction as their most significant challenge, with self-advocacy and activity modification management strategies. Participants with moderate hemophilia reported challenges centered on activity restriction and education of peers, with management strategies being self-advocacy and planning ahead. There were no differences in themes identified when analyzed based on type of bleeding disorder.

Conclusions
This study characterizes the unique challenges and management strategies described by individuals with bleeding disorders. The themes highlighted the importance of patient voice and can be used to inform individual care decisions.
Patient Satisfaction with US Hemophilia Treatment Centers: National Trends 2017

QLO 049

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Objective: Patient satisfaction with healthcare services is a measure of patient centeredness, influences treatment adherence, and increasingly affects reimbursement. In 2018, the US Hemophilia Treatment Center Network (USHTCN) launched the second national Patient Satisfaction Survey (PSS).

Methods: A Steering Committee and Regional HTC Coordinator work group updated, piloted, and finalized the two-page survey for patient self-administration online, at clinic, or at home, in English or Spanish, and mailed to households. Survey content and format were based on national health surveys to enhance comparability and scientific robustness. Questions included assessed patient demographics, satisfaction with team members, and care processes aligned with HRSA goals. An open ended question sought qualitative data. Respondents were anonymous but the HTC where they received care was identified. Participation was voluntary. Persons with genetic bleeding disorders who had HTC contact in 2017 were eligible. Since March 2018, HTCs sent surveys to approximately 31,650 households. Parents were asked to complete surveys for children under age 15. No reminders were sent. Data were entered and analyzed at a central site and aggregated at national, regional and HTC levels. Survey remains open through summer 2018.

Results: 4042 individuals (12.8%) from 125 (90%) of the 139 Centers in the USHTCN returned surveys by June 12, 2018. National analyses on 4042 surveys reveal that 93% - 98% were ‘always’ or ‘usually’ satisfied with HTC care processes: shared decision making (97%); care coordination (97%); obtaining understandable information (97%); getting timely services (95%); enough time with staff (97%); being treated respectfully (98%); and HTC Factor Program/Pharmacy (340b) (96%). 95% - 97% were ‘always’ or ‘usually’ satisfied with core HTC team members. 91% of 12-17 year olds were ‘always’ or ‘usually’ satisfied with HTC encouragement regarding becoming more independent, and 92% with how the HTC discussed caring for a bleeding disorder upon reaching adulthood. Insurance and language were ‘always’ or ‘usually’ a problem for 14% and 9% respectively. 31% of respondents were female and 10% Hispanic. 80% were Caucasian, 5% African-American, 4% Asian/Pacific Islander or Native Hawaiian, 4% Multiple races, and 7% did not respond. Over 60% had severe or moderate FVIII or FIX deficiency or VWD Type 3. Ages ranged from newborns to over 90 years: 37% under 18, 18% age 18 – 34, and 45% over age 35.

Conclusions: Implementing a National Patient Satisfaction Survey for the USHTCN remains feasible, is supported by HTCs nationally, and provides valuable information. Satisfaction with HTC services including 340B pharmacy is high. Insurance and language pose problems for 9-14%. Future analyses will examine additional national data and regional variation, and identify trends from the first national PSS conducted in 2014.

Persons With Hemophilia Reinforce Their Desire to be More Active: US Findings From an International Patient Survey

QLO 059

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Objectives: Increased access to prophylaxis has significantly improved quality of life for persons with hemophilia (PWH). However, PWH continue to experience acute and chronic disease manifestations, are still limited in physical and daily living activities and endure treatment burdens. A patient survey was developed to understand how PWH define different levels of activity throughout their daily lives, how hemophilia affects that activity, and the impact of treatment. The objective of this study was to understand current unmet needs and aspirations of PWH.

Methods: A 25-minute web-based survey was conducted on patient perception of impact of hemophilia on daily activities. The study is planned to enroll ~300 patients with moderate/severe hemophilia A, aged 2–65 years, from the US, France, Italy, and other EU countries. Patients <18 years required caregiver involvement. Surveys were administered after screening phone interviews. Quantitative results were reported by age group. A subanalysis of US patients was completed.

Summary: A total of 110 PWH (64 patients and 46 caregivers) from the US were recruited (88% severe hemophilia, 12% moderate hemophilia). Age ranges were 2-17 (n=46 [42%]), 18-30 (n=29 [26%]), and ≥31 years (n=35 [32%]). Patients were either on prophylaxis (88%) or on-demand treatment (12%). Survey results showed that being active was important across all age groups. However, 93% of patients wish to be more active in all aspects of life, including daily activities, indoor/gym and outdoor activities and contact/non-contact sports. Activities of daily living were most important across all age groups. Patients also reported adjusting activity levels due to past experience and fear of breakthrough bleeds, pain, or future joint damage. Activity levels were adjusted an average of 2 days a week (1-2 days for patients <30 years; 3-4 days for patients ≥31 years). Approximately 75% of patients believed that less pain and better protection would lead to more activity. Most respondents (85%) agreed that hemophilia made them stronger people. Patients who switched products did so in hope of longer periods of bleed protection for activities (36%), increased protection from bleeds (32%), and lower infusion frequency (32%).

Conclusions: Findings from this survey reinforce a desire by PWH to be more active, an aspiration considered achievable with less pain and greater bleed protection. The ultimate goal will allow for activity and treatment flexibility to become the new standard, allowing PWH to live fuller, more active lives. Collection of survey data from other countries is ongoing.

Joint health in patients with hemophilia A: analysis from the CHOICE survey

QLO 060

Wendy Owens, Anissa Cyhaniuk, Karina Raimundo, Anisha Patel, Elaine Chan

Background: One of the most serious long-term complications of hemophilia A (HA) is arthropathy. Hemophilic arthropathy can require a variety of joint procedures, including surgery, to alleviate arthropic symptoms, and severely decrease patients’ quality of life. The CHOICE Project was conducted in partnership between the US Centers for Disease Control and Prevention (CDC) and the Hemophilia Federation of America, a non-profit, community-based organization, to survey persons with bleeding disorders (PWBD), including HA. We describe the burden of arthropathy in patients with hemophilia A (PwHA) with and without inhibitors using data from CHOICE.

Methods: Demographic and clinical information was collected through CHOICE, a cross-sectional survey in the US from 04/2013- 07/2015 among adults (≥18 years) and caregivers of children with bleeding disorders. Participants were recruited to take a 20-minute survey in English or Spanish, online or on paper. As survey participants could choose not to respond to certain questions, sample size could vary by question. Self-reported joint-related outcomes and quality of life by inhibitors status among PwHA were
Results: A total of 439 PwHA were surveyed, of those, 11% (n=50) reported current inhibitors. Mean age was 27 years (median: 23), 83% were male, and 65% were white. The majority of PwHA reported severe HA (mild: 17%; moderate: 13%; severe: 69%). 92% of PwHA with inhibitors and 66% of PwHA without inhibitors reported severe HA. Joint bleed rates in the past year and history of major joint procedures were similar for PwHA with and without inhibitors, respectively (joint bleeds: 70% vs 75%, p: 0.44; joint replacement surgery: 21% vs 19%, p: 0.51; joint fusion: 6% vs 7%, p: 0.9; synovectomy: 26% vs 16%, p: 0.31). A proportion of PwHA reported joint problems (inhibitors: 20%, without inhibitors: 49%, p: 0.07) and about a third responded that these problems “always” or “frequently” limited their daily (work/school) and/or recreational activities, and/or self-care (inhibitors: 39%, without inhibitors: 26%, p:0.12). A few PwHA reported that they required help to perform self-care (inhibitors: 27%, without inhibitors: 11%, p: 0.09). The majority of PwHA reported use of over-the-counter pain medication in the last 30 days (inhibitors: 63%; without inhibitors: 65%, p: 0.86) and a few PwHA reported use of prescription pain medication over the same period (inhibitors: 19%, without inhibitors: 35%, p: 0.2).

Conclusion: Patients with hemophilia A with and without inhibitors can experience joint complications because of their disease. Avoiding joint bleeds is still an important goal of treatment to prevent long-term complications, regardless of disease severity and inhibitor status. Future analysis will examine treatment and care patterns among PwHA with joint damage.

**Patient perspectives on the value of reduced infusion frequency and longevity of protection for prophylactic treatment of hemophilia A**

QLO 068

Jane Wells, Sophia Kessabi, PharmD, Parth Vashi, Adam Gator, Chris Marshall, Theo Tritton

Objective:
Prophylactic Factor VIII (FVIII) replacement therapy can reduce bleeding and improve joint outcomes among people with severe hemophilia A. Most commonly used therapies require administration schedules of every 2 to 3 days. Such administration schedules can be burdensome to patients, impacting concepts that patients associate with health-related quality of life (HRQoL) and adherence. Extended half-life FVIII, such as BAY 94-9027, offer the potential for increased protection against bleeds with less frequent infusions. The objective of this study was to explore the impact of prolonged protection from bleeds and infusion frequency on HRQoL and treatment satisfaction from the perspective of patients with experience using an extended half-life recombinant FVIII therapy (BAY 94-9027).

Methods:
A qualitative interview study was conducted among patients taking part in an extension study to a phase 2/3 trial designed to assess the safety and efficacy of BAY 94-9027 in patients with severe hemophilia A; PROTECT VIII. During PROTECT VIII patients received open label treatment with BAY 94-9027 either on-demand to treat bleeds or prophylactically for 36 weeks, and could then continue with treatment as part of an extension study for a median of 3.9 years. For participation in these interviews, adult patients were recruited from study sites in Israel, the Netherlands and the United States. Patients from three treatment arms were recruited for interview: receiving prophylaxis once every 7 days, 5 days or twice weekly. All patients had previously been on regular prophylaxis prior to participation in the trial. Patients took part in 30 minute semi-structured telephone interviews that included open-ended questions in their local language. English transcripts were coded in Atlas.ti using thematic analysis.

Summary:
A total of 16 adult patients (age range 29-68 years) with representation from each treatment arm were interviewed. 13/16 patients were being treated with BAY 94-9027 at the time of interview. Feedback from patients indicated that the combination of reducing infusion frequency and longevity of protection are among the most important aspects influencing satisfaction with treatment and patient HRQoL. Patients on every 5 or 7 days infusions reported noticeable benefits to their daily lives including more freedom to schedule and complete activities and less planning required to adhere to the treatment regime. Patients reported an emotional benefit from the greater longevity of protection thus, giving patients confidence and peace-of-mind. As a result patients reported a greater ability to participate in usual activities (e.g. physical, household and social activities), with fewer absences from work and greater productivity.

Conclusions:
Infusion frequency and efficacy are important factors that can influence treatment satisfaction and HRQoL of men with Hemophilia A. BAY 94-9027 provides patients extended dosing intervals with longer protection, improving confidence in treatment and lessening impact on activities of daily living.

Impact of hemophilia on employment - Insights from the PROBE Study

QLO 076

Mark Skinner, JD, Chatree Chai-Adisaksopha, MD, Randall Curtis, MBA, Alfonso Iorio, MD Ph.D. FRCP, Michael Nichol, Ph.D., Declan Noone, MEng, Brian O'Mahony, David Page, Alexandra Pastarnak, Jeff Stonebraker, Ph.D.

Objective. The impact of hemophilia on working life, the ability to pursue a desired career or sustain full employment have been previously reported. The aim of this analysis was to seek a better understanding of hemophilia-related health problems likely to impact employment.

Methods. The analysis utilized data from the Patient Reported Outcomes Burdens and Experience (PROBE) study. Participants selected from among 7 possible responses (working full-time, working part-time, student full-time, student part-time, long-term disability, early retirement and other (e.g., unemployed, parental leave, retired)) to describe their current employment or school status. People with severe hemophilia A and B (PwSH) and controls with no bleeding disorder (NoBD) were compared for the proportion (percentage) reporting either working part-time due to their health or having retired early due to their health, the proportion reporting working full-time. Descriptive statistics were used to present the results as n (%), and odds ratio (95% CI) were calculated for the associations and assessed for their statistical significance.

Summary. Data from 1009 participants (550 PwSH, 458 NoBD) ≥age 18 from 21 countries was analyzed. Mean age of participants was 39 (14.4 SD) for PwSH and 45.3 (13.7 SD) for NoBD. 250 PwSH (45.5%) and 263 NoBD (57.4%) reported working full time; 86 PwSH (15.6%) and 80 NoBD (17.5%) reported working part-time. 27 of the 86 PwSH (31.4%) and 3 of the 80 NoBD (3.8%) reported working part-time due to health. 52 PwSH (9.5%) and 28 NoBD (6.1%) reported taking early retirement. 25 of the 52 PwSH (48.1%) and 1 of the 28 NoBD (3.6%) reported taking early retirement due to health. Analysis of the association between reporting a health-related problem and reporting to be working part-time or taking early retirement due to health include [odds ratio (95% CI), positive numbers indicating #times higher chance of being part-time/retired early]: use of mobility aids 77.7 (3.8-1645), acute or chronic pain 41.2 (2-831.8), use of pain medication 23 (2.05-258.1), participants with any health problems 22.5 (2-252.6), chronic pain 16.5 (1.5-179.2), difficulties with activities of daily living 16.5 (1.5-179.2), and history of joint surgery 7.3 (0.4-148).

Conclusion. PwSH are more likely to report working part-time or having taken early retirement due to
health-related problems than people with NoBD. Among the study population, we find a significant negative impact of hemophilia on employment status. PwSH is associated with a higher rate of working part-time or retiring early due to health than age-matched controls. Use of mobility aids, acute and chronic pain, difficulties with activities of daily living and history of joint surgery are associated with working part-time or retiring early.
Collaboration/Team Models:

Surveying Nurses’ Knowledge and Confidence of Discussing Oral Health with Patients with Bleeding Disorders

CTM 006

Stefanie VanDuine, BSDH, MSDH

Background: Many hemophilia treatment centers (HTCs) have a comprehensive care clinic in which a variety of providers see patients with bleeding disorders. Registered dental hygienists (RDHs) are, in some cases, a part of the comprehensive care clinic due to an access to dental care issue for those with bleeding disorders. The RDH may educate patients with bleeding disorders about oral health and act as a liaison between the patients’ hematologist and dentist. Objective: To determine if HTC nurses who work with RDHs are more confident in addressing patients’ oral health than nurses who do not. Methods: HTC nurses in the United States were sent a 10-item survey to evaluate presence of a RDH within the HTC, oral health related services provided to patients, and level of confidence and knowledge in discussing oral health with patients. IRB approval was obtained prior to data collection. Results: Response rate=49.7%. 45% of nurses that responded stated their HTC employs a RDH (n=31). There were not statistically significant differences in confidence levels between nurses working with a RDH versus those that do not. Data revealed that RDHs help patients find access to dental care, educate patients on oral health, and act as a liaison between the hematologist and the patient’s dentist. 19.4% of nurses that do not have a RDH do not help patients find access to dental care. Nurses that worked more often were more likely to help patients find access to dental care (p=0.01) and more confident in the relationship between oral health and bleeding disorders (p=0.001) and in discussing oral health with patients (p=0.002). Conclusions: Although there were no statistically significant differences in the two groups of nurses when measuring confidence, knowledge, and services provided, the study shed light into what services RDHs are providing within the comprehensive care setting. Due to the many complications patients with bleeding disorders can face during treatment, it would be beneficial to have a specialized oral health care provider incorporated into the HTC team to educate patients on preventing oral disease. This model of an RDH as a part of the comprehensive care clinic could translate into additional career opportunities for the RDH.
Peer Support/Outreach/Integration Models:

Bleeding Disorders Education Day for School Nurses

PSO 019

Ruthtolen Martinez, RN-BC, BSN, Terea Giannetta, DNP, Vinod Balasa, MD

Bleeding Disorders Education Day for School Nurses

Introduction and objective: As a nursing quality improvement project, the Hemophilia Treatment Center of Valley Children’s Hospital found an unmet need to educate school nurses regarding their responsibilities caring for children with bleeding disorders. Coordinated effort was develop and implemented for an eight county and 29 school district to address the needs in elementary to secondary schools. School nurses are often the first medical professionals to see children in our service area. At Valley Children’s, 25,000 of 146,000 unique patients in 2016 did not have primary care physicians. By surveying school districts, a half-day conference was organized for school nurses at Valley Children’s Hospital campus on Saturday August 27, 2016 from 8:00 am to 12:30 pm. Invitations were sent to school districts in eight counties served by our clinic. Valley Children’s funded the event at no cost to participants.

Materials and methods: To announce the conference, each VCH, HTC patient was given a flyer to return to their schools. Additionally, school districts within the eight-county service area were sent email, FAXs, mailed formal invitations or reached by phone.

Results: There were 29 school districts within the eight-county area represented. The 86 participants represented the following disciplines; 2 Nurse Administrators, 69 School Nurses; 7 Acute Care Nurses; 5 LVN’s; 1 Medical Assistant; 1 Teacher and 1 Health Aide. One participant traveled 130 miles. Physicians, pediatric nurse practitioners, registered nurses, and social workers gave presentations about hemophilia A/B, and von Willebrand Disease. Reviews of physiology and case data illustrated various issues school nurses encounter. Nurses were encouraged to question hospital staff and explain their unique needs. Particular attention focused on services clinic staff could offer. Pre-test and post-test analysis showed improvement from 57% to 91% correct knowledge, indicating a significant increase in nurses’ knowledge. Participants expressed the need to learn more about Hemophilia A/B, von Willebrand’s Disease, including Women and girls with bleeding disorders.

Improving the screening for and evaluation of bleeding disorders in the primary care setting

PSO 030

Jessica Daley, MD, Philippa Sprinz, MD, MSc, Caitlin Montcrieff

Background: Bleeding symptoms are a common complaint in pediatric primary care practices, with epistaxis and easy bruising being reported in 39% and 24% of children respectively. The assessment for bleeding disorders and interpretation of test results are frequent reasons for referrals to pediatric hematologists. The NHLBI has developed both validated questions for screening patients for bleeding disorders and an algorithm for further laboratory testing, due to the difficulty of differentiating benign bleeding symptoms from those indicative of a true bleeding disorder. When receiving referrals from primary care pediatricians (PCPs) to our hematology clinic, there is a high incidence of initial laboratory work up not part of those recommendations, as well as incorrect interpretation of the laboratory results.
Objective: To assess the approach and knowledge of PCPs in the evaluation of bleeding disorders, with clinical scenarios and test results, with the goal of improving the assessment of bleeding disorders by PCPs.

Design/Method: This was a three step study: we sent an electronic survey to 200 primary care providers in Rhode Island, including hospital based residents and community pediatricians asking for responses to the management of specific clinical scenarios. We then distributed a set of guidelines on how to evaluate for possible bleeding disorders to the same providers. Finally we emailed a second survey, after distribution of the guidelines, to assess for change in attitude and knowledge.

Results: We received a response rate of 20% to our initial survey - 67.5% resident response, 22.5% faculty at an academic center, 10% primary care attendings in the community, and 57% response rate from our initial responders to our second survey after intervention (11% of total initially surveyed) with similar breakdown of respondents. There was an increase in provider confidence in initial screening questions for bleeding disorder, in initial laboratory evaluation, and in interpretation of laboratory results. Additionally, there was an increase in correct response to survey questions regarding screening and interpretation of laboratory values.

Conclusion: There is clearly a need for pediatric hematologists to work alongside residents and community pediatricians to help with the evaluation of a possible bleeding disorder in an otherwise healthy child. Our response rate was low but did indicate that with guidelines, the providers were able to better understand how to approach this problem. We predict this intervention will help reduce unnecessary referrals to specialty clinics which utilize patient and provider time and resources. Our plan is to send an explanatory letter and the NHLBI guidelines to all primary care providers in RI. An additional goal is to track referrals and provide guidelines to providers who send referrals for evaluations that are not concerning for a bleeding disorder.

Understanding and finding symptomatic undiagnosed women

PSO 070

Kate Nammacher, MPH

Introduction and Objectives: Up to an estimated 1% of women in the United States have a bleeding disorder, but many with symptoms go undiagnosed. The National Hemophilia Foundation (NHF) conducted a needs assessment of currently diagnosed women to understand their path to diagnosis to help inform creation of an awareness campaign called Better You Know. Materials and Methods: In 2015, NHF fielded a survey of diagnosed women, yielding 184 responses. Informed by the needs assessment and input from a working group of medical providers and consumers, NHF launched the Better You Know campaign in 2016, which includes a website with a validated screening tool, resources on where to find providers on the path to diagnosis and treatment, outreach videos, social media posts, promotional postcards, paid media articles, accredited medical provider webinars, and mini-grants to select chapters for local outreach. Results: NHF found that women finally sought care for their symptoms for the following reasons: significant bleeding incident (surgery, childbirth, etc.), symptoms got too bad, or a family member was diagnosed. Women reported seeing the following providers first on their path to diagnosis: 38% hematologist; 23% primary care physician, 16% OB/GYN, and 15% pediatrician. About 80% of women also reported going to other people they know with a bleeding disorder for information and support. This lead to the creation of betteryouknow.org and other related campaign elements. From launch in July 2016 through October 2017, the website drew 4107 sessions, with 413 completing the
screening tool and 86% of those being at risk. There were 108 clinicians who received accreditation for the provider webinars. NHF has developed partnerships with feminine hygiene product companies to spread the word, and pushes out campaign messaging via social media, chapters and some paid media. Total audience (website visits, social media impressions, etc.) for the campaign to date is over 252,500,000. Conclusions: Undiagnosed women with bleeding disorders face true challenges due to their bleeding symptoms. NHF will continue to raise awareness with providers and women, utilizing findings for effective methods of communication and education, through the Better You Know campaign.

**Inhibitor Teams: building stronger connections and deeper learning**

**PSO 071**

Sarah Waite-Ardini, MA, Kate Nammacher, MPH

Introduction and Objectives: The National Hemophilia Foundation (NHF) has offered the Inhibitor Education Summits (also known as the summits), a live consumer education conference, annually for more than ten years. The summits are for people with hemophilia A or B with an active or tolerized inhibitor and their support network. In 2017, NHF introduced a new component to the conference: Inhibitor Teams. Materials and Methods: NHF met with the National Inhibitor Summit Steering Committee in 2016 and developed the idea of Inhibitor Teams as a way to better engage participants by connecting them with other members of the inhibitor community that they might not otherwise meet. Inhibitor Teams are small groups of randomly assigned participants that meet three times throughout the conference. Some Inhibitor Summit faculty and NHF staff moderated their pre-assigned group’s discussions as Inhibitor Team Leaders. Inhibitor Team Leaders were trained prior to each summit. Each participant’s badge included their Inhibitor Team name on it as a way for participants to easily identify their team members. The conference app was adapted to foster team member connection. Results: A total of 214 families (727 individuals) attended the summits in 2017. Of these families, 11.21% had never attended summit before, so connecting with fellow participants was particularly meaningful. Likewise, active inhibitors were represented in 56% of the families; through their Inhibitor Teams they could connect with others that have been or are going through the challenge of an active inhibitor. Participants on average agreed (4.19 on a 5 point Likert Scale) that they found value in meeting with their Inhibitor Team. Qualitative evaluation data collected also supports this. For example, one participant said, “teams were a great way to meet folks I otherwise may or may not have met or got [the] chance to talk to. Like meeting others that share same life experiences as myself and my family.” Conclusions: Inhibitor Teams were a welcomed addition to the Inhibitor Summit program in 2017 with participants finding value in the time spent with their team.

**Giving men with vwd a voice**

**PSO 072**

Kate Nammacher, MPH, Felix Olaya

Introduction and Objectives: Von Willebrand disease (VWD) is the most common bleeding disorder, affecting men and women equally. Despite this, awareness surrounding VWD is low. Outreach efforts often only target women, leaving many to assume VWD does not affect men. To begin changing this perception, the National Hemophilia Foundation (NHF) conducted a needs assessment to understand men’s awareness of VWD and experience getting a diagnosis for future programming. Materials and Methods: On behalf of NHF, The Harris Poll conducted a nationally representative online survey. From
2015 to 2016, 1,002 adult men in the US were interviewed to learn about their health behaviors and awareness of VWD. A second online survey was conducted by NHF targeting men who were diagnosed with VWD to learn about their path to diagnosis and the impact of VWD on their lives. This survey was given to adult men in the US from 2016 to 2017 and 49 responses were included in the analysis. Results: The Harris Poll found that only 28% of men say they are aware of VWD and 68% are not sure of the symptoms. Medical providers (69%) are the main sources the men turned to for information about their health, followed by internet sources (40%). The second survey found an average of 8 years from first symptoms to final diagnosis, with almost 60% of respondents diagnosed at 18 years of age and older. When asked what motivated them to seek medical care, 45% cited a significant bleeding incident. Over half reported limitations to work, physical and social activity. Medical providers were one of the most common sources of information and support for men with VWD and the first place men went for information. Conclusion: More awareness of VWD is needed and outreach focused online and to medical providers. Diagnosed men need more education and support surrounding their disorder. NHF will continue to pursue outreach efforts and creation of resources for men with VWD.

**Factor X deficiency consumer education program’s inaugural year**

PSO 073

Kate Nammacher, MPH, Sarah Waite-Ardini, MA

Introduction and Objectives: Factor X (FX) deficiency is an extremely rare factor deficiency, with an estimated incidence of 1 in 1 million births. Living with or supporting someone with a serious, extremely rare bleeding disorder can be stressful, especially when they don’t have a comprehensive understanding of their condition. There is little consumer education for people living with FX deficiency in the United States leaving this community with minimal support or education. As a result, the National Hemophilia Foundation (NHF) created The Power of Ten, a live educational conference. Materials and Methods: Families were recruited starting with outreach to local chapters, NHF’s social media channels and local HTCs. From there, initial families were recruited and then awareness of the program spread by word of mouth. A physician and a nurse were recruited to lead two separate educational sessions. One session focused on the medical aspects of FX deficiency (genetics, diagnosis and treatment). The other session, led by a nurse, focused on the psychosocial aspects of living with FX deficiency. Participants were asked to fill out an evaluation form at the end of the conference. Results: A total of 11 families attended the inaugural conference, which was a total of 43 individuals. Of those, 30 participants that completed an evaluation, on a 5 point Likert Scale, participants said they “agreed” to “strongly agreed” (4.76) with the following statement: “I found value in meeting with other people affected by FX deficiency.” From a qualitative perspective, 15 comments related to meeting other people affected by FX deficiency were found the participant evaluations. For example, one of these comments reflected the sentiment of the response: “It was amazing to meet others with FX deficiency for the first time. I'm finally not the only one!” Conclusions: The inaugural year of this program has allowed people affected with FX deficiency to meet and build a community of those affected by this rare and serious bleeding disorder.

**Bringing families affected by Factor XIII deficiency together for a novel educational program**

PSO 074
Introduction and Objectives: Factor XIII (FXIII) deficiency is an extremely rare factor deficiency, with an estimated incidence of 1 in 3 million births. Living with or supporting someone with a serious, extremely rare bleeding disorder can be stressful, especially when they don’t have a comprehensive understanding of their condition. There is little consumer education for people living with Factor XIII deficiency in the United States leaving this community with minimal support or education. As a result, the National Hemophilia Foundation (NHF) created the Strength in Numbers: F13 Family Conference, a live educational conference. The program has been held annually since 2015. Materials and Methods: Families were recruited through word of mouth and attended an on-site reception with other FXIII program participants, as well as two educational sessions in 2017. The first educational session focused on the basics of FXIII deficiency from a medical standpoint, while the second focused on the psychosocial aspects of living with FXIII deficiency. Results: Since 2015, the number of families in attendance increased by 33%. In 2017, a total of 16 families attended (46 individuals, 19 of which are affected). Not all families had previously attended—37.5% of families were new to the program in 2017 and 50% were new in 2016. Overall, participants find value in the program for two reasons: meeting and bonding with people affected by FXIII deficiency and learning alongside of them. In 2017, overall participants said they strongly agreed with the value in meeting other people affected by FXIII deficiency. They also strongly agreed that the educational sessions were relevant to them. One participant’s comments sum up both of these sentiments: “Finding the patients and what symptoms they have had and just the information on FXIII helps when going back home.” Conclusions: The growth of this program alone demonstrates the need for consumer education for those living with FXIII deficiency. The program has not only brought people affected with FXIII deficiency together, but it has helped build ongoing networks of social support.
Law/Ethics/Health Policy:

NHF’s State Based Advocacy Coalitions (SBAC) Program

LEH 075

Nathan Schaefer, Brendan Hayes, Bill Robie

Introduction and Objective:
The National Hemophilia Foundation (NHF) consistently prioritizes the need for consumers to engage with their legislative and administrative officials regarding access to care needs/issues affecting those with bleeding disorders. This is true at the national level, but also locally. The NHF State Based Advocacy Coalition (SBAC) program began in 2012 with 5 key states to respond to various advocacy challenges affecting access to care for the bleeding disorders community. Now in its sixth year, the NHF SBAC program is providing support to 21 states that include over 30 NHF chapters, representing thousands of families with bleeding disorders across the USA.

Materials and Methods:
The SBAC program requires the following elements.

Year One:
• Host a Strategic Advocacy Strategy Session with NHF
• Identify state advocacy priorities for the year
• Establish an Advocacy Committee with appropriate leadership positions filled (chair, vice chair, secretary etc.) that meets monthly
• Develop a 3-year Strategic Advocacy Plan
• Host an Advocacy Day at the state capital with training for volunteer advocates

Year Two:
• Demonstrate year ‘round advocacy through chapter programming
• Define a mechanism for advocacy communications (newsletter, social media, web)
• Adhere to a regularly scheduled advocacy committee meeting (monthly and quarterly)
• Host a stakeholder meeting in preparation for the upcoming legislative season (fall)
• Update the coalition’s Strategic Advocacy Plan yearly
• Demonstrate success in growing grassroots advocates (grasped concepts of Advocacy 101, functioning in a leadership capacity for chapter’s advocacy efforts, etc.)

Results:
One measure of success of the SBAC program is the increased interest in advocacy by NHF chapters and an expressed desire to be part of the program. Our collective presence at state capitals around the country and relationship building with agency officials has substantially increased awareness and improved access to care. An important byproduct of the program is record breaking participation from grassroots advocates at both state and federal levels.

Conclusions:
We have found the greatest success has come from the technical expertise that is offered to chapters along with the opportunity for ongoing education and networking. Another key area of success stems from the accountability to objectives required to participate in the program.
Do Hemophilia Treatment Centers Want Or Need A Regional Ethics Committee?

LEH 078

Kristie Ostash, MD

Objective:
The NHF Ethics Working Group’s (EWG) mission is to promote integrity and ethical behavior in the bleedings community. The EWG wants to determine if our Hemophilia Treatment Centers (HTCs) want or need a regional ethics committee to help work through ethical dilemmas.

Method:
A 16 question needs assessment survey was written and distributed to all 12 regional HTC’s healthcare providers within NHF’s database. The data was collected from January 25, 2018 thru March 6, 2018 and analyzed via Monkey Survey.

Summary of Results:
The survey was distributed to 1322 HTC staff members, 192 responded to the survey, with a response rate of 14.4%. All 12 HTC regions had participants..

A variety of professionals participated in the survey: nurses (26%), social workers (23%), physicians (16%), physical therapist (12%) advanced practice providers (9%) & non-clinical staff (3%).

Ethical dilemmas were difficult to resolve according to 61% of participants while 9% thought they were easy to resolve. Ethical dilemmas were also described by 32% as confusing, 45% as frustrating and 60% as interesting.

The frequency of ethical dilemmas varied; 43% monthly, 25% yearly, 23% weekly and 5% daily.

When resolving an ethical dilemma 22% resolved them on their own. Others liked to collaborate with colleagues (96%), consult with their institution’s ethics committee (36%), consult the NHF EWG (4%) and 2% avoided them. When dealing with an ethical dilemma, most people were sometimes comfortable (42%), usually comfortable (41%), always comfortable (9%) and never comfortable (6 %).

When our respondents consulted their colleagues, 13% responded that their concerns were always adequately addressed, 53% usually, 28% sometimes, 2% never and 3% n/a.

Over 50% of our respondents have never consulted their institution’s ethics committee.

When asked if a confidential regional ethics committee would be a valuable HTC resource only 8% responded no.

If there was a regional ethics committee, 27% said they would like to be involved and 40% responded maybe.

Only 45% of our participants knew of NHF Ethics Working Group and 70% were interested in a case based ethical presentation by the NHF Ethics Working Group.

Conclusion:
Ethical dilemmas occur frequently and are difficult to resolve. Most people did not consult their institution’s ethics committees and the majority of participants didn’t know that NHF had an ethics working group. There is interested in ethical educational presentations/discussions with the EWG. Participants thought that a regional ethics committee would be a valuable HTC resource and greater than a quarter of the participants showed interested in being involved with the regional ethics committee.