Enhanced properties of blood clotting factor IX variants with elevated membrane affinity

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Objective: Blood Coagulation factor IX is a member of a family of vitamin K-dependent proteins that contain multiple gamma-carboxyglutamic acid (Gla) residues in homologous amino terminal Gla domains. The second gamma-carboxyl is incorporated with participation of Vitamin K cofactor. Without Gla, members of this protein family do not bind calcium or phospholipid and are biologically inactive. Despite sequence homology, individual members of the vitamin K-dependent protein family display a range of affinities for phospholipid membranes. Factor IX is among those with lowest affinity. The objective of this study was to generate factor IX molecules with enhanced membrane affinity and enhanced function.

Methods: This report describes site-directed mutation of the factor IX polypeptide. Three residue changes near the amino terminal were examined individually and in combination (Y1A/G4Y/K5L). Proteins were expressed in K293 cells and were purified to homogeneity. Mass spectrometry analysis indicated complete carboxylation of all variants produced.

Summary: The triple mutant resulted in a factor IX protein with 27-fold increased membrane affinity, comparable to the highest affinity proteins of this family. The Y1A and G4Y changes showed synergy. That is, in the membrane binding assay Y1A showing no benefit over wild type protein while G4Y showed 2.5-fold enhancement and 4.3-fold when combined with Y1A. The K5L offered improvement that was not affected by other sites. The triple variant factor IX showed approximately 10-fold enhanced rate of activation by Tissue factor-factor VIIa. Activated factor IXa showed 10- to 25-fold increase in function in various blood coagulation assays. In the absence of factor VIII, the triple factor IXa variant displayed 6% of the blood clotting activity observed in the presence of factor VIII. This latter activity may allow variant factor IXa to act in a manner that bypasses factor VIII. The zymogen of the triple mutant gave detectable coagulation in a whole blood clotting assay in factor VIII-deficient blood. All of the functional changes were dependent on use of membranes that mimicked biological membrane affinity for vitamin K-dependent proteins. Standard assay kits often involve proprietary membrane compositions that provide very high affinity for vitamin K proteins and mask the true benefit of these variants.

Conclusions: Overall, factor IX/IXa molecules with enhanced membrane binding affinity may have several attractive properties for possible use in blood coagulation therapies, either by protein replacement, bypass agent or genetic modification. They also offer novel reagents for study of blood clotting mechanisms.
The cytokine storm which follows joint bleeding: identifying a plasma signature of joint bleeding

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Objective: Joint bleeding is the most common site of serious hemorrhage in patients with severe hemophilia and results in a chronic arthritis characterized by synovial inflammation and vascularization then cartilage and bone destruction. The mechanisms by which these sequelae of bleeding occur are not known. We hypothesize that inflammatory and angiogenic mediators play key roles in these processes. Here we describe our initial efforts to define the pattern of cytokine expression in plasma of experimental mice and compare these with the histological changes in joints following hemarthrosis.

Methods: Joint bleeding was induced in mice deficient in factor VIII expression and then quantified on day 1, 2 and 3 using a visual bleeding scoring system. Mice with similar degrees of joint bleeding were subsequently used in experimental groups and compared to unaffected control animals. Mice were sacrificed from 1-30 days after hemarthrosis and the plasma collected for analysis of 15 cytokines involved in inflammation and 27 in angiogenesis pathways using a multiplex immunoassay (Luminex).

Summary: The results of these experiments demonstrate that a cytokine storm ensues which can be identified in the plasma of mice following induction of joint bleeding. The pattern of cytokine expression may provide a signature by which a biomarker of joint bleeding can be identified. The utility of such biomarker/s in clinical practice would enhance the ability to identify subclinical, micro-joint hemorrhages providing an opportunity for earlier intervention.
The cytokine storm which follows joint bleeding: relationship of plasma cytokine concentrations and joint tissue gene expression in acute stage of hemarthrosis

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Objective: Joint bleeding is the most common site of serious hemorrhage in patients with severe hemophilia and results in a chronic arthritis characterized by synovial inflammation and vascularization then cartilage and bone destruction. The mechanisms by which these sequelae of bleeding occur are not known. We hypothesize that inflammatory and angiogenic mediators play key roles in these processes. Here we describe the relationship of mouse joint tissue gene expression and plasma cytokine concentrations during the first 3 days following hemarthrosis.

Methods: Hemarthrosis was induced in factor VIII deficient mice and those with similar degrees of joint bleeding were selected for further analyses. Mice were sacrificed 1, 2 or 3 days after hemarthrosis and the joint tissue and plasma collected. The same strain of mice with unaffected joints served as a control. The joint tissue expression of 83 genes was determined using Mouse Inflammatory Cytokines & Receptors PCR Array kit (SABioscience) and the plasma concentrations of 32 cytokines were determined using a multiplex immunoassay (Luminex).

Summary: The patterns of expression of genes involved in inflammation pathways demonstrate that the source of the plasma cytokine storm is from the joint tissue, likely provoked by the joint bleeding.
Association of Overweight and Obesity with the Use of Self and Home-based Infusion Therapy among Males with Hemophilia

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Objective: The ability to infuse clotting factor at home allows persons with hemophilia to treat bleeding episodes promptly and conveniently and enhances adherence to prophylactic regimens. Self-infusion promotes the treatment of bleeds with minimal delay and affords patients increased independence. However, an elevated body mass index (BMI) may make venipuncture more difficult. We sought to learn whether above-normal BMI is associated with decreased use of home infusion treatment (HI) and self-infusion (SI) of factor among males with hemophilia in the United States.

Methods: We analyzed data from 10,814 males with hemophilia A and B (45% with severe disease) aged 6-79 years enrolled in the Centers for Disease Control and Prevention Universal Data Collection surveillance project between 1998 and 2008. Exclusion criteria also included a diagnosis of HIV or symptomatic liver disease, inhibitor titer ≥5 Bethesda units and immune tolerance therapy at the time of visit. The prevalence of HI and SI was calculated for each level of demographic and clinical characteristics. Bivariate relationships were assessed using Chi-square tests; independent associations between BMI and the use of HI and SI were evaluated using logistic regression.

Summary: Fifty percent of hemophilia males in the sample were overweight or obese, similar to rates reported among the general US population. Twenty percent of children and 22% of teens were obese, as were 28% of adults. Fifteen percent of youths aged 6-19 had extreme, or morbid, obesity (BMI-for-age ≥97%). Overall, 70% of the sample used HI; 44% of those who used HI also used SI. Overweight and obese individuals were each less likely to use HI than those of normal weight (OR 0.8; 95% CI, 0.7-1.0 and OR 0.7; 95% CI 0.6-0.8, respectively). Obese teens and adults were also less likely to practice SI than teens and adults of normal weight (OR 0.8; 95% CI, 0.7-0.9 for each). SI use declined among the entire sample after age 40, regardless of severity or treatment regimen.

Conclusions: This analysis suggests that obese persons with hemophilia are less likely to use HI and SI, possibly because of the increased difficulty of venipuncture caused by adiposity. The inability to perform HI and SI may lead to a delay in treatment of bleeding episodes and reduce the effectiveness of the treatment, placing those with above-normal BMI at increased risk of complications from hemophilia.
Characteristics and Treatment Patterns of Medicaid Patients with Hemophilia A Receiving Prophylaxis vs. On-Demand Factor VIII Therapy

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Objective: Few data sources contain sufficient patient count to study the real-world efficacy of factor VIII (FVIII) therapy in patients with hemophilia A (HA). Health insurance claims databases offer that opportunity. This study sought to identify patients with HA receiving prophylaxis versus on-demand FVIII regimens and describe their characteristics and treatment patterns utilizing data from Medicaid programs.

Methods: Healthcare claims from Florida, Iowa, Kansas, New Jersey, and Missouri Medicaid programs covering 1996 to 2011 were used. Patients with ≥2 HA diagnoses (ICD-9 286.0), ≥2 dispensings for FVIII after age 2, continuous Medicaid eligibility ≥6 months before (baseline period) and ≥12 months after the first FVIII fill, and no evidence of bypassing agents or desmopressin use were included. Prophylaxis and on-demand regimens were identified using an algorithm calibrated to distinguish the regimens within five age groups based on the annual total units of FVIII dispensed regardless of the severity level: 16,480 IU (2–7 years old); 32,770 IU (8–12); 66,920 IU (12–16); 98,349 IU (17–21); 204,552 IU (≥22). The algorithm was developed using prescription records of 1,311 patients from three U.S. specialty pharmacy databases. FVIII treatment patterns and patient demographic and clinical characteristics were examined.

Summary: From the approximately 14.8 million covered lives encompassed in the five Medicaid databases, a total of 2,408 (0.016%) patients with ≥2 diagnoses for HA were identified; 448 met the study eligibility criteria with 229 (51.1%) patients receiving prophylaxis FVIII and 219 (48.9%) patients receiving on-demand FVIII. Younger patients were more likely to receive prophylaxis therapy (percent by age group: 61% [2–7]; 70% [8–12]; 63% [12–16]; 51% [17–21]; 20% [22+], mean (SD) age, prophylaxis: 10.8 (9.8) years old; on-demand: 18.7 (14.4) years old). Mean (range) observation period was 5.6 (1.0-15.2) years for prophylaxis patients and 5.6 (1.0-15.2) years for on-demand patients.

Conclusions: In a population of 448 Medicaid patients with HA, this study found that 51.1% and 48.9% patients received prophylaxis and on-demand FVIII regimens, respectively. With the average observation of patients for more than 5.5 years, this database offers the potential for long-term follow-up to assess the relative efficacy of prophylaxis versus on-demand FVIII regimens in decreasing the incidence of bleeding events. These evidences from claims databases are critical to payers and decision makers as they reflect real-world clinical practice and patterns of FVIII use. Information on HA severity level was not available in the databases used.
Low inhibitor incidence in previously untreated patients with severe haemophilia A treated with octanate® - Update from the PUP-GCP clinical trial

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Background: Octanate is a highly purified, double virus inactivated, human plasma-derived factor VIII (FVIII) concentrate with all coagulation FVIII bound to its natural stabilizer VWF in a VWF:RCo/FVIII:C ratio of approximately 0.4. Five prospective GCP studies with octanate were conducted in 77 previously treated patients (PTPs) with severe haemophilia A. None of these 77 PTPs developed an inhibitor.

Aim: To assess the immunogenicity in previously untreated patients (PUPs), a prospective clinical trial has been initiated in 2000. This included 48 PUPs with severe hemophilia A after treatment with octanate for an observational period of 100 exposure days and at least 6 months.

Methods: Patients with severe haemophilia A without previous exposure to FVIII or FVIII containing products were enrolled. Efficacy and tolerability are assessed by a 4-point verbal rating scale. Inhibitor assay, according to modified Bethesda method is tested pre-treatment, every 3-4 exposure days (ED 1-20) and every 10 EDs (ED 21-100) but at minimum every three months.

Results: Two of 48 (4.2%) subjects receiving treatment developed clinically relevant inhibitor titers over the course of the study. Another two displayed inhibitors that disappeared spontaneously without change of dose or dosing interval. All inhibitors developed under on-demand treatment and before ED 50. From the 48 subjects, 42 had exceeded 50 EDs at the time of this analysis. octanate was well-tolerated and the adverse event profile was consistent with the population studied. The haemostatic efficacy in prophylaxis and treatment of bleeding were generally rated as “excellent” and no complication was reported for any surgical treatment.

Conclusion: Despite frequent inhibitor testing and predominant on-demand treatment, octanate showed a low rate of clinically relevant inhibitor formation (4.2%) in this cohort of patients.
Assuring the Virus Safety of Source Plasma for Further Manufacturing by Establishing Epidemiological Limits in Donor Centers

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Objective: For any given plasma-derived clotting factor concentrate with effective virus reduction, the margin of safety regarding the blood-transmissible viruses HIV, HCV, and HBV depends on the virus load in the pooled donations before further manufacturing and the epidemiology of the donor population. The objective of this study was to define an upper nucleic acid testing (NAT)-only incidence rate in the donor population (per donor center) in order to reach a defined minimum safety margin per final vial of a clotting factor product produced from normal source plasma (NSP).

Methods: A Monte Carlo simulation model was developed to estimate the risk of virus contamination of a plasma pool for fractionation derived from NSP; the contamination rate is due to donations with virus loads below the limit of detection of sensitive NAT/PCR assays for HIV, HCV, and HBV. A defined high safety margin factor regarding virus safety of a theoretical “worst case” product is used, combined with a minimal virus reduction capacity for the above mentioned viruses, to calculate an acceptable epidemiology for these relevant blood-borne viruses in donor centers. This calculation takes into account test sensitivity of NAT, frequency of donation, virus doubling time, and the 60-day inventory hold, which allows removal of donations when a donor converts to positive for a virus.

Summary: The model permits estimates of likelihood of contamination at different incidence rates for the 3 different viruses. At an incidence rate of 0.02%, the likelihood of contamination of a plasma pool by HIV, HCV, or HBV due to a donation below the limit of detection of the NAT assay (ie, containing at least 1 virus particle per donation) is approximately 0.1%, 0.2%, and 2%, respectively. Even at an incidence rate of 0.1%, which greatly exceeds the rate in the NSP-qualified donor population, the safety margin of products (amount of virus particles per vial) after the manufacturing process with virus inactivation/removal capacity is approximately –10.0 log₁₀ for HIV, –12.0 log₁₀ for HCV, and –8.5 log₁₀ for HBV.

Conclusions: This method allows the calculation of a process limit (ie, the maximum allowed annual number of virus-positive donations from repeat-tested donors per year) that demonstrates plasma-derived products have a very high safety margin of less than 10⁻⁷ virus particles per vial at a 95% confidence level due to the virus reduction capacity of the manufacturing process. An upper incidence rate of 0.1% would achieve this safety margin.
**Pathogen Safety of Plasma-Derived Clotting Factor Concentrates Demonstrated by Validation of Inactivation and Removal Steps in the Manufacturing Process**

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**Objective:** To assure plasma-derived clotting factor concentrates are pathogen safe, virus inactivation and removal methods are applied to the manufacturing process. The effectiveness of currently used methods and procedures was demonstrated.

**Methods:** The virus reduction capacity of the manufacturing process for a specific product was quantitated for selected steps of the manufacturing process. A prerequisite of such virus validation studies is a valid downscaling of the manufacturing process to a laboratory scale. After spiking product intermediates with a panel of viruses the same as or similar to known and emerging pathogens, the manufacturing steps were performed according to the defined procedures and the reduction factors for the different viruses measured. Prion reduction was also studied, employing both a microsomal preparation (membrane-associated prions) and purified prion protein. Methods in the manufacturing process solely for the purpose of pathogen reduction, such as pasteurization, solvent-detergent treatment, dry heat treatment of the final container, and virus (nano) filtration, as well as manufacturing steps for purification and concentration of the desired protein(s) such as partitioning by precipitation or chromatography, were studied. The residual risk of transmitting pathogens was assessed based on the results of these studies and the potential virus load in the plasma pool used to produce these products.

**Summary:** For a pasteurized FVIII/vWF concentrate, the overall log reduction factors were \(\geq 10.2\) for HIV, \(\geq 11.7\) for BVDV, 10.2 for PRV, 7.8 for HAV, and 6.0 for CPV, as well as 6.4 and 7.9 for the 2 prion preparations, respectively. For a FVIII/vWF concentrate using solvent-detergent and dry heat, values were \(\geq 12.5\) for HIV, \(\geq 13.1\) for BVDV, \(\geq 11.4\) for PRV, \(\geq 12.2\) for HAV, and 6.7 for parvoviruses, as well as 4.0 and 4.9 for the 2 prion preparations. For a FIX concentrate using affinity chromatography and virus filtration, values were \(\geq 10.2\) for HIV, \(\geq 12.6\) for BVDV, \(\geq 12.8\) for WNV, \(\geq 16.1\) for PRV, \(\geq 6.7\) for HAV, and \(\geq 14.8\) for parvoviruses. For a FXIII concentrate using adsorption, chromatography, heat treatment, and virus filtration, values were \(\geq 10.2\) for HIV, \(\geq 12.6\) for BVDV, \(\geq 12.8\) for WNV, \(\geq 16.1\) for PRV, \(\geq 6.7\) for HAV, and \(\geq 14.8\) for parvoviruses, as well as 9.8 and 9.7 for the 2 prion preparations.

**Conclusions:** Pathogen safety is based on the overall pathogen reduction factor considerably exceeding the amount of pathogen potentially entering the manufacturing pool. Validation studies verify that safety is attained for currently manufactured plasma-derived clotting factor concentrates.
Patients’ and Caregivers’ Perspectives on Stability of Factor VIII Products for Hemophilia A: A Web-Based Study in the United States and Canada

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Objective: Hemophilia A treatment involves lifelong replacement of coagulation factor VIII (FVIII) through intravenous infusions. Patients must keep FVIII accessible at all times in case of a bleed; thus, FVIII storage and stability are challenging. Obtaining patients’ and caregivers’ perspectives is critical to understanding disease management, particularly with rare conditions like hemophilia A. The primary study objective was to assess hemophilia A patients’ and caregivers’ experiences and preferences around FVIII storage and stability attributes in the United States (US) and Canada via a web-based survey. A secondary objective was to evaluate the use of the social media site Facebook in recruiting adult patients and caregivers of children with hemophilia A.

Methods: Members of two state hemophilia organizations in the US and one national organization in Canada were invited to complete the survey assessing FVIII ordering, usage, and storage. Invitations were posted on the organizations’ websites and/or sent via e-mail to their member lists. Additionally, two organizations posted study advertisements on their Facebook pages. The organizations received a donation for their assistance in study recruitment.

Summary: Of the 145 individuals who responded to the survey invitation, 101 (70%) completed the survey (67% caregivers [82% female]); 58% were recruited through Facebook. Respondent characteristics (e.g., age, education) were generally similar between Facebook and non-Facebook respondents. More than two-thirds of the sample (69%) reported primary prophylactic use of FVIII. Nearly half (48%) of respondents ordered FVIII monthly, and 8% reported often having FVIII expire before use. FVIII storage challenges included refrigeration when traveling (28%) and carrying an insulated tote bag (27%). More than half of respondents (54%) indicated that the ability to store FVIII longer at room temperature was more important than the ability to store it longer in the refrigerator (5%). Most (80%) indicated that they would be very or somewhat interested in an FVIII product that could be stored at a higher room temperature for longer durations because it would make traveling easier, allow them to keep more FVIII at home, and provide easy access when needed.

Conclusions: This web-based study provides a real-world perspective from patients and caregivers on FVIII attributes. There is a need for an improved FVIII product that is more convenient and accessible to patients in daily life and while traveling. Additionally, flexibility in storage could reduce the frequency of FVIII waste. Finally, there is potential value in the use of social media sites in recruiting hard-to-reach populations.
Global Development Plan for a Double Virus Inactivated Fibrinogen Concentrate for the Treatment of Congenital Fibrinogen Deficiency

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Introduction: Congenital afibrinogenaemia and hypofibrinogenaemia are rare inherited disorders occurring in homozygotic patients with an estimated incidence of 1 in 10^6. Patients present with frequent severe bleeding episodes since birth or early childhood. Bleeding may occur after a minor trauma or a small surgical intervention, into the skin, mucosa, muscles, gastrointestinal tract, or the brain. Therapeutic substitution with human fibrinogen concentrate can correct the haemostatic defect and arrest the bleeding in patients with these fibrinogen deficiencies. Octafibrin is a highly purified, lyophilized, human plasma fibrinogen concentrate, without added albumin. Octafibrin is double virus inactivated using 2 dedicated virus inactivation/removal steps, solvent/detergent treatment, and nanofiltration.

Aim: A plan for the global development of Octafibrin has been prepared taking into account discussions with European Regulators and the FDA. This plan also involves discussions with the European pediatric committee (PDCO) which oversees the inclusion of pediatric subjects into drug development under the new EMA guidelines.

Methods: The development plan calls for a prospective, randomized, open label, multinational, pivotal PK comparison of Octafibrin to an existing marketed product in 18 adult and adolescent patients, including comparison of a surrogate efficacy endpoint measured by TEG. In a second study the efficacy and safety of the product in bleeding and invasive procedures will be assessed in 24 adult and adolescent patients. Finally a pediatric PK, efficacy and safety study in patients below 6 years will be performed but because of the rarity of these patients this study will not need to be completed before review and approval by the regulatory agencies.

Results: A double virus inactivated, plasma derived fibrinogen concentrate (Octafibrin) will be globally developed in an ultra rare congenital disease after harmonized discussions with EU and US regulators. Pivotal comparative PK data and interim efficacy and safety data will be available at time of regulatory submissions while the finalization of the pediatric study is deferred. Clinical studies have started with 3 patients enrolled in the FORMA 01 PK study as of May 2013.

Conclusion: Effective management of congenital fibrinogen deficiencies in bleeding situations is necessary for the prevention of potentially life-threatening bleeding episodes. This clinical program will help to confirm that fibrinogen substitution is able to successfully control bleeding, increase the fibrinogen plasma levels, and reduce the amount of transfusions needed with allergenic blood products. In addition, it will give additional information on the tolerability and overall safety profile of fibrinogen replacement therapy.
Use of a double virally inactivated FVIII/VWF in 30 children and young people with von Willebrand's disease - a single centre experience

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Objective: Children and young people (CYP) with von Willebrand's disease (VWD) have mild to severe bleeding manifestations which appear spontaneously or following trauma or surgical intervention. Treatment is given to prevent or treat bleeding; for some this requires treatment with plasma derived concentrates. UK treatment guidelines recommend using plasma products which have been manufactured to the highest standards to limit exposure to potential blood borne viral disease. A double virally inactivated VWF/FVIII concentrate was licensed for use in the UK in September 2009. All children treated at our centre since then have received this new product. A prospective monitoring record, documenting safety and efficacy and outcomes of treatment was established, registering dose frequency, response to treatment and adverse events.

Methods: Since introduction of the new product, treatment of CYP, unresponsive to Desmopressin, has been recorded on a central database. All treatments are recorded including reason for treatment, dose, and response to treatment: bleed resolution, breakthrough bleeds for those on prophylaxis, surgical outcomes and adverse events. The data is analysed regularly to assess results of treatment, adverse events and treatment outcomes.

Summary: To date 30 CYP (14 girls; 16 boys, 21 type 1, 1 type 2M, 6 type 3 VWD, 2 acquired) aged 1 day to 17.8 years have been treated either on demand for bleeds (4 subjects for 23 bleeds), for prophylaxis (4 have had continuous prophylaxis) or surgeries (27 subjects have undergone 35 surgical procedures). Surgical procedures varied from minor to major surgery (dental extractions to spinal, cardiac and neurosurgery). Treatment was administered for 1-5 days. For major procedures FVIII and VWF levels were monitored to ensure adequate haemostasis without any evidence of accumulation of FVIII or VWF postoperatively. No postoperative bleeding, complications or adverse events were seen. The CYP treated prophylactically have experienced no breakthrough bleeds on a dose regimen of 28-53IU/kg/dose, administered at home every 48-72 hours, maintaining a 48 hour trough level >1IU/dl. CYP treated on demand have responded to a single dose of ~50IU/kg.

Conclusion: This study of a heterogeneous group of CYP with VWD confirms data obtained in previous clinical trials that this product is efficacious, safe and well tolerated. Bleed resolution or prevention is 100% in this cohort. For CYP on home treatment ease of reconstitution and infusion and absence of breakthrough bleeding promotes treatment concordance.
Clinical Study in Children with Severe Haemophilia A Investigating Efficacy, Immunogenicity, Pharmacokinetics, and Safety of Human-cl rhFVIII

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Background: Human-cl rhFVIII is the first recombinant factor VIII concentrate expressed in a human cell line (Human Embryonic Kidney 293F cells). Studies in previously treated severe haemophilia A patients demonstrated bio-equivalence to a full length rFVIII concentrate, safety and efficacy in preventing and treating bleeding episodes (BEs).

Aims: The objectives of this GCP study were to evaluate the pharmacokinetics (PK), efficacy, safety, and immunogenicity of Human-cl rhFVIII in previously treated children between 2 and 12 years.

Methods: First, patients were to undergo an in-vivo recovery (IVR) investigation with Human-cl rhFVIII. In a subset of patients, the PK of Human-cl rhFVIII was assessed in comparison to the patient’s previously used FVIII product. After an injection of 50 IU/kg, blood samples were collected up to 48 hours for PK analysis and up to 2 hours for IVR. IVR was repeated in patients after 3 and 6 months. FVIII coagulant activity (FVIII:C) was measured by chromogenic and one-stage assay in a central laboratory. Patients were treated prophylactically with Human-cl rhFVIII every other day or 3x weekly with 30-40 IU Human-cl rhFVIII per kg for 6 months. Human-cl rhFVIII was also used in case of breakthrough bleeds. Inhibitors were measured before, during and at the end of the study by modified Nijmegen Bethesda assay in a central laboratory. Adverse events were recorded throughout the study.

Results: 59 patients (29: 2-5 years; 30: 6-12 years) were enrolled from 15 sites in Europe. 13 children of each age group participated in the comparative PK investigation. Mean PK parameters of Human-cl rhFVIII were similar to those of the previous FVIII product, both for the chromogenic and the one-stage assay: AUC_{norm} 0.23 vs. 0.24 h*IU/mL/[IU/kg]; IVR 1.88 vs. 1.61% per IU/kg; T_{1/2} 9.7 vs. 12.5 h. IVR remained stable throughout the study. There were a total of 108 BEs in 32/59 patients treated with Human-cl rhFVIII. The majority of treated BE were traumatic (60.2%) and minor (56.5%). The mean±SD monthly rate of all types of BEs/patient was 0.34±0.43 (spontaneous BEs: 0.12±0.27; traumatic BEs: 0.19±0.29). No patient discontinued the study because of an AE. Two possibly related AEs (mild headache, mild back pain) in two patients, and no inhibitor development was reported.

Conclusion: The data indicate that Human-cl rhFVIII is efficacious and safe in preventing and treating BEs in previously treated children. The PK of Human-cl rhFVIII and the previous product was very similar.

Keywords: Recombinant factor VIII, Haemophilia A, Pharmacokinetics, Paediatric
Results of a prospective, non-interventional clinical study in 170 VWD patients with a new generation of VWF/FVIII concentrate in Germany

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Objective: With marketing authorization in 2005, a non-interventional study (SET = Surveillance of Efficacy and Tolerability) with a double virus inactivated VWF/FVIII concentrate (Wilate®) was initiated in Germany. After the duration of 7 years, the inclusion of patient documentation was terminated to finally evaluate the study data. At data lock point, 170 patients suffering from von Willebrand’s disease (VWD) had been included. The presented study was performed to assess the haemostatic efficacy and safety of a newly introduced VWF/FVIII product in the treatment of all types of VWD patients in every day clinical setting and to validate the results from pivotal clinical trials.

Methods: Patients of any age suffering from hereditary or acquired VWD, requiring replacement therapy were included. Apart from demographic and anamnestic data, details of all injections for treatment of bleeding episodes, surgeries and prophylactic treatment were documented. Clinical efficacy and tolerability were rated by the treating physicians using four-point verbal scales. All data underwent a pre-defined data management process including double data entry and plausibility checks by an independent statistical institute.

Summary: 26 treatment centers provided data of 170 patients suffering from VWD, reflecting the broad spectrum of disease severity. About two thirds of the patients are female; the age ranges from 1 to 85 years at study entry. Six cases of acquired VWD and 7 type 3 VWD patients were included. Type 2 VWD of various subtypes accounts for about 30% of the patients with the remaining patients suffering from type 1 VWD. 108 surgical procedures in 82 patients were documented. In all rated surgical procedures, the efficacy of the concentrate was assessed to be “excellent” or “good”. Efficacy in 156 bleeding episodes was assessed as “excellent/good” in 95.2% of ratings. Prophylactic treatment of 13 patients resulted in a drop of bleeding frequency to below 1 bleeding episode per month. Five patients had experienced suspected adverse drug reactions - all without sequelae. The ADR rate per injection was as low as 0.1%.

Conclusion: The results presented reflect the experience of routine use of Wilate® in all types of VWD in various clinical settings. They confirm the excellent efficacy and tolerability which had been demonstrated previously during an extensive panel of clinical trials.
Clinical Study to Investigate the Immunogenicity, Efficacy and Safety of Treatment with Human-cl rhFVIII in Previously Untreated Patients with Severe Haemophilia A

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Background: Human-cl rhFVIII is a B-domain deleted, human cell-line derived recombinant FVIII concentrate for intravenous use, which will be provided in single use vials containing a nominal potency of 250, 500, 1000 or 2000 IU each of freeze-dried rFVIII concentrate to be reconstituted in 2.5 mL of WFI. Due to the absence of immunogenic epitopes seen in recombinant FVIII concentrates from hamster cell lines Human-cl rhFVIII is thought to be potentially less immunogenic. Five prospective GCP studies with Human-cl rhFVIII were conducted in 135 adults and children with severe haemophilia A. In these studies pharmacokinetics, efficacy and safety of the product was evaluated. Observational period per patient was at least 6 months and at least 50 exposure days. The data indicates that Human-cl rhFVIII is bioequivalent to Kogenate FS (both analyzed by the one-stage and the chromogenic assay) and effective in the treatment and prophylaxis of bleeding episodes. There was no product related adverse event and none of the PTPs treated with Human-cl rhFVIII developed an inhibitor.

Aim: To assess the immunogenicity in previously untreated patients (PUPs), a prospective, multicentre, open-label, non-controlled clinical trial is planned in about 45 clinical centres worldwide, starting by early 2013.

Methods: 100 patients with severe haemophilia A without previous exposure to any FVIII concentrate or FVIII containing products will be enrolled. An inhibitor assay according to modified Bethesda method will be performed pre-treatment, every 3-4 exposure days (ED 1-20) and every 10-12 EDs (ED 21-100) but at least every three months. Secondary objectives are the assessment of the efficacy of Human-cl rhFVIII during prophylactic treatment (based on the frequency of spontaneous breakthrough bleeds), the assessment of the efficacy during treatment of bleeds, and in surgical prophylaxis. Also the safety, tolerability and pharmacoeconomic aspects of Human-cl rhFVIII will be assessed. The optional assessment of predictive factors for the development of inhibitors is included in the study protocol.

Results: The study started in Q1 2013.

Conclusion: Based on available data in PTPs Human-cl rhFVIII seems to be bioequivalent to a licensed full-length rFVIII and safe and effective in the treatment and prevention of bleeding episodes with no occurrence of an inhibitor. A global GCP-study is currently started in order to investigate whether the reduced immunogenic profile of Human-cl rhFVIII will translate into a lowered inhibitor incidence in PUPs.

Keywords: recombinant FVIII, haemophilia A, safety, FVIII
Objective: Describe social worker and nurse perspectives on the Hemophilia Experiences, Results and Opportunities (HERO) results from Canada.

Methods: Adults with hemophilia (“adults,” ≥18 years) and parents of children (<18 years) with hemophilia (“parents”) were recruited through local hemophilia organizations and completed an online psychosocial assessment. Advisory board meetings with Canadian social workers and nurses were held to discuss the HERO results in January and April 2013, respectively.

Summary: Key psychosocial issues identified by social workers and nurses included issues with sex life, pain, and employment. One-half (9/18) of adults with hemophilia in Canada reported that hemophilia had affected the quality of their sex life. Social workers noted that there is a need for more discussions and professional support regarding sexual intimacy, in addition to a need for more training for healthcare professionals (HCPs) on how to engage in conversations about sexual intimacy. Possible solutions to this issue provided by nurses include handouts to start conversations, education on strategies for HCP seminars, websites with patient testimonials, and information nights through local hemophilia chapters. Overall, 9/30 adults with hemophilia reported that pain had interfered with their daily life extremely or quite a lot. Of 27 adults, 9 reported pain all the time and 13 reported pain all the time that gets worse when they have a bleed. Social workers noted that there is a lack of chronic pain care and there needs to be an increase in sensitivity toward pain issues. Solutions proposed by nurses included a literature review about pain-assessment tools for hemophilia, developing tools to teach parents how to assess pain, developing an application for assessing and managing hemophilia-specific pain, offering pain intervention, developing distraction tool kits, and teaching alternative ways to cope with pain. Only 15/29 Canadian adults with hemophilia were employed; 35/39 parents were employed. Social workers noted that there is discrimination at work and school. To improve career guidance, nurses suggested the following: explore vocational issues, increase hemophilia treatment center (HTC) awareness, capture facts around what is or is not possible with respect to jobs, vocational support programs to start earlier, and clarify the HTC’s role in advocacy.

Conclusions: HERO provided key insights into psychosocial issues facing Canadian adults with hemophilia and Canadian parents of children with hemophilia. Nurses and social workers provided strategies that could help improve the lives of both patients and parents.
Successful buffalo hump removal using liposuction in two men with severe hemophilia and HIV

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Objective: To describe successful buffalo hump removal in 2 patients with Hemophilia and HIV.

Methods/Case Description: Development of a dorsocervical fat pad, or buffalo hump, occurs in 2-13% of HIV infected individuals, the etiology is unclear. Two HIV positive patients, one with severe Hemophilia B and the other with severe Hemophilia A had symptomatic buffalo humps for 12 and 7 years respectively. Symptoms included headaches, sleep disturbances, neck stiffness and pain. These symptoms adversely affected activities of daily living. Their HIV disease was well controlled and stable. Both patients had been offered an open excision over liposuction, but the former carries a higher risk of bleeding and pain, as well as poor cosmetic result. The decision was made by a second plastic surgeon to attempt removal through liposuction. For hemostasis they received:

<table>
<thead>
<tr>
<th>Subject #1</th>
<th>Pre-procedure</th>
<th>Follow up dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Plasma derived Factor IX</td>
<td>70 un/kg every 12 hours x 2 then daily x 3, then resumed prophylaxis</td>
</tr>
<tr>
<td>Subject #2</td>
<td>Recombinant Factor VIII</td>
<td>34 un/kg every 12 hours x 4 then daily x 4, then resumed prophylaxis</td>
</tr>
</tbody>
</table>

Both patients underwent similar liposuction procedures. 400-600cc of a tumescent solution containing epinephrine and Xylocaine was infiltrated into the subcutaneous tissue in order to minimize bleeding. Traditional liposuction was then performed through 4-5 stab incisions using a variety of cannulas with multiple passes through the fatty tissue attempting to aspirate and break up the fibrous septum connecting the buffalo hump to the cervical fascia. The deeper peri-fascial fat was removed first with later passes aimed at removing the more superficial fatty tissue. Lastly, multiple passes were made in a fan-like distribution to create an even and level contour of the back. Before closing the incisions, the remaining tumescent solution was infiltrated into the remaining cavity to prevent post-operative bleeding and to help with pain control. Both patients tolerated the procedures well with no peri-operative complications and were done in a same day surgery suite, admission was not required.

Results: Both patients had complete resolution of pre-surgical symptoms and achieved a cosmetically pleasing outcome. Neither patient experienced any recurrence of the fat accumulation 8 and 5 months after the procedures.

Conclusions: Liposuction is a minimally invasive modality that can be used to successfully remove buffalo humps in people with severe hemophilia, allowing for resolution of pain and improved quality of life.
Efficacy of a strength training program for improving elbow joint range of motion and function in adults with hemophilia

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Objective: To investigate the effect of modified pull-up exercises on elbow range of motion (ROM) and function for people with arthropathy secondary to hemophilia and recurrent bleeding

Methods:

A) Participants: Men above age 18 years with hemophilia, and greater than 5 degrees ROM loss due to arthropathy from recurrent joint bleeding

B) Design and procedure: This pilot study was a prospective case series. Subjects were asked to perform a home exercise program consisting of modified pull ups three times per week for 8 weeks. Data was collected prior to start of program, at 3-5 weeks and at 8-10 weeks. Outcome measures included elbow ROM, pain, upper arm girth and activities of daily living (ADL) related reaching tasks. Information on how often the exercises were being performed, as well as episodes of bleeding was collected each week.

C) Analyses: A paired t-test was used to compare pre and post intervention measurements.

Summary: Ten subjects have been recruited with ages ranging from 26-45 years. All have severe hemophilia A. Six subjects have completed the 8 week program to date. Those who completed the program demonstrated a mean increase of 5.3° of elbow flexion ROM (p=0.007). There was a trend toward increase in supination ROM between the two time points (p=0.058). No significant difference was seen in pre and post measurements for extension and pronation ROM. The only ADL related reaching task that demonstrated change between the two time points was palm of hand to occiput. Distance between the palm of hand to the occiput decreased 2.2 inches (p=0.009). Only 2 of the 6 subjects reported having pain in their elbow prior to the start of the program and it was unchanged during the course of the study. Arm girth data only existed for 5 of the 6 subjects and was measured at 3-5 week and 8-10 weeks. There was a trend toward increase in upper arm girth (p=0.078). There have been three reported episodes of elbow bleeding; only one was attributed to the exercises according to subject's report.

Conclusion: Preliminary results suggest that an eight week exercise program consisting of modified pull-ups may increase elbow flexion ROM in men with elbow joint contracture due to recurrent joint bleeding from hemophilia. Continuation of this study as well as development of others is needed to further determine if strength training is beneficial to improving elbow movement and function in those with hemophilic arthropathy.
Translation and Validation of an Instrument to Measure the Care-related Quality of Life of Informal Caregivers in English for the United States

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Objective: Caregivers of hemophilia patients may experience physical, social, emotional and financial problems as a result of their care tasks. Measurement of the caregiver experience is important in hemophilia as the majority are informal caregivers; typically unpaid family or friends. In order to carry out studies within the United States, a need exists for a translated and validated instrument to measure informal caregivers' care-related quality of life in English for the U.S.

Methods: The CarerQol instrument, covering 7 domains measuring the care-related quality of life of informal caregivers, including fulfillment, relational, mental and physical health problems, social impact, receipt of family support and financial impact, was selected on which to base an English U.S. version. The Dutch (Netherlands) source was translated into English (U.S.) by two forward linguists, working independently, who then collaborated to create a harmonized version. The project team, consisting of the forward translators, project manager, survey research analyst and independent Dutch (Netherlands) reviewer, discussed the harmonized English (U.S.) version to make necessary revisions. The English (U.S.) harmonization was then back-translated into Dutch (Netherlands), and a second Dutch linguist compared the back-translation to the source Dutch to ensure conceptual equivalence of the English forward translation and Dutch source. A client representative, who is a native English (U.S.) speaker, reviewed the English translation against the Dutch as an additional quality measure. After the English (U.S.) harmonization was finalized, it was debriefed via telephone interviews with 5 volunteers using screenshots of the questionnaire's web version.

Summary: A total of 5 subjects from the U.S. participated in debriefing interviews. Subjects ranged in age from 24 to 59 years, with educational levels ranging from 11 to 16 years. Sixty percent (60%) of the sample was female. Interview data confirmed that the English (U.S.) harmonized translation is conceptually equivalent to the source Dutch, and is understood by subjects in the United States.

Conclusion: Per the cognitive debriefing results, the English (U.S.) harmonized translation based on the Dutch CarerQol instrument adequately captures the concepts in the original Dutch and, overall, is easily understood and confirmed as culturally appropriate by subjects in the United States. The resulting instrument is validated for use by English speakers in the United States, and captures the 7 quality of life domains as included in the source instrument.
Stepping Up and Reaching Out to the Community

Edward J. Kuebler, Madeline Cantini

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Objective: Who better to understand and help advocate for the bleeding disorders community than those who live it every day? Step Up Reach Out (SURO) was created to help foster the next generation of leaders in the bleeding disorders community.

Method: SURO is an international leadership program designed to help build tomorrow's leaders in the bleeding disorders community. The program was created by the University of Texas Health Science Center, Gulf States Hemophilia and Thrombophilia Center (UTHS) in 2007 with support from Bayer HealthCare.

SURO brings together young people (18-24 years old) from around the world for learning, personal growth and collaboration. This one-year program consists of two sessions of leadership training, activities focused on developing communications skills, and individual and group projects. During the time between the two sessions, participants are asked to identify an area in their communities for which they would like to step up and define an action plan, putting into practice the skills they have acquired. They continue to learn from and support one another through the SURO Alumni Network.

Summary: To date, the SURO program has trained nearly 100 individuals from more than 20 countries, ranging from the US to Mexico, India and beyond. SURO alumni have come out of the program ready to put their action plans to the test, developing programming to support their local community needs.

Conclusions: SURO helps participants build self-esteem, develop concrete thinking abilities and make decisions that will help make them become leaders in their own right.
Predicting PK/PD advantages of modified activated coagulation factor VII molecules

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Background: Recombinant Factor VIIa (rFVIIa) is a factor (F)X-cleaving blood coagulation enzyme licensed for treatment of bleeding episodes in hemophiliacs with inhibitory antibodies. The proteolytic activity is mediated by two non-competing co-factors, tissue factor (TF) and phospholipids (PL). Laboratory evidence suggests that peak pharmacological concentrations of rFVIIa can be active through the low-affinity binding to PL exposed on activated platelets. Moderate rFVIIa concentrations can also work through the more efficient TF pathway.

Objective: Several rFVIIa analogues with altered co-factor binding, proteolytic activity and circulatory half-life have entered clinical trials in recent years. In this study, kinetic constants of rFVIIa interaction with co-factors and inhibitors were used to predict the relationship between the pharmacokinetics (PK) and pharmacodynamics (PD) of rFVIIa analogues.

Methods: In silico PD model, FXa generation, was validated in vitro with thrombin generation experiments and applied to evaluate the changes in the TF- and PL-based mechanisms of action and predict the PD and PK/PD of different doses of rFVIIa analogues.

Summary: Our PK/PD simulations predicted similar efficacy of rFVIIa at a single dose of 270 µg/kg or 3 doses of 90 µg/kg. In addition, the model agreed with the published PK/PD curves for NovoSeven and BAY 86-6150 analogue. Changes to the half-life and TF affinity had the most pronounced effect on PD. Proteolytic activity and binding to platelets were less likely to give dosing advantages.

Conclusions: We conclude that many alterations of the rFVIIa molecule may not translate into the meaningful advantages of a prolonged dose-effect or a lower-than the currently licensed dose schedule.
Determining the impact of instrument variation and automated software algorithms on the thrombin generation test under hemophilia treatment conditions

Samuel A Woodle, Timothy K Lee, Mikhail V Ovanesov

US FDA, CBER, Bethesda, MD, USA

Background: Despite increasing recognition as a more precise test of in vivo hemostatic conditions and ubiquitous use in clinical trials to support development of novel coagulation products, standardization of the thrombin generation test (TGT) continues to hinder its development as routine clinical practice. Prior method harmonization efforts largely focused on comparing the effects of experimental conditions and different reagents. However, multiple commercialized and in house methods continue to be used worldwide on a variety of reader instruments and processed using individualized algorithms.

Objectives: Our study compared the effect of instrument and software choices on the processing of the TG curve and its common endpoint parameters under hemophilia and normal conditions.

Methods: Hemophilia A plasma supplemented with buffer or Factor VIII, mimicking hemophilic or normalized samples respectively, was monitored for TG on seven different fluorescent microplate readers. Each instrument was optimized for TGT signal recording prior to testing. An automated software package containing various mathematical algorithms was developed for this study to compute the TG curves and parameters, and compare different known TG processing and calibration approaches. Effects of fluorogenic substrate artifacts (inner filter effect, substrate consumption) and correcting algorithms (e.g., internal thrombin calibration) were compared in normalized and hemophilic samples.

Results: Instruments produced unique noise profiles and end-point parameters that were incomparable in absolute signal terms. However, similar relative hemophilic responses across various instruments were obtained when normalized plasma sample was used as a standard. Relatively simple smoothing algorithms were able to correct destructive instrument noise. Interestingly, correction of the fluorogenic substrate artifacts did not provide advantages for the evaluation of the differences between hemophilic and normalized plasma.

Conclusions: Instrument-induced errors from numerical differentiation during TG curve processing cannot be eliminated by external or internal calibrators, and require careful qualification of the instrument and implementation of noise-reducing software algorithms.
POIM53

Speaking Frankly to Young Adults with Hemophilia

Edward J. Kuebler, Pia Petrini Petrini, Diego Gavidia, Eviatar Weizman, Jose Omolara Oyesiku

1University of Texas Gulf States Hemophilia and Thrombophilia Center, Houston, Texas, USA, 2Karolinska University Hospital, Stockholm, Sweden, 3Asociación Peruana de la Hemofilia, Lima, Peru, 4Board member, Speaking Frankly about Hemophilia, Givat Ada, Israel, 5Oxford Haemophilia and Thrombosis Centre, Churchill Hospital, Oxford, UK

Objective: Few online resources are available for teens and young adults living with hemophilia. Frankly.net aspires to serve as a candid, trusted resource on real issues of concern for this age group. Our online forum provides news, tips and information to help young adults with hemophilia live the lives they choose.

Method: In 2008, an editorial board was established to guide the creation of Frankly.net, an online magazine targeting young men with hemophilia. Board members include experts in the areas of healthcare, social work and advocacy, and two are young men living with hemophilia.

Frankly.net content is controlled exclusively by the editorial board and sponsored by Bayer Healthcare with the goal of casting light on often taboo subjects within the community, such as sexuality, drugs and depression. An editorial calendar is maintained to ensure fresh content is published regularly.

Frankly.net is mobile-optimized and includes rich video content. Users are encouraged to keep up with the latest content by following @FranklyNet on Twitter.

Summary: Since its inception, the editorial board has guided the creation of more than 80 stories. Articles include topics that resonate with young adults such as travel, entertainment, relationships and sex. Engaging video stories are also available in English and Spanish.

To date, Frankly.net has seen nearly 7,500 visitors from more than 125 countries across the globe, including the US, India, Germany, Canada.

In 2013, Frankly.net underwent a site makeover, re-launching with a new look and feel. Plans to further engage with an international audience are also underway. Korea launched a fully translated site in early 2013 under the guidance of a Korean editorial board. A Latin American version is in development and content from the site has been repurposed and translated in a dozen countries.

Conclusions: Frankly.net is a unique resource for teenagers and young adults with hemophilia around the world. It continues to push boundaries as a way to help young men navigate the ups and downs of living with hemophilia.
Objective: To assess the dental experiences of patients with von Willebrand disease for the purpose of developing guidelines for screening and dental management.

Methods: A 13-question survey was administered to individuals at the National Outreach von Willebrand Conference, held in Phoenix, AZ in February 2012. A total of 55 respondents answered questions regarding oral hygiene habits, frequency and types of prior dental visits, dentists' attitudes and knowledge of the disease, adverse bleeding events and quality of communication between dentist and haematologist.

Results: Eighteen percent of respondents reported being refused dental treatment upon disclosure of von Willebrand disease history, while 81% of respondents reported that their dentist did not consult their haematologist prior to rendering treatment. More than half of those surveyed (56%) reported adverse bleeding events following dental procedures. Finally, 37 respondents reported gingival bleeding and 21 had not visited a dentist in the past six months.

Conclusions: The results of this pilot study indicate that there is a need to educate the dental profession about von Willebrand Disease, especially its oral manifestations. Simultaneously, patients with von Willebrand Disease need to be educated as to the importance of maintaining oral health. Much more research needs to be done on the effects of poor oral health on the severity of bleeding disorders.
Better Adherence to Prescribed Treatment Regimen is Associated with Less Chronic Pain among Adolescent and Young Adults with Moderate or Severe Hemophilia

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¹Northern Regional Bleeding Disorders Center, Traverse City, MI, Region V-E, U.S. Virgin Islands, ²Pfizer Specialty Care, Medicines Development Group, Collegeville, Pennsylvania, U.S. Virgin Islands, ³Henry Ford Adult Hemophilia & Thrombosis Treatment Center, Detroit, MI, Region V-E, U.S. Virgin Islands, ⁴University of Michigan Hemophilia Treatment Center, Ann Arbor, MI, Region V-E, U.S. Virgin Islands

Background/Aim: Little data exist, especially for adolescents and young adults (AYAs), about the relationship between adherence to prescribed hemophilia treatment regimens and chronic pain (CP).

Methods: A convenience sample of hemophiliacs aged 13-25 completed an IRB-approved, online survey addressing regimen-specific adherence and CP between April through December of 2012. Adherence was assessed for prophylactic (VERITAS-Pro) and on-demand (VERITAS-PRN) participants. VERITAS scores range from 24 (most adherent) to 120 (least adherent). CP was measured using the revised Faces Pain Scale (FPS-R). CP was dichotomized as high (‘moderate’ to ‘worst pain possible,’ i.e., ≥4) or low (‘mild’ or ‘no pain,’ i.e., <4). Multivariable, parsimonious logistic regression models assessed factors associated with high vs low CP levels. Separate models were constructed to evaluate a combined VERITAS score among prophylactic and on-demand patients and the VERITAS-Pro score among prophylactic patients only. Small sample size precluded analysis of on-demand (only) participants.

Results: Ninety-three AYAs participated. Mild patients (n=13) were excluded. Of the remaining 80 participants (79 male), 91% had severe disease, 86% infused prophylactically, and 91% had Hemophilia A. Fifty-one percent were aged 13-17, most were white (76%), non-Hispanic (88%), and never married (93%). The majority (94%) had some type of health insurance.

Mean VERITAS-Pro (n=69) and PRN (n=11) scores were 49.6 ±12.9 (range 25-78) and 51.0 ±11.6 (range 35-74), respectively. CP was reported as high for 35% of respondents (36% for prophylactic vs 27% for on-demand, p=.74). Mean VERITAS-Pro scores for those with high and low CP were 53.6 ±12.3 vs 47.4 ±12.9, p=.05. VERITAS-PRN scores were similar across CP status. Logistic regression analysis revealed that for each 10-point reduction (increase in adherence) in the combined VERITAS score (Pro and PRN) there was a 35% (OR=0.65; 95%CI=0.44, 0.96; p=.03) reduction in the odds of having high CP. Among prophylactic respondents: for each 10-point reduction in the VERITAS-Pro score there was a 39% (OR=0.61; 95%CI=0.39, 0.96; p=.03) reduction in the odds of having high CP and compared to whites, non-whites were 4.42 (95%CI: 1.21, 16.1; p=.02) times as likely to report high CP.
**Collaborative partnership helps resolve cultural barriers in patient receiving continuous infusion of factor (ACAT Protocol) in the home setting.**

Jay Bryant-Wimp\(^1\), Tamara Hopkins\(^2\), Lisa Holm\(^2\), Stacy Bryant-Wimp\(^1\)

\(^1\)Accurate Rx Pharmacy, Columbia, MO, USA, \(^2\)University of Missouri Columbia, Columbia, MO, USA

**Objective:** When a surgical procedure is required in a patient with hemophilia, continuous infusion of factor (CIF) is a safe and effective alternative to bolus dosing.\(^1\)\(^\text{-}5\) However, when cultural values collide with best practices, a patient-centered collaborative care plan is necessary to help ensure a positive outcome while respecting the core values of the patient.

**Method:** Our team collaborated with our local Hemophilia Treatment Center (HTC) physicians and nurses to plan CIF for an Amish patient who required a total knee replacement. After interviewing the patient, the care team recognized when the patient transitioned on CIF to the home, we would need to respect the cultural beliefs of the patient without compromising the care.

The HTC physician and nurse ordered continuous infusion of factor for the patient with goal factor levels to remain between 70-100% on post-op days 1-7 and between 50-70% on post-op days 8-14. The home infusion team collaborated with the family and HTC team to finalize the care plan. The patient-centered decision prompted the use of a battery powered ambulatory infusion pump and the use of pre-approved sliding scale factor orders (ACAT protocol) with daily factor levels. Our biggest barrier was in respect to communication with the patient. In our local Amish community, telephones are not accessible. Our brainstorming lead to our COO suggesting we include a battery operated phone that would be attached to the pump and only be used for pump emergencies.

**Summary:** The patient was discharged to home post-op day three with recombinant factor VIII running at 2.5 units/kg/hour via a battery operated ambulatory pump. Levels on post-op day four were below 70, prompting the nurse to call on the “pump phone” and return for a visit that night to increase the rate to 2.7 units/kg/hour. The rate remained the same throughout the remainder of the therapy and the levels stayed within the range designated by the physician.

**Conclusion:** The patient-centered multidisciplinary care plan allowed for a positive outcome while respecting the patient’s culture.
Reduced Joint Range of Motion in Females with FVIII Deficiency

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Objective: Our hypothesis was that females with FVIII deficiency enrolled in the Universal Data Collection (UDC) project have reduced mean joint range of motion (ROM) compared to historic controls from the Normal Joint Study.

Methods: We employed a cross-sectional study design utilizing the UDC dataset. The overall joint ROM was the sum of the ROM measurements of the five joints for the females with FVIII deficiency and the normal females. Results were displayed as mean overall joint ROM by age group and factor deficiency with differences between groups assessed using the Wilcoxon-rank-sum test.

Summary: A total of 513 females were identified with FVIII deficiency; 144 females were removed because of a lack of verification for factor deficiency, one female lacking recorded range of motion data. Of the 368 females, the median age was 26 years (range 0-78). Final analysis was performed on 247 females with FVIII deficiency between the ages of 2-69 (excluding very obese females) for comparison to the control group. The mean overall joint ROM worsened with decreasing FVIII activity and in most cases was lower than that of the controls (see table 1).

Conclusions: Females with FVIII deficiency enrolled in the UDC project had reduced mean ROM compared to normal females without deficiency.

Table 1. Mean overall joint ROM in females with FVIII deficiency by age and factor activity.

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>n</th>
<th>Normal joint study Mean ROM® (95% CI)</th>
<th>n</th>
<th>FVIII ≥40% and &lt;50% Mean ROM® (95% CI)</th>
<th>n</th>
<th>FVIII &gt;5% and &lt;40% Mean ROM® (95% CI)</th>
<th>n</th>
<th>FVIII ≥1% and ≤5% Mean ROM® (95% CI)</th>
<th>n</th>
<th>FVIII &lt;1% Mean ROM® (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 to 8</td>
<td>39</td>
<td>1878 (1856-1890) SD = 67</td>
<td>6</td>
<td>1786 (1674-1897) SD = 106 p NS</td>
<td>29</td>
<td>1725 (1683-1767) SD = 111 p &lt; 0.0001</td>
<td>6</td>
<td>1667 (1575-1759) SD = 87 p 0.0002</td>
<td>9</td>
<td>1634 (1591-1677) SD = 56 p &lt; 0.0001</td>
</tr>
<tr>
<td>9 to 19</td>
<td>56</td>
<td>1753 (1736-1769) SD = 61</td>
<td>11</td>
<td>1685 (1639-1732) SD = 69 p = 0.05</td>
<td>55</td>
<td>1687 (1661-1714) SD = 94 p &lt; 0.0001</td>
<td>2</td>
<td>1663 (939-2387) SD = 81 NS</td>
<td>5</td>
<td>1597 (1439-1755) SD = 127 p 0.014</td>
</tr>
<tr>
<td>20 to 44</td>
<td>143</td>
<td>1745 (1734-1755) SD = 63</td>
<td>14</td>
<td>1662 (1583-1741) SD = 137 p = 0.01</td>
<td>69</td>
<td>1650 (1625-1674) SD = 102 p &lt; 0.0001</td>
<td>5</td>
<td>1494 (1313-1675) SD = 146 p 0.0002</td>
<td>11</td>
<td>1463 (1341-1584) SD = 181 p &lt; 0.0001</td>
</tr>
<tr>
<td>45 to 69</td>
<td>123</td>
<td>1688 (1677-1700) SD = 66</td>
<td>1</td>
<td>1653 23</td>
<td>1603 (1543-1664) SD = 140 p &lt; 0.0001</td>
<td>1</td>
<td>1570 --</td>
<td>--</td>
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</tbody>
</table>
Efficacy and safety of a novel rFIX (BAX326): phase III study in previously treated patients with severe or moderately severe hemophilia B undergoing surgical or other invasive procedures

Jerzy Windyga, Toshko Lissitchkov, Oleksandra Stasyshyn, Vasily Mamonov, Helieh Ghandehari, Miranda Chapman, Sandor Fritsch, Borislava G. Pavlova, Wing-Yen Wong, Brigitt E. Abbuehl

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Objective: The purpose of this ongoing study is to evaluate the hemostatic efficacy and safety of BAX326 (a novel recombinant FIX (rFIX) manufactured without the addition of any materials of human or animal origin, and with two viral inactivation steps [solvent/detergent treatment and nanofiltration]) in previously treated patients (N=14; 12 to 65 years old, no history of FIX inhibitors) with severe (FIX Level < 1%) or moderately severe (FIX Level ≤ 2%) hemophilia B undergoing major or minor elective or emergency surgical, dental or other invasive procedures.

Methods: The BAX326 dose administered was tailored to maintain FIX pre-infusion levels of 80%-100% of normal for major surgeries and 30%-60% of normal for minor surgeries. The treatment regimen was determined by the type of surgery, intensity and duration of the hemostatic challenge, consistent with the standards of care of the study site. Intra- and postoperative hemostatic efficacy are graded on a scale of “excellent,” “good,” “fair” and “none.” and the actual intraoperative blood loss at the end of surgery is compared to the average and maximum blood loss as predicted preoperatively. Safety is evaluated in terms of product-related AEs, antibodies to FIX and thrombotic events.

Summary: The present results are based on an interim analysis of data from 11 major (7 of which were orthopedic) and 3 minor surgeries. Intraoperative hemostatic efficacy was assessed as “excellent” for all 14 surgeries. Postoperative efficacy was rated as ‘excellent’ in 7/11 and as ‘good’ in 4/11 major surgeries. Actual intraoperative blood loss in major surgeries with a drain placed (N=7) matched the predicted average during 5/7 surgeries and was below the prediction during 2/7 surgeries; postoperative blood loss was higher than maximum predicted blood loss in 4/7 surgeries, and equal to or below the predicted maximum in 3/7 surgeries. However, due to the nature of invasive procedures, a number of variables such as inadequate prediction of surgery conditions (e.g. unplanned drainage, use of tourniquets) or insufficient target FIX levels in some subjects have been identified as factors contributing to the higher than predicted postoperative blood loss. BAX326 was safe and well-tolerated; no adverse events related to treatment, no severe allergic reactions, no bleeding episodes, no inhibitor formation and no binding antibodies to FIX or thrombotic events were observed.

Conclusions: The results indicate that BAX326 is safe and efficacious in Hemophilia B subjects who received BAX326 for peri-operative management in surgical hemostasis.
Prospective Clinical Trial of a Novel Recombinant Factor IX in Previously Treated Patients

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Objective: This prospective clinical trial was conducted to assess the safety, efficacy and PK of BAX326 (a novel recombinant FIX [rFIX] manufactured without the addition of any materials of human or animal origin, and with two viral inactivation steps [solvent/detergent treatment and nanofiltration]) in previously-treated patients aged 12 to 65 with severe (FIX level < 1%) or moderately severe (FIX level ≤ 2%) hemophilia B.

Methods: Hemostatic efficacy after twice weekly prophylaxis with BAX326 was determined in terms of annualized bleeding rate (ABR) compared with a historical control group treated on-demand. PK equivalence was assessed between BAX326 and a commercial rFIX in a crossover design. Safety was evaluated by the occurrence of adverse events.

Summary: In subjects on twice weekly prophylaxis with BAX326 over at least 3 months (N=56), 24 (43%) did not bleed throughout the study observation period, and the ABR was substantially lower when compared with a historical control group (79% reduction, p<0.001). Joint bleeds (major joints: wrist, elbow, shoulder, hip, knee, ankle) occurred at a mean ABR of 2.85 ± 4.25 compared with 1.41 ± 2.87 in non-joint bleed sites. Of the 32/56 subjects with bleeds, 90.6% (29/32) had arthropathy at screening and only 28.1% (9/32) did not have target joints, as compared to subjects without bleeds, of whom 79.2% (19/24) had arthropathy and 50% (12/24) did not have target joints at screening. Higher mean ABRs were observed in subjects with arthropathy (N=46) versus without arthropathy (N=8) (4.54 vs. 2.57 for all bleeds, 3.16 vs. 1.02 for joint bleeds, and 1.97 vs. 0.25 for spontaneous bleeds). A similar pattern was observed for the ABRs of joint bleeds and spontaneous bleeds in subjects with target joints (N=35) (mean ABR: 2.41 ± 3.79) and those with no target joints (N=21) (mean ABR: 0.58 ± 1.63). Most bleeds were controlled with 1-2 infusions of BAX326 and with an efficacy rating of “excellent.” BAX326 was equivalent to the comparator rFIX in terms of AUC 0 72 h /dose. BAX326 is safe and well tolerated in hemophilia B patients, with no signs of immunogenicity or thrombotic events.

Conclusions: BAX326 has a positive safety profile and is efficacious in treating bleeds and in routine prophylaxis in PTPs aged ≥12 years with hemophilia B. The results also demonstrate that subjects with target joints and hemophilic arthropathy receiving secondary prophylaxis tend to have higher ABRs as compared to those without these underlying conditions.
Turoctocog alfa, a new B-domain truncated, recombinant factor VIII (rFVIII) developed by Novo Nordisk for the prevention and treatment of bleeding episodes in hemophilia A patients

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**Objective:** Hemophilia A patients in the US benefit from safe, efficacious, and reliable factor VIII (FVIII) treatments. Novo Nordisk (Bagsværd, Denmark) has developed turoctocog alfa, the first new recombinant (r) FVIII in over a decade.

**Methods & Summary:** Turoctocog alfa is a state-of-the-art, B-domain truncated rFVIII product manufactured without the use of human or animal proteins. Truncation of the B-domain was chosen as this domain does not have any function with respect to FVIII clotting activity. Once activated by thrombin, the turoctocog alfa truncated B-domain is cleaved, leaving an active FVIII molecule similar to the endogenous form. Turoctocog alfa is produced in Chinese hamster ovary cells, a reliable, well-established cell line used for the production of recombinant proteins for medicinal purposes. To ensure a homogenous product, isolation of turoctocog alfa uses a five-step purification process; detergent inactivation and concentration, immunoaffinity chromatography, anion exchange chromatography, nanofiltration (20 nM filter), and gel filtration. The turoctocog alfa production method, together with its molecular structure ensures that all six FVIII tyrosines are fully sulfated. Tyrosine sulfation is important for physiologic binding of FVIII to its co-factor von Willebrand Factor, essential for FVIII stability when in circulation. Turoctocog alfa plasma concentration can be measured using standard one-stage clotting or chromogenic assays without the need for an external standard.

Turoctocog alfa has been clinically tested in the guardian™ trials, one of the largest pivotal trial programs undertaken in hemophilia A with over 200 previously treated patients (PTPs) dosed. The safety and efficacy of turoctocog alfa was tested in adults and adolescents (guardian™1) and children (guardian™3). For adults and adolescents, turoctocog alfa had a success rate of 85% in management of bleeding episodes, and 89% of bleeds were successfully treated with 1-2 doses. For children, the success rate was 94%, and 95% of bleeds were treated with 1-2 doses. When used for prophylaxis, the median annualized bleeding rate for adults and adolescents was 3.7, while for children it was 3.0. In all surgical procedures performed in guardian™1 and 3, the success rate was 100% with no safety concern. For both trials, no turoctocog alfa inhibitors were reported, and no safety concerns were observed. A clinical trial in pediatric previously untreated patients (guardian™4) is ongoing.

**Conclusions:** Turoctocog alfa is the new rFVIII treatment from Novo Nordisk, offering an alternative treatment option for patients with hemophilia A.
Overview of a global clinical trial program with turoctocog alfa, a new recombinant factor VIII: the guardian™ program

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Objectives: Novo Nordisk is developing turoctocog alfa, a new recombinant FVIII (rFVIII) for prevention and treatment of bleeding in hemophilia A. Because of the rarity of the condition, clinical trials investigating hemophilia therapeutic agents need to be multicenter/multinational, to enroll a sufficient number of patients, and to ensure that patients of different ethnicity are included. Our aim here is to present an overview of a global clinical trial program assessing the pharmacokinetics (PK), safety and efficacy of turoctocog alfa for the treatment and prevention of bleeding in patients with severe congenital hemophilia A (baseline FVIII ≤1%).

Methods: The turoctocog alfa registration clinical program involves seven clinical trials. The first in human dose trial, performed during 2009, investigated turoctocog alfa PK and included a comparison with octocog alfa. The phase 3a guardian™1 and guardian™3 trials investigated safety and efficacy of turoctocog alfa in the prevention and treatment of bleeds in previously treated adult/adolescent (>12 years of age) and pediatric (<12 years of age) patients, respectively. Both trials included PK assessments, while guardian™1 also had a surgical subtrial. Guardian™1 and guardian™3 were both completed during 2011; participating patients were offered continued turoctocog alfa treatment in the guardian™2 extension trial, a long-term safety and efficacy trial which will continue until turoctocog alfa is commercially available in the respective countries. Two further PK trials investigated turoctocog alfa PK in Japanese subjects using different production lots. Finally, guardian™4, a phase IIIb safety and efficacy study in previously untreated patients (PUPs), is ongoing. Approximately 60 PUPs will be enrolled and followed for ≥100 exposure days (initiated September 2012; estimated study completion date: September 2016).

Summary: The PK properties of turoctocog alfa have been studied in >60 patients and shown to be comparable to those of commercially available rFVIII and plasma-derived FVIII. To date, more than 210 patients have been dosed with turoctocog alfa in 18 countries worldwide. The total turoctocog alfa clinical experience is in excess of 50,000 exposure days and 340 patient years. More than 110 patients have now been on preventive treatment with turoctocog alfa ≥18 months.

Conclusions: This comprehensive global clinical trials program investigating turoctocog alfa PK, safety and efficacy will provide an extensive clinical database. Ongoing work includes defining some of the many possible further analyses of the available data. Future studies will add further important information to the database on turoctocog alfa long-term safety and efficacy in specific patient populations.
The influence of co-morbidities on annualized bleeding rates in patients with severe hemophilia A: experiences from the pivotal turoctocog alfa prophylaxis trial (guardian™1)

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Objective: Individual bleeding rates in severe hemophilia A patients often show high variability. This may be due to differences related to biologic and behavioral patterns, as well as differences in co-morbidities and regional treatment practice. Novo Nordisk has developed turoctocog alfa, a new recombinant FVIII with a truncated B-domain. In the guardian™1 trial, 150 (24 adolescents, 126 adults) previously treated severe hemophilia A patients were given prophylaxis with turoctocog alfa. This trial included patients from 15 countries worldwide. Interestingly, large variation between countries in the annualized bleeding rates was observed, despite following the prophylactic dosing regimen specified in the protocol. The objective here is to investigate the potential influence of frequent co-morbidities on the annualized bleeding rate as a possible explanation of the variation between countries and patients.

Methods: Patients with severe hemophilia A (≤1% FVIII activity), aged 12 years and above, with no history of inhibitors and at least 150 exposure days to other FVIII products, were included. Informed consent was obtained from all patients before any trial-related activity and the trial protocol was approved by appropriate ethics committees or institutional review boards. The trial was conducted in accordance with the Declaration of Helsinki and principles of good clinical practice. At baseline, concomitant illnesses were recorded and a physical examination was performed. For each patient, we will assess two frequent co-morbidities: joints with hemophilic arthropathy and hepatitis C status. The association between these co-morbidities and individual annualized bleeding rates during prophylaxis with turoctocog alfa will be investigated.

Summary: A total of 499 treatment-requiring bleeds were reported by 105 patients, of which 389 were joint bleeds reported by 94 patients. The remaining 110 bleeds were non-joint bleeds reported by 51 patients, while 45 patients did not experience any bleeds during the trial. There was large variation in the country-specific bleeding rates, and for some countries the rates were significantly different. Country-specific annualized bleeding rates ranged from 1.3 bleeds/patient/year (95% Confidence Interval [CI]: 0.5-3.3) based on 6 bleeds in 9 patients to 23.2 bleeds/patient/year (95% CI: 14.6-37.0) based on 58 bleeds in 5 patients. The association between each of the two frequent co-morbidities and individual annualized bleeding rates will be explored graphically and statistically.

Conclusions: Several potential factors may have influenced variation between countries in annualized bleeding rates. The impact of two frequent co-morbidities as potential explanations for the observed variation in the country-specific bleeding rates will be analyzed.
Motivational Interviewing and Health Behavior Change: An Educational Intervention for Healthcare Professionals

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**Objective:** Patient adherence to complex medical treatment regimens is an ongoing concern. Non-adherence is a multifaceted problem, especially for patients with a chronic disease. Patients with hemophilia face many challenges and rely on members of the healthcare team for support, guidance, and assistance. The principles of motivational interviewing (MI) have been shown to impact patient adherence. An educational workshop in the principles of MI, health behavior change (HBC), and stages of change was customized for healthcare teams who care for patients with hemophilia. Program evaluation was conducted for impact and utility.

**Methods:** Healthcare teams at both Hemophilia Treatment Centers (HTCs) and Specialty Pharmacy Providers (SPPs) were invited to attend. Workshops were conducted by Pfizer medical staff in collaboration with each clinical site. The workshops are designed to be interactive to facilitate learning and sharing of clinical experience. Video vignettes illustrate differences in communication style, content and delivery. Specific case studies were developed to address unique issues of non-adherence in hemophilia patients. The program covers the behavioral model, 4 general principles of MI – **REDS** (Roll with Resistance, Express Empathy, Develop Discrepancy, Support Self-efficacy) and Stages of Change. Participants completed a 10-question knowledge assessment prior to and after the workshop and a program evaluation. Each participant identified 2 to 3 principles / strategies that they could “put into practice” following the workshop.

**Summary:** Between March 2012 and June 2013, ten (10) workshops were conducted (7 SPPs, 3 HTCs) and included 98 participants. Results of the knowledge assessment prior to and following the workshop increased from 67% to 85% correct responses, representing an increase of 18%. Overall satisfaction with the workshop was high - greater than 97% of participants agreed or strongly agreed that the workshop helped them to understand the concepts of adherence, MI, HBC and would be able to utilize techniques to enhance their own communication skills and effectiveness when engaging with patients. The concepts most frequently sited that could be “put into practice” included: MI; use of open-ended questions; elicit-provide-elicit technique; assess importance and confidence; and enhancing one’s listening skills.

**Conclusions:** Non-adherence is a multifaceted problem and no single intervention overcomes the many challenges faced by the hemophilia patient. Motivational interviewing is not widely known or practiced by healthcare professionals. The potential exists for enhanced communication, collaboration, patient engagement, adherence and patient outcomes using the concepts of MI, HBC and stages of change.
Characterization of the Binding of a Novel Recombinant Single-Chain FVIII to von Willebrand Factor

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Objective: The binding behavior of rVIII-SingleChain to plasma-derived von Willebrand Factor (pdVWF) was assessed in surface plasmon resonance (SPR) studies.

Methods: The purification of VWF from human plasma–yielded pdVWF free of factor VIII (FVIII). Subsequently, isolated pdVWF was immobilized on a SPR gold chip using monoclonal antibodies (MAbs). Thereafter, the binding behavior of rVIII-SingleChain and full-length rFVIII molecules were studied and binding kinetics were calculated. Regeneration of pd-VWF was performed with calcium chloride, while regeneration of the covalently coupled anti-VWF MAbs was achieved in the presence of an acidic pH.

Summary: The affinity of CSL Behring’s rVIII-SingleChain to pdVWF was significantly higher than those of commercially available rFVIII full-length molecules. The higher affinity was derived from a higher association rate constant, while the dissociation rate constants were comparable. Intriguingly, the higher affinity had no influence on other functional characteristics of rVIII-SingleChain (e.g., the binding to phospholipids, thrombin generation capacity, and FVIII enzymatic activity were comparable to full-length rFVIII). The results obtained from the SPR studies in vitro appear consistent with the observation of improved pharmacokinetic characteristics for rVIII-SingleChain in comparison to full-length rFVIII. After treatment of hemophilia A mice with single doses of rVIII-SingleChain or full-length rFVIII, the systemic availability and mean residence time were found to be increased for rVIII-SingleChain compared to full-length rFVIII. In addition, a decreased clearance rate and an enhanced terminal half-life were observed for rVIII-SingleChain, while in vivo recovery and volume of distribution of rVIII-SingleChain were comparable to full-length rFVIII.

Conclusion: Overall, it seems conceivable that the higher affinity of CSLB’s rVIII-SingleChain to pdVWF may have a positive effect on its systemic availability by a delayed elimination from plasma.
Preclinical PK/PD Characteristics of rVIII-SingleChain, a Novel Recombinant Single-Chain FVIII

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Objective: A novel recombinant coagulation factor VIII, rVIII-SingleChain, produced without added animal- or human-derived materials, is currently in a clinical phase I/III program (AFFINITY). The present non-clinical studies were conducted to investigate the pharmacokinetic (PK) profile of rVIII-SingleChain in animals to support assessment of its PK/pharmacodynamic properties for future clinical use.

Methods: The PK behavior of rVIII-SingleChain was explored in hemophilia A mice, rats, and monkeys. Intravenous doses of 50-250 IU/kg for rVIII-SingleChain or a marketed full-length rFVIII concentrate were given. Systemic FVIII activity or antigen levels were recorded in plasma samples after injection. A thrombin generation assay was conducted to assess coagulation parameters ex vivo after treatment of hemophilia A mice with 250 IU/kg of rVIII-SingleChain or full-length rFVIII.

Summary: In all animal species, treatment resulted in improved PK properties for rVIII-SingleChain compared to full-length rFVIII. Increased systemic availability and mean residence time were observed for rVIII-SingleChain. Correspondingly, the clearance rate was decreased and the terminal half-life was enhanced in comparison with full-length rFVIII. In vivo recovery and volume of distribution of rVIII-SingleChain were equivalent to full-length rFVIII. Consistent with the PK characteristics, rVIII-SingleChain showed a more favorable thrombin generation potential compared to full-length rFVIII between 2-6 days after treatment of FVIII-deficient mice. Results obtained showed that thrombin peak levels were kept between 50-250 nM for an increased period of time by rVIII-SingleChain compared to full-length rFVIII, with an average extension of 20 hours.

Conclusions: The current investigations demonstrated favorable PK properties of rVIII-SingleChain in animal species. The presented results support the evidence necessary for conducting human trials to explore whether such favorable non-clinical PK characteristics may translate into clinical benefit.
Preclinical Characteristics of a Recombinant Fusion Protein Linking Activated Coagulation Factor VII With Albumin (rVIIa-FP)

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Objective: Recombinant factor VIIa (rFVIIa) is approved to control bleeding in hemophilia patients who have developed inhibitory antibodies to replacement therapy. The short half-life of rFVIIa necessitates frequent injections and considerably limits prophylactic use. A recombinant fusion protein linking activated factor VII with albumin (rVIIa-FP) was developed to extend the half-life of rFVIIa. The present studies were conducted to gather knowledge about the procoagulant effect of rVIIa-FP in a venous stasis model and to assess the safety profile in animals to support evaluation of the efficacy and tolerability of rVIIa-FP for clinical use.

Methods: During a good laboratory practice-compliant toxicity program in several animal species, the allergic, immunogenic, and prothrombotic potential of rVIIa-FP; its impact on safety pharmacology variables; and systemic toxicity parameters, as well as the local tolerability, were assessed. When investigating dose responses or duration of effect, rVIIa-FP and NovoSeven®, a licensed rFVIIa, were administered intravenously to normal rabbits before induction of venous stasis. Clot formation and systemic hemostasis parameters were determined to assess pharmacodynamic activity. FVIIa activity was recorded in plasma samples after treatment.

Summary: Overall, the toxicology program showed that administration of rVIIa-FP was well tolerated, with no findings indicative of adverse systemic toxicity or allergic reaction and without any safety pharmacology or local intolerance concerns. Under acute conditions the procoagulant effect of rVIIa-FP was not different from NovoSeven®, whereas at later time points the prolonged systemic availability of rVIIa-FP translated into sustained hemostatic activity.

Conclusions: Consequently, the non-clinical toxicology and safety program proved prolonged activity and a favorable tolerability profile of rVIIa-FP. The presented investigations did not reveal any safety concerns and support the evidence necessary for further clinical development (PROLONG-7FP) in humans.
Relative importance of treatment characteristics to patients and parents of children with hemophilia

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Objective: The importance patients and parents place on different aspects of hemophilia treatments is not well understood, and rating scales are believed to trigger socially desirable responses that may disguise preferences. An alternative technique, referred to as conjoint analysis, can be used to elicit the relative importance placed on different features of a treatment by observing how they trade off different levels of one feature against those of another through a series of hypothetical choices. The current study was conducted to assess the relative importance of frequency of administration, efficacy, and other attributes for hemophilia treatments using this technique.

Methods: Adults with hemophilia and parents of minors with hemophilia were identified through a panel of patients originally recruited from hemophilia treatment centers and associations. Panelists reporting moderate or severe hemophilia A or B were invited to complete an on-line questionnaire including a set of 10 scenarios, each presenting a different treatment, where respondents rated how likely they would be to switch to the described treatment. The attributes of the treatment (efficacy, frequency of administration on prophylaxis, number of vials per infusion, diluent volume, reconstitution device, and manufacturer) and levels (level of efficacy, how frequently administered, etc.) included in the task were selected based on previous research and features of current and upcoming products, and were specific to the type of hemophilia. Analysis was conducted separately for hemophilia A and B using hierarchical Bayes estimation modeling. The protocol and questionnaire were approved by an institutional review board, and all respondents provided informed consent.

Summary (of results obtained): In hemophilia A, frequency of administration on prophylaxis, efficacy, and manufacturer account for over 88% of the total impact of the elements included in the study on the treatment decision process, with frequency of administration having the highest relative importance (46%), nearly twice that of efficacy (24%). Similar results were found in hemophilia B, with those attributes accounting for 95% of the total impact of the elements on the treatment decision process, with frequency of administration again being almost twice (48%) as important as efficacy (26%).

Conclusions: The current study showed that frequency of administration had the greatest impact on hypothetical choices to switch treatments in hemophilia A and B. These results must be interpreted in the context of the range of levels of the attributes presented in the study.
Objective: Adherence to treatment has an important impact on health outcomes in chronic conditions, but the relationship between adherence to prophylactic infusions and outcomes in hemophilia is not well documented. This study was conducted to assess the relationship between adherence to prophylaxis and outcomes, including patient-reported health status and bleeding.

Methods: Adults with hemophilia and parents of minors with hemophilia were identified through a panel of patients originally recruited from hemophilia treatment centres and associations. Panelists reporting moderate or severe hemophilia completed an on-line questionnaire, which included the Validated Hemophilia Regimen Treatment Adherence Scale-Prophylaxis (VERITAS-Pro) for adherence to prophylactic treatment, a measure of health status (adults: SF-12v2 questionnaire; parents of pediatric patients: SF-10) and items assessing the number of times they experienced clinical outcomes, such as breakthrough bleeds, ER visits, hospital admissions, and missed days from work/school due to bleeding episodes. All measures were through self- or parent-report. Generalized linear models were used to assess the relationship between adherence and outcomes, adjusting for age (adults only). The protocol and questionnaire were approved by an institutional review board and all respondents provided informed consent.

Summary (of results obtained): A total of 53 adults with hemophilia A (n=43) or B (n=10) treated with prophylaxis completed the survey and provided age information. In analyses combining these groups, lower adherence was associated with more days of work or school missed due to bleeding episodes in the past year (p<0.05), as well as the number of bleeding episodes requiring administration of replacement factor in the past year (p<0.001). The relationship between adherence and bleeding episodes was also significant in analyses separating A and B patients (p<0.01 and p<0.05, respectively), as was the link between adherence and days missed in hemophilia A (p<0.05). Adherence was not significantly associated with physical health status (p=0.91) among adults. Among pediatric patients treated with prophylaxis (n=56), the relationship between adherence and number of bleeding episodes in the past year was not significant (p=0.95). Adherence was associated with clinical outcomes related to bleeding episodes over the past year, such as infection at the injection site (p<0.05), hospital stay due to bleeding episodes (p<0.001), and missed days from work/school due to bleeding episodes (p<0.01). Furthermore, physical health status was better among more-adherent pediatric patients (p<0.01).

Conclusions: Though sample sizes were limited, greater adherence to prophylaxis was associated with better self-reported clinical outcomes among both adult and pediatric hemophilia patients.
Dosing intervals and bleeding rates before and following treatment with recombinant Factor IX Fc fusion protein in patients with severe hemophilia B: Experience from the B-LONG study

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Objective: Safety and efficacy of long-lasting recombinant factor IX Fc fusion protein (rFIXFc), currently being developed to provide extended protection from bleeding in hemophilia B patients, were demonstrated in the phase 3 B-LONG study, where a half-life of 82 hours was observed. Here we describe how patients in B-LONG who were on prophylaxis with FIX prior to study entry were treated with rFIXFc and their clinical outcomes during B-LONG.

Methods: Patients who were on prophylaxis with FIX prior to study entry were identified. Patients’ self-reported FIX dosing regimen and bleeding rates pre-study were compared to their rFIXFc dosing regimen and annualized bleeding rates on study. All patients were monitored for safety, including inhibitor formation.

Summary: Of 123 patients enrolled, 48 received prophylaxis with FIX pre-study: 33 in Arm 1 (weekly prophylaxis: rFIXFc 50 IU/kg once weekly, dose adjusted based on FIX activity); 15 in Arm 2 (individualized dosing interval: rFIXFc 100 IU/kg every 10 days, interval adjusted based on FIX activity). The most common pre-study dosing intervals were twice weekly (67%), thrice weekly (18%), and once weekly (13%). The 21 patients in Arm 1 reporting twice-weekly dosing pre-study had a median pre-study dose of 36.4 IU/kg per injection (total weekly dose: 72.7 IU/kg); in their last 3 months on-study, these patients received a median dose of 36.4 IU/kg rFIXFc once weekly. The 9 patients in Arm 2 reporting twice-weekly dosing pre-study had a median pre-study dose of 37.9 IU/kg per injection (total weekly dose: 75.9 IU/kg); in their last 3 months on-study, these patients received a median dose of 103 IU/kg rFIXFc at a median interval of once every 13.5 days. Overall, Arm 1 patients on prophylaxis pre-study reported a bleeding rate of 2.5 in the 12 months prior to study entry; on-study, they had an annualized bleeding rate of 2.1. Arm 2 patients on prophylaxis pre-study reported a bleeding rate of 2.0 in the 12 months prior to study entry; on-study they had an annualized bleeding rate of 0.0. Based on population pharmacokinetic modelling, approximately 95% of people with hemophilia B receiving 50 IU/kg rFIXFc once weekly were predicted to maintain FIX trough levels above 1% at all times. In the B-LONG study, rFIXFc was well tolerated and no inhibitor development was detected.

Conclusions: Prophylaxis with rFIXFc may provide patients who are currently on prophylaxis the option for dosing every 1-2 weeks with low bleeding rates.
The National Hemophilia Program Coordinating Center – Assessing Support Needs of HTC Staff

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Objective: In June 2012, the Health Resources and Services and Administration (HRSA) funded the American Hemostasis and Thrombosis Network (ATHN) to establish the first National Hemophilia Program Coordinating Center (NHPCC). The NHPCC’s goal is to improve the lives of person with bleeding disorders by facilitating collaboration and coordinating activities among the eight regional Hemophilia Treatment Center (HTC) networks to strengthen HTC healthcare delivery nationwide. As a first step, the NHPCC conducted a nationwide assessment of HTC staff support needs (services, tools, training and expertise).

Method: A third party consultant, Rural Health Center of South Carolina, conducted a needs assessment of the eight HRSA regional HTC core centers by reviewing their grant applications to develop a matrix of common themes. Using this matrix they interviewed the regional leaders to determine their perception of how the NHPCC could support the national HTC network. To validate the regional leaders’ perception of HTC staff support needs, the consultant sent an e-survey to the multidisciplinary staff at the HTCs to assess their technical assistance needs defined as the provision of knowledge, tools, models and other resources that improve the quality of care, access to care, and availability of services to persons with bleeding disorders. The HTC staff survey uncovered additional assistance needs and preferred delivery methods.

Summary: Regional HTC leadership identified that the NHPCC should: 1. identify gaps in the support needs of the providers through an HTC needs assessment, 2. implement a national patient needs assessment, 3. share best practices across regions, 4. develop a program evaluation, 5. establish standards of care, and 6. assist with quality improvement initiatives.

Conclusion: The information from the staff needs assessments will serve as a framework for the development of national priorities, strategies for quality improvement initiatives, and evaluation of the national program.
Effect of Albumin Fusion on the Biodistribution of Recombinant Factor IX-FP

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Objective: The present study has been conducted to explore the biodistribution of rIX-FP, a recombinant fusion protein linking the human coagulation factor IX to human albumin (CSL Behring GmbH), which is currently being investigated in clinical phase II/III trials (PROLONG-9FP) for prophylaxis and on-demand treatment of bleeding in hemophilia B patients.

Methods: Therefore, [³H]-rIX-FP, [³H]-rFIX, or [³H]-albumin were administered intravenously to male rats at a single radioactive dose of 320-420 µCi/kg. Using whole-body autoradiography, tissue radioactivity was determined up to 240 and 24 h following [³H]-rIX-FP and [³H]-albumin, and [³H]-rFIX administration, respectively. In addition to full body sections, the hind limbs were analyzed separately and plasma, urine, and feces were collected to calculate excretion balance and assess physiological elimination pathways.

Summary: Overall, the tissue distribution of [³H]-rIX-FP and [³H]-rFIX was comparable; both penetrated predominantly into well-perfused tissues, were rapidly present in synovial and mineralized regions of knee joint sections, and seemed to mostly localize to the zone of calcified cartilage within the growth plate regions of long bones, with the longest retention time observed in the bone marrow and endosteum of long bones. Intriguingly, [³H]-rIX-FP signal was detectable over 72 h, whereas comparable [³H]-rFIX signal could only be detected until 24 h post-dosing. Elimination occurred primarily via the urinary route. For [³H]-rIX-FP, after 240 h, 73% of radioactivity was recovered in urine, ≤5% of radioactivity was eliminated in feces, and approximately 20% of radioactivity was present in tissues.

Conclusions: The study shows that rIX-FP exhibits equal biodistribution compared to other marketed recombinant FIX products, but clearly distinguishes itself from rFIX (BeneFIX®) by its extended plasma half-life, allowing a reduction in dosing frequency leading to increased therapeutic convenience and compliance.
Great Plains Regional Girls with Bleeding and Clotting Disorders Camp

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Objective: Camp programs are one of the most successful and valued educational and experiential programs children and teens with a bleeding or clotting disorder can be involved in. Typically, in the bleeding disorders community, females are not diagnosed and/or treated in the same timeframe as males. The time interval between diagnoses and treatment of females is measured in years, which can leave a void in the development of specific programs for these women. As such, The Great Plains Regional Girl’s Camp (GPRGC) was designed to meet the specific needs of girls with a bleeding or clotting disorder.

Methods: In April 2013, the first girls-only camp was organized for young women (12 and 17 years of age) with a bleeding or clotting disorder. The camp was designed as a supplement to the Great Plains Regional Women’s with Bleeding and Clotting Disorders Educational Retreat, which has taken place for the past 14 years.

The primary goals of the GPRGC were to provide a camp environment and experience unique to their specific needs, to create a safe environment that encouraged personal growth, independence and empowerment, and to provide current medical education directed specifically to this age group and diagnosis.

Attendees came from an 8-state geographical area including Texas, Oklahoma, Arkansas, Louisiana, Kansas, Iowa, Nebraska and Missouri. Approximately 30 applications were mailed out, and a total of 8 girls attended the camp, 7 of whom were diagnosed with von Willebrand’s disease and one who had a clotting disorder.

Summary: We found this first girls-only camp to have been a success. Evaluations completed by the attendees were all positive and ranked the program to be excellent. The program content was strong and diverse for the age-group. Additionally, the agenda had a great balance of activities, education and personal wellness.

Currently, there are plans to further develop and enhance this program, and organize a second camp next year, in which we hope to double the number of attendees. The projected three-year plan is to expand the program and provide a full week of camp for these girls.

Conclusions: The GPRGC is a unique camp for young women who are diagnosed with a bleeding or clotting disorder. Its primary goal is to meet the specific needs of this population with respect to education and their diagnoses. The camp can be a potential model for girls with any bleeding or clotting diagnosis to have a camp experience.
Biodistribution of rVIIa-FP, a Recombinant Fusion Protein Linking Coagulation Factor VIIa With Albumin, in Rats

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Objective: The recombinant fusion protein linking the human coagulation factor VIIa to human albumin, rVIIa-FP (CSL Behring GmbH), is currently undergoing clinical investigation in the clinical trial program PROLONG-7P. The present study has been conducted to evaluate and better understand the biodistribution of rVIIa-FP.

Methods: [3H]-rVIIa-FP, [3H]-rFVIIa, or [3H]-albumin were administered intravenously to male rats at a single radioactive dose of 300-400 µCi/kg. Using whole-body autoradiography, tissue radioactivity was determined up to 24 ([3H]-rFVIIa) or 240 ([3H]-rVIIa-FP, [3H]-albumin) hours. In addition to full body sections, the hind limbs were separately subjected to autoradiography to obtain more detailed information on the product distribution within the bone marrow, articular capsule, and synovial region of the knee joints. In parallel, plasma, urine, and feces were collected at pre-dose and at several sampling points throughout the 240-h study period to calculate excretion balance and assess physiological elimination pathways.

Summary: Overall, both [3H]-rVIIa-FP and [3H]-rFVIIa were distributed predominantly into well-perfused tissues and organs and were rapidly present in synovial and mineralized regions of knee joint sections and seem to mostly localize to the zone of calcified cartilage within the growth plate regions of long bones. The longest retention time was observed in the bone marrow and endosteme of long bones. While [3H]-rVIIa-FP–associated radioactivity was well detectable at 72 h, comparable [3H]-rFVIIa–derived signals could only be observed up to 24 h after administration. The major route of elimination was urinary excretion. At 240 h, 74% and 18% of radioactivity was recovered in urine and feces, respectively. Plasma profiling showed that up to 8 h, 100% of the radioactivity could be assigned to unchanged [3H]-rVIIa-FP.

Conclusions: Consequently, this study shows that rVIIa-FP exhibits biodistribution characteristics comparable to competitor products,1 but clearly distinguishes itself by its extended tissue half-life, potentially allowing a reduction in dosing frequency leading to increased convenience and compliance in hemophilia patients with inhibitors.

Psychosocial Intervention To Improve Compliance with Comprehensive Care Visits

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Objective: Patients with hemophilia have been receiving comprehensive care at Hemophilia Treatment Centers (HTC) for the past 30 years which includes: annual medical and psychosocial assessments, training for home infusions of factor, physical therapy evaluations and treatment.

As many of our patients with Hemophilia now self-infuse, they require less visits to the HTC, Emergency Department and hospitalizations. We have noted over the past few years that many patients are delinquent in keeping yearly comprehensive visits. In an effort to increase attendance at comprehensive clinic, and introduce and assess the success of psychosocial interventions, on increasing compliance with appointments, a standard assessment form was created to identify reasons for non-attendance at comprehensive care visits.

Methods: Data collection included characteristics of the household such as marital status and family size, last comprehensive re-evaluation and ages of patients (<18 or >18 years). Assessment of barriers included: drug addiction, school related issues relating to academic success, value of comprehensive clinic during a non-emergent time, DYFS involvement, major psychosocial issues, transportation and work related issues such as financial concerns and concern for using days for non-emergent reasons.

Each identified patient was contacted by the social worker to assess reasons for non-compliance utilizing the standard assessment form. Following the assessment, the social worker created and implemented an individually tailored plan developing interventions and employing education, counseling and supportive services.

Summary: A total of 26 patients were identified as delinquent in comprehensive care visits. Eight were pediatric patients and eighteen were adult patients. All identified patients were called and assessed for barriers to compliance with clinic visits. The major barrier identified was both parents’ and patients’ value of comprehensive clinic during a non-emergent time (46% of patients). The second major barrier was work related issues (31% of noncompliance). Major psychosocial issues (15%) and school issues (8%) accounted for the remaining causes of non-compliance with clinic appointments. Individual plans to address barriers were made and implemented. Following the psychosocial intervention 46% of the previously non-compliant patients made comprehensive clinic visits.

Conclusions: Identification of psychosocial reasons for non-compliance to comprehensive care clinic with the development of individual plans to address needs lead to improved compliance with visits.
EXAMINING THE IMPACT OF PARENT DEMOGRAPHICS, CHILD CHARACTERISTICS AND CHILD HEMOPHILIA RELATED HISTORY ON PARENTAL STRESS AND PARENT SUPPORT

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Objectives: Hemophilia is a chronic disorder characterized by an increased tendency toward hemorrhage that is due to a gene defect in one of two blood clotting proteins, factor VIII (hemophilia A) or factor IX (hemophilia B). Hemophilia A occurs in 1 in 5,000 and hemophilia B in 1 of 30,000 live male births. In 2011, the Centers for Disease Control and Prevention reported that 18,038 individuals with hemophilia were enrolled into the Universal Data Collection in the United States (www.CDC.gov, 2011). Standard hemophilia treatment typically occurs in the home to facilitate early bleeding recognition and management. Consequently, the burden of care falls to parents or caregivers leading to heightened caregiver stress, often in the face of limited caregiver support networks. Our aim is to evaluate how parent demographics, child characteristics and child hemophilia-related history influence parenting self-reported stress and support networks.

Methods: This descriptive study will use a quantitative research method design. Parents of children (<18 years old) with hemophilia will be actively recruited through social media; Facebook (social networking sites of parents of children with hemophilia), websites of national organizations, local chapters, HTCs and CDC Regional Coordinators. There is no medical risk to this data collection. Data is a one-time collection by web-base survey and does not contain information that is individually identifiable. Parents will be asked to complete a brief questionnaire and the Pediatric Inventory for Parents (PIP) (Streisand, etc., 2001) via a web-based electronic survey (SurveyMonkey). The PIP tool is grouped into 4 domains: Communication, Emotional Functioning, Medical Care and Role Function. Survey link is as follows: https://www.surveymonkey.com/s/ParentingHemophilia

Summary: Data will be managed with Microsoft Excel 2010 and analyzed with SPSS software. Frequencies, descriptive statistics and histograms will be used to describe data and assess normality. Parametric tests will be performed for normally and non-parametric tests will be performed for ordinal and non-normally distributed continuous data. Any major findings will be distributed by post on the RUSH Hemophilia and Thrombophilia Center website at www.rush.edu/whybloodclots.

Conclusion: Interpretation of these data will add to existing research in order to further contribute to the development of successful parenting programming treatment efforts to reduce stress and improve health outcomes, quality of life and wellbeing of parents and caregivers of children with hemophilia.
Prolonged factor IX expression after AAV-mediated gene transfer in adults with severe hemophilia B

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Objective: A phase I/II clinical trial is currently testing the efficacy and safety of factor IX gene transfer using a novel adeno-associated viral vector construct. This vector is pseudotyped with AAV serotype 8 capsid, encodes a codon-optimized human FIX transgene, has a self-complementary genome, and is delivered by peripheral vein. We have previously reported early results on 6 patients with severe hemophilia B following vector infusion of 1 of 3 vector doses (low: 2x10¹¹ vg/kg; intermediate: 6x10¹¹ vg/kg; or high dose: 2x10¹² vg/kg) (Nathwani et al, NEJM 365:2357-65, 2011). Participants achieved FIX expression at 1-6% after initial follow-up of 6-14 months. Longer follow-up data are now reported as well as findings in additional participants recently infused at the high dose vector level.

Methods: A single dose of the novel, FIX gene containing AAV vector (scAAV2/8-LP1-hFIXco) was administered to 10 adult participants with severe hemophilia B at low dose in 2, intermediate dose in 2, and high dose in 6 participants.

Summary: Participants have been followed for 0.5 to 3.3 years after vector infusion and maintain FIX levels between 1-8%. Participants having received the low and intermediate vector dose have FIX levels of 1-3%; 2 participants are off prophylaxis, 1 participant remains on prophylaxis due to significant hemarthropathy, and 1 has significantly prolonged the intervals between prophylactic factor infusions. Participants receiving the high dose are off prophylaxis, have achieved FIX levels greater than 3%, and have not had any significant spontaneous bleeding. No serious adverse events were observed in participants receiving the low and intermediate vector dose. Several of the high dose participants developed acute, asymptomatic liver inflammation during week 7-9 post infusion. Transaminase elevation was associated with a rise in circulating capsid-specific T-cells in some, but not all cases, indicating cytotoxic T-cell response towards transduced liver cells. The transaminits resolved completely in all cases in response to a short course of oral prednisolone while FIX expression was maintained.

Conclusions: These results represent the first successful, long-term expression of FIX after AAV-mediated gene transfer via peripheral vein. Immune-mediated destruction of transduced liver cells remains a concern, but can be overcome with short-term oral prednisolone. Further evaluation of efficacy, risks, and optimal vector dose is necessary in a larger cohort. This gene therapy approach has the potential to change a severe bleeding phenotype of hemophilia B into a milder form for a prolonged period of time.
Long-Term Follow-Up of Arteriovenous Fistulae in Bleeding Disorders

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Objective: Treatment of bleeding disorders consists of factor replacement on-demand in response to acute bleeding or prophylactically to prevent bleeding. Venous access is a critical aspect of hemophilia care. Placement of Arteriovenous Fistulae (AVF) has previously been reported (Urgo, J et al 2008). We are reporting the long-term use of the AVF and an additional 3 patients.

Methods: All patients who received an AVF had their records reviewed and they were evaluated for their AVF usage patterns, perceived appearance, longevity of use, and overall satisfaction. The insertion protocol has been previously reported. Each patient’s AVF was assessed routinely at each clinic visit.

Summary: There were 17 AVF insertions in 16 patients: two von Willebrand disease, 12 Hemophilia A (3 inhibitor), and 3 Hemophilia B (1 inhibitor). Mean follow-up was 5 years (1-13 years). 15 patients had excellent results with adequate flow and patients/caregivers were able to easily access the AVF for treatment. 1 patient, who underwent 2 procedures, had a poor surgical result with inadequate blood flow to the AVF. No patients had bleeding complications from AVF creation. No patients have an AVF related infection over 5 years. Patients have not experienced any difficulty accessing the AVF for administration of factor. Four patients have reported dissatisfaction with the appearance of the AVF. All reported embarrassment over appearance, self-consciousness, wear clothing to hide the AVF, and limited participation in activities where others may question the AVF. All report the AVF works well, no issues with access, and increased confidence in self-infusion. These patients all had enlarged AVF with increased blood flow as demonstrated by fistulogram. 1 patient had revision with banding that had excellent results as well as improved appearance and continued excellent intravenous (IV) access. Two more patients are scheduled for revision. The 4th patient had removal of the AVF due to increased availability of peripheral access.

Conclusion: AVF continues to be a viable option in patients who do not have IV access and have had repeated complications with other methods of IV access. The complication rate for insertion is 3/17 (18%). Excellent IV access was achieved in 15/16 (94%) patients. Overall satisfaction is good with 9/13 (69%) patients reporting excellent function, ease of access, and satisfaction of the cosmetic appearance of the AVF.
Specialty Pharmacy Educational Program, BE EMPOWERED, decreased joint bleeds in adults and increases RICE utilization among caregivers.

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\textbf{Objective:} Hemophilia Treatment Centers (HTC) have historically provided hemophilia education for patients and families. Once the diagnosis and treatment regimen have been established, HTC contact can be episodic. More frequent contact with health care providers may support enhanced adherence to factor therapy and application of RICE. In the area of hemophilia, specialty care pharmacies (SCP) can support educational reinforcement of HTCs, support patient self management and education re their medication therapy. A SCP was utilized to administer a multi-module educational program (BE EMPOWERED) to determine if an SCP, utilizing BE EMPOWERED materials, would improve outcomes in patients with Hemophilia B.

\textbf{Methods:} Patients with Hemophilia B and their families were enrolled in the BE EMPOWERED program which consisted of 3 printed educational modules focused on managing hemophilia, tips for maintaining a healthy lifestyle, and creating healthy environments. SCPs made regular telephone contact 1 week after each module was mailed, to assure understanding, use and answer questions. Bleeds were tracked. A Pre and Post questionnaire was administered to determine the effect of education on use of RICE, annualized bleed rates (ABR)and quality of life (QoL; HAEMO-QoL-A) scores.

\textbf{Summary:} A total of 39 caregivers and 32 patients completed the program. Participation and completion of the BE Empowered program among caregivers was associated with a statistically significant increase in RICE utilization (baseline 81%, follow-up 95%, \(p=0.05\)). Figure 1 illustrates a statistically significant decrease (ABR) for total bleeds (4.7 \(\rightarrow\) 2.5) at program completion and Figure 2 for a significant decrease in joint bleeds (3.5 \(\rightarrow\) 1.7; \(p<0.02\)) in adults but not among children (1.1\(\rightarrow\)1.2). Overall, adult QoL scores were lower than those of children.

\textbf{Conclusions:} The use of SCPs to support education in the care of Hemophilia B patients represents an additional and unique support service that has frequent, continuing patient and family contact. The BE EMPOWERED education program increased RICE utilization among caregivers and lowered ABR among adults. Future work will utilize the program with additional SCPs and HTCs to extend these findings. This manuscript is under review by the Journal of Managed Care Pharmacy.
Accommodating cultural needs and crossing language barriers in bleeding disorder patients: Results from a provider-patient survey by home infusion provider

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Objective: To demonstrate that providing homecare services to bleeding disorder patients with limited English proficiency in a culturally sensitive manner and in their native language can improve quality and outcomes of care.

Methods: Provider and patient surveys were developed to measure the perceived value of interventions. Respondents were asked to rank dimensions of clarity of translated information, cultural sensitivity, satisfaction, and patient outcomes following homecare interventions on a scale of 1-9. Four patients from different ethnic backgrounds as well as their respective medical providers responded to a survey developed by the authors.

Results: Our survey and its results, despite small numbers, demonstrate that patients as well as providers see value and improved outcomes when bilingual/bicultural professionals, interpreters and/or qualified translators were provided. Out of a total possible score of 9, an average score of 8.75 to 9 was obtained on the patient surveys. Patient respondents agreed that the information related to their treatment or care was provided in a language that was easy to understand and agreed the homecare service providers accommodated their cultural, religious or spiritual belief practices. Among the surveyed providers, services were ranked at an average of 8.75/9. The providers agreed that the language needs and cultural barriers of their patients were well addressed. It was reported that they “strongly believed” their patients “received accurate instruction on the prescribed treatment plan in a language that was easy for the patient/caregiver to understand” and addressing those needs “exceeded their expectations”.

Conclusion: According to the Hemophilia Data Set (HDS) there has been a 236% increase in the Hispanic population and a 71% increase for other ethnic populations from 1990 to 2010. Our program has also seen a significant rise in the number of non-English speaking patients on service. This changing demographic landscape necessitates reform in the service delivery in terms of accommodating the needs of cultural diversity and overcoming language barriers. In order to do so, a continuous channel of communication is of high value to monitor and modulate changes in the population. Our survey and its results, demonstrate our success towards those ends, and hopefully will contribute to the continuous quality improvement (CQI) process in the provision of culturally competent care.
Understanding the psychosocial undercurrents in spontaneous bleeds in severe hemophilia A to facilitate collaboration and customized/personalized regimens: a case study

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Objective: To examine the causes for spontaneous bleeds in severe hemophilia A patients on prophylaxis in an effort to increase care collaboration, decrease these incidents and optimize care.

Methods: From our company’s bleeding disorders patients’ prescriptions and assessment records databases between April 1, 2011 and March 31, 2012 (12 months period), prescriptions and assessment records were analyzed for prophylaxis (factor VIII) patients with severe hemophilia A who did not have inhibitors and who had at least one bleed (self-reported) requiring extra factor in the last 12 months. Due to limitations related to data retrieval from different databases, we eliminated all the patients where accuracy of match was doubtful resulting in a reduced “N”. Out of the 52 patients, 17 were identified with at least one spontaneous bleed. To identify details of psychosocial environment that might have contributed to the bleeds, chart reviews were done on five among them who reported two or more spontaneous bleeds.

Results:

Patients with four bleeds:

Patient A developed a left ankle target joint. Patient has not consistently reported bleeds to HTC. Specialty RPh notified HTC for evaluation of dose and to report bleed pattern.

Patient B frequently missed doses resulting in spontaneous bleeds.

Patients with three bleeds:

Patient C communicated well with home care and HTC. This collaboration contributed to care plan personalization and an increase in dose and frequency resulting in cessation of spontaneous bleeds.

Patients with two bleeds:

Patient D is a toddler making it difficult to identify spontaneous versus trauma induced bleeding. Homecare nurse communicated frequently with HTC leading to dosing adjustments resulting in rare spontaneous bleeds.

Patient E is a non-compliant teen and at times does not adhere to his prophylactic regimen.

Conclusion: The goal of prophylaxis should be zero spontaneous bleeds. There are a variety of factors that might contribute to the bleeds such as lack of compliance, development of target joints, age, growth spurts, or improper dosing frequency and amount. Collaborating with a home infusion company or specialty pharmacy can afford an opportunity to identify and address some of these factors to take corrective actions wherever possible and hence to optimize outcomes.
H. Pylori as a cause of iron deficiency in children with bleeding disorders.

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Objective: Describe the role of \textit{H. pylori} as a cause of chronic iron deficiency in children with congenital bleeding disorders.

Methods: As part of their routine comprehensive care children at our haemophilia treatment center have a CBC done. Over the past year 4 children who underwent diagnostic workup for microcytic anemia were found to have iron deficiency associated with \textit{H. pylori} infection. We describe the clinical findings in these children and their outcomes after appropriate therapy.

Summary: From March 2012 to March 2013, 4 children were identified with iron deficiency anemia due to \textit{H. pylori}. None of the 4 patients gave a history of excessive blood loss and none had GI symptoms such as weight loss, abdominal pain, vomiting or diarrhea. Clinical and laboratory findings at presentation are summarized below. No patients had thrombocytopenia.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (yr)</th>
<th>Gender</th>
<th>Diagnosis</th>
<th>Hgb (g/dl)</th>
<th>MCV (fl)</th>
<th>Retic (%)</th>
<th>Ferritin (ng/ml)</th>
<th>H. pylori</th>
</tr>
</thead>
<tbody>
<tr>
<td>IM</td>
<td>8</td>
<td>M</td>
<td>FVIII def</td>
<td>9.4</td>
<td>73.7</td>
<td>2.5</td>
<td>11</td>
<td>Neg</td>
</tr>
<tr>
<td>RG</td>
<td>14</td>
<td>M</td>
<td>FVIII def</td>
<td>6.4</td>
<td>67.7</td>
<td>3.8</td>
<td>4</td>
<td>Pos</td>
</tr>
<tr>
<td>SG</td>
<td>13</td>
<td>M</td>
<td>FVIII def</td>
<td>10.7</td>
<td>68.3</td>
<td>1.6</td>
<td>12</td>
<td>Pos</td>
</tr>
<tr>
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<td>19</td>
<td>F</td>
<td>vWD</td>
<td>10.7</td>
<td>79.6</td>
<td>8</td>
<td>8</td>
<td>Neg</td>
</tr>
</tbody>
</table>

Only one patient had positive occult blood in stool (RG) and underwent endoscopy. Diagnosis of \textit{H. pylori} was made on gastric biopsy. RG also had 4 weeks of IV iron sucrose therapy. All patients were seen by gastroenterology and successfully treated with triple therapy consisting of amoxicillin, Biaxin, and omeprazole. RG had a recurrence and was retreated with quadruple therapy consisting of amoxicillin, metronidazole, omeprazole, and bismuth subsalicylate. All 3 patients with FVIII deficiency were also on secondary prophylaxis.

Conclusions: \textit{H. pylori} is a common cause of gastritis and often presents with upper gastrointestinal symptoms. It is also associated with idiopathic thrombocytopenic purpura. However, in children with congenital bleeding disorders, it may present with few symptoms and an incidental finding of iron deficiency anemia. We suggest that children with bleeding disorders should be screened for \textit{H. pylori} as a cause of iron deficiency.
Preclinical Research with Recombinant Factor VIIa Fusion Proteins with Enhanced In vitro Activity and Improved Half-Life in Mice

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Objective: Recombinant activated factor VII (rFVIIa) is approved for on-demand treatment of bleeding episodes in hemophilia patients with inhibitors. However, multiple doses of rFVIIa at high concentration are often required in part due to its low affinity for platelets and short half-life. The objective of this work was to explore a new method to increase the activity of rFVIIa by directing the protein to the surface of platelets, the site of pharmacological activity of rFVIIa in bypass therapy, by fusion to single-chain fragment variable (scFv) antibodies against the most abundant protein found on the surface of platelets, the integrin αIIbβ3. In order to increase the half-life of platelet-targeted rFVIIa molecules, they were fused to XTEN, an unstructured hydrophilic polypeptide with a large hydrodynamic radius that shields the resulting fusion protein from clearance.

Methods: Monoclonal antibodies raised against human αIIbβ3 were characterized in a series of in vitro and in vivo assays to select ones that neither inhibited platelet function nor caused platelet activation. The optimal candidate antibodies were then converted to scFv and fused to FVIIa, and the activity of these fusion proteins was assessed in assays that utilized platelets, such as whole blood rotation thromboelastometry (ROTEM) assays. The FVIIa-scFv fusion protein with highest activity was selected and fused to a 288 amino acid XTEN sequence in a number of configurations, and the activity characterized in similar assays. Finally, the half-life of the optimal platelet-targeted rFVIIa-XTEN fusion protein was examined in vivo.

Summary: Antibodies and rFVIIa-scFv fusions were characterized, and a number were found to be inert with respect to affecting platelet function, but increased the rFVIIa activity in platelet-containing assays up to 50-fold relative to rFVIIa. Although fusion of XTEN to rFVIIa decreased its activity, the configuration of the FVIIa/scFv/XTEN fusion was optimized to increase the activity 2-5 fold relative to rFVIIa, as well as increase the half-life significantly in hemophilia A mice.

Conclusions: Targeting FVIIa to platelets was found to increase the activity in platelet-based assays, while not affecting any other platelet function. The combination of platelet-targeting with fusion to XTEN generated molecules with significantly longer half-lives in mice as well as increased activity over rFVIIa alone. These technologies may lead to improved bypass therapies utilizing a wildtype FVII sequence, which differentiates this approach from previous methods that introduced mutations to increase activity, but were terminated after clinical trials demonstrated that these mutant proteins generated antibodies against them.
A-LONG: Phase 3 Study of Long-Lasting Recombinant Factor VIII Fc Fusion Protein (rFVIIIFc) in Hemophilia A

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Objective: Currently available recombinant factors (rFVIII) for hemophilia A have short half-lives; thus, frequent injections are needed to effectively prevent bleeding and/or resolve bleeding episodes. A long-lasting replacement therapy could help people with hemophilia A overcome this barrier by reducing the injection frequency and providing prolonged protection from bleeding. Fc fusion is an established technology that leverages a naturally-occurring recycling pathway involving a receptor called the neonatal Fc receptor (FcRn) and was used to extend the half-life of FVIII. We report herein one of the largest clinical studies conducted in hemophilia A. The purpose of the A-LONG study was to assess the efficacy, safety, and pharmacokinetics (e.g., how long the drug stays in the body) of rFVIIIFc for prevention and treatment of bleeding episodes, and controlling bleeding during surgery in people with hemophilia A.

Methods: Previously-treated males ≥ 12 years of age with severe (<1 IU/dL) hemophilia A were enrolled in the A-LONG study. There were three treatment arms: Arm 1 (individualized prophylaxis with pharmacokinetic-driven adjustment of dose and interval), Arm 2 (weekly prophylaxis with a constant dose throughout study), and Arm 3 (episodic treatment, i.e. rFVIIIFc injections as needed to treat bleeding episodes).

Summary: The study included 165 participants from 60 sites in 19 countries. rFVIIIFc had a mean half-life of 19.0 hours, longer than the 12.4 hours observed with rFVIII (Advate®), p<0.001. Most participants in Arm 1 achieved a dosing interval of 3.5 days or longer, and approximately 30% of these participants achieved a dosing interval of 5 days during the last 3 months of study. The median number of bleeding episodes per year was 1.6 in Arm 1 (individualized prophylaxis) and 3.6 in Arm 2 (weekly prophylaxis), each less than that of Arm 3 (episodic treatment), 33.6. A single injection was sufficient to resolve 87.3% of the bleeding episodes. In participants undergoing major surgery during the study, control of bleeding with rFVIIIFc was rated as excellent or good in all 9 cases. None of the study participants developed inhibitors to rFVIIIFc, and reported adverse events were consistent with that expected in the general hemophilia A population.

Conclusion: The A-LONG study is the first clinical study to demonstrate the efficacy and safety of rFVIIIFc in the prevention and treatment of bleeding in people with severe hemophilia A. The long-lasting protection provided by rFVIIIFc may potentially reduce the burden of treatment and improve adherence in people with hemophilia A.
Objective: Prophylactic factor IX (FIX) therapy is the optimal treatment for hemophilia B; however, currently available products have short half-lives, and require frequent intravenous injections (2-3 times/week) to maintain protective FIX levels. People with hemophilia B may benefit from a longer-lasting FIX, which may provide prolonged protection from bleeding and require less frequent injections. Recombinant factor IX Fc fusion protein (rFIXFc) utilizes a naturally-occurring pathway to delay the breakdown of the clotting factor and cycle it back into the bloodstream in order to prolong FIX activity. We report here the results of the B-LONG study, one of the largest clinical studies conducted in hemophilia B. The purpose of this study was to assess the safety, efficacy, and pharmacokinetics (e.g. how long the drug stays in the body) of rFIXFc for prevention and treatment of bleeding episodes, and controlling bleeding during surgery in people with severe hemophilia B.

Methods: Previously-treated males ≥ 12 years of age with severe hemophilia B (<2 IU/dL) were enrolled in the B-LONG study. There were four treatment groups: Arm 1 (weekly prophylaxis with pharmacokinetic-driven rFIXFc dosage adjustment), Arm 2 (individualized interval prophylaxis with rFIXFc and adjustment of time between injections), Arm 3 (episodic or on-demand treatment with rFIXFc injections as needed to treat bleeding episodes), and Arm 4 (participants undergoing major surgery using rFIXFc to control bleeding).

Summary: This study included 123 males at 50 sites from 17 countries. The mean half-life for rFIXFc was 82.1 hours, significantly longer than that of rFIX (BeneFIX®), p<0.001. For all participants in the individualized interval group (Arm 2), the length of time between rFIXFc injections was at least one week; >50% of participants achieved a dosing interval of 14 days or longer. The median number of bleeding episodes per year was 3.0 in Arm 1 and 1.4 in Arm 2, each less than that of Arm 3, 17.7. 90.4% of bleeding episodes were treated with a single injection. Bleeding control was rated excellent or good in all major surgeries performed on study. rFIXFc was generally well-tolerated, and no inhibitors were detected in any participants.

Conclusions: rFIXFc is well-tolerated in individuals with hemophilia B, and has a longer half-life than rFIX. These data demonstrate that rFIXFc may improve management of acute bleeding events and increase time between injections for prophylactic regimens used in severe hemophilia B, potentially reducing treatment burden and improving adherence in people with hemophilia B.
Prevalence and Predictors of Food Insecurity in Children with Hemophilia

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Objectives: The purpose of this pilot study was to quantify prevalence of food insecurity and determinants among households including children with hemophilia. Food insecurity, the limited or uncertain availability of nutritionally adequate and safe food, negatively affects children’s development and health. Households including people with hemophilia may be at increased risk for food insecurity due to hemophilia-related medical expenses and employment limitations.

Methods: Food insecurity and health status, as assessed at annual comprehensive visits from May 2012-January 2013 were obtained by chart review. A two-question, validated screening tool was used to assess food insecurity status. Descriptive statistics were applied to summarize participant characteristics. This study was approved by the Oregon Health & Science University Institutional Review Board.

Summary: Data were available for forty-two male participants, aged 0-18 years, 42.9% had mild or moderate hemophilia and 57.1% severe. Prevalence of food insecurity overall was 16.7% (95% CI 5.4-28.0%), similar to national averages; food insecurity was rare among those with mild and moderate disease (5.6%) and concentrated among those with severe disease (25.0%; 95% CI 7.7-42.3%). Additionally, children who were older, taller, heavier, had higher body mass index (BMI) status, or were identified as a minority race or ethnicity were at increased risk for food insecurity (all P>0.05).

Conclusions: This study provides pilot data showing the need for food insecurity screening and linkage to resources as a routine part of care, and the need for improved understanding of the determinants of food insecurity in this population.
The use of Low Molecular Weight Heparins in Pregnancy: A single center experience 2002-2012

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Objective: Thrombophilias have been associated with recurrent fetal loss. Second and third trimester fetal losses have strong evidence to suggest that an inherited or acquired thrombophilia increases the risk of fetal loss and low birth weight. Successful pregnancy outcome is dependent on the placental-utero circulation. Antithrombotic therapy with a low molecular weight heparin (LMWH) may prevent pregnancy loss in women with thrombophilias. There is a wide variation for monitoring LMWH during pregnancy – from no monitoring or adjustment to frequent anti-factor Xa monitoring. We report our 10 years of experience with Dalteparin in pregnancy.

Methods: All pregnant women sent for referral were considered for the use of a LMWH and low dose aspirin. Criteria for use of LMWH were recurrent fetal loss, fetal loss with a thrombophilia, history of a thrombus, and failure to conceive with a thrombophilia. Women began a LMWH at time of ovulation or conception and continued until a minimum of 28 weeks of gestation. If the woman had a previous history of thrombosis, the anticoagulation was continued up until time of delivery and for a minimum of 6 weeks post-partum. Anti-Factor Xa activities prior to the dose and 2 hours post-dose were obtained 3 days after starting the LMWH and every 2 weeks. The goal anti-Xa activity was 0.01-0.2 trough and 0.25-0.4 peak. The LMWH was held for 24 hours prior to delivery when possible. We have reviewed data from 2002 – 2012 for women who were pregnant and receiving LMWH at this prophylactic dose. All women received calcium supplementation while taking LMWH.

Results: 128 women had 169 pregnancies. Eighty one of these pregnancies have been evaluated to date. The average daily dose of Dalteparin was 78466 (3500 – 13077) units given once to two times a day. During second trimester the majority of women had low trough anti-Xa activities and had to increase the frequency of injections to twice daily. On average women spent 29 (8-42) weeks on LMWH therapy with an average trough anti-Xa activity of 0.07 (0.02-0.18) and a peak of 0.34 (0.24 – 0.51). All women tolerated the LMWH well without bleeding complications. Ten of the 81 pregnancies (12%) did not progress beyond the first trimester. There was no post-partum bleeding and no fetal bleeding.

Conclusion: LMWH is safe for use during pregnancy. Anti Xa activities should be monitored especially during the second trimester due to an increased clearance during this stage of pregnancy.
Burden Of Bleeding Episodes Among Persons With Hemophilia B

Objective: To characterize the one-year bleeding pattern and assess the burden of bleeding among persons with hemophilia B, a subgroup of individuals with hemophilia that is frequently under-represented in population-based and health services surveillance.

Methods: Hemophilia Utilization Group Study Part Vb (HUGS-Vb) collected prospective information about bleeding episodes, healthcare utilization, and burden of illness among persons with hemophilia B who obtained comprehensive care at one of ten hemophilia treatment centers in eleven geographically diverse states. Participants completed an initial interview and quarterly follow-up surveys. This analysis reports on baseline and one-year follow-up data from 93 participants. Wilcoxon-Mann-Whitney tests were used to determine the differences among subgroups. Spearman correlation coefficients (rho) were used to assess the relationship between bleeding episodes and utilization of health-related care.

Results: Of the 93 participants, 50 (54%) were children. Forty-four (47%) participants (24 children) had severe hemophilia B, of whom 26 (59%) (16 children) reported using prophylactic therapy at initial interview. Fifty-eight (62%) participants reported having at least one bleeding episode within the one-year follow-up period. Mean number of bleeding episodes among participants with mild, moderate or severe hemophilia were 2.11±2.75, 3.47±6.25 and 6.53±7.66, respectively. Participants with severe hemophilia on prophylactic therapy had significantly (p=0.0203) fewer bleeding episodes (4.67±6.31), compared to those on episodic therapy (9.22±8.76). Significantly fewer outpatient visits (rho=0.2831, p=0.0060) and emergency room visits (rho=0.2810, p=0.0064) were reported among participants with fewer bleeding episodes. Mean absent days from work/school due to hemophilia among all participants was 2.24±4.58, and it was 0.98±2.16 days among parents of children under 18 years. Increased bleeding episodes were positively associated with increased days absent from work/school among both participants (rho=0.4598, p<0.0001) and parents of children (rho=0.3433, p=0.0147). Moreover, Positive relationship were found between increased bleeding episodes and increased time spent on the telephone with hemophilia centers (rho=0.5399, p<0.0001), pharmacists (rho=0.3373, p=0.0009) and employer/school personnel (rho=0.2230, p=0.0317).

Conclusions: The HUGS Vb study documents the considerable burden of illness imposed by frequent bleeding episodes on persons with hemophilia B. These episodes increase patient and caregiver absenteeism from work/school, due to increased healthcare utilization and work/school coordination. As participants on prophylactic therapy have significantly fewer bleeding episodes than those on episodic therapy, prophylaxis should be encouraged among persons with hemophilia.
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Factor for Felons; Management of Incarcerated Hemophiliacs

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Objectives: In 2011, 6.98 million offenders were documented in the adult correctional system. In 2001, the state operating costs designated 12% towards medical care or $11.97/day per inmate for the general population. Common co-existing health problems identified are: arthritis (13%), hypertension (11%), asthma (10%), and heart problems (6%). Less than 5% of inmates have health issues related to cancer, diabetes, liver or renal problems, and communicable diseases. The leading cause of death is suicide (33.2%), followed by heart disease (26.1%). Despite these statistics, and the increased need for health care, quality is lacking. Efforts to develop quality measurement systems focused on cancer care, geriatrics, infections disease, metabolic diseases to name a few are in progress. Given these statistics, one would expect that a small proportion of patients from HTCs will spend some time within the justice system. Currently there is no data addressing hemophilia care needs while incarcerated.

Methods: This presentation will review the current health care issues in the adult correctional system. Additionally, at 6 case reports of incarcerated hemophiliacs, whether in the city, state, or federal system will be highlighted exploring the successes and challenges with maintaining hemophilia care, addressing the priority of meeting the hemophilia care needs verses the penal system regulations.

Summary: It can be expected that at some point, the HTC will experience a patient incarcerated for some period of time. The HTC will continue to advocate for their patient within this system, despite the many challenges faced.

Conclusions: Despite the challenges outlined, ongoing communication and education with the correctional system, education of the medical personnel, and prison personnel remains the priority as we advocate for our patients.
PROSPECTIVE STUDY OF PLASMA-DERIVED FACTOR VIII/VWF IN IMMUNE TOLERANCE INDUCTION THERAPY: THE SPIRIT REGISTRY

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Objectives: Hemophilia A patients who develop inhibitors are difficult to manage clinically and resultant treatments can lead to significant healthcare expenditures. Other than the International Immune Tolerance Study, prospectively collected data that describe how patients respond to immune tolerance induction (ITI) therapy are lacking. The objectives of the SPIRIT registry are to understand patients’ response to ITI treatment with a plasma-derived factor VIII/VWF complex (Alphanate®, Grifols, Los Angeles, CA), assess tolerance to ITI dosage regimens with FVIII/VWF, and to estimate the frequency of adverse events that are known to occur during ITI therapy.

Methods: Hemophilia A patients with evidence of persistent inhibitors and receiving Alphanate for ITI therapy are eligible for enrollment. Participants must have recently initiated ITI treatment with Alphanate for primary or rescue therapy. The primary outcomes will include efficacy (success, partial success, or failure), adverse events, and quality of life. Patients whose inhibitors resolve will be followed for an additional 12 months. This prospective observational registry will be conducted at hemophilia treatment centers (HTC) in the US.

Summary: The SPIRIT registry will enroll hemophilia A patients with inhibitors receiving a plasma-derived factor VIII/VWF product. The registry will collect prospective data on primary as well as rescue ITI therapy.

Conclusion: The SPIRIT registry will complement currently available information and provide important, prospective data to support the management of hemophilia A patients with inhibitors.
Cardiovascular management in hemophilia: acute coronary syndromes – an assessment by the ADVANCE Working group on applicability of the ESC Guidelines

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Objective: Age is a major risk factor for cardiovascular disease. Comprehensive care and the improved safety of factor replacement therapy and therapeutic approaches, such as prophylaxis, have increased life expectancy for people with hemophilia (PwH).

PwH may acquire cardiovascular risk factors (such as diabetes, hypertension, hyperlipidemia, obesity and renal disease) as a consequence of advancing age, lifestyle and hemophilia-related conditions, yet little information is available on cardiovascular risk assessment among PwH.

The ADVANCE Working Group, an expert panel of European hemophilia centers supported by an educational grant from Bayer Healthcare, convened to raise awareness of age-related comorbidities among PwH. There are currently no evidence-based guidelines for antithrombotic management in PwH presenting with acute coronary syndrome (ACS). ADVANCE met to perform a review of the current European Society of Cardiology guidelines, and to consider how best they should be adapted for PwH.

Methods: Structured communication techniques based on a Delphi-like methodology were used to achieve expert consensus on key aspects of clinical management.

Summary: The main final statements are: a) ACS and myocardial revascularization should be managed promptly by a multidisciplinary team that includes a hemophilia expert; b) Each comprehensive care center for adult PwH should have a link to a cardiology centre with an emergency unit and 24 hour availability of PCI; c) PCI should be performed as soon as possible under adequate clotting factor protection; d) Bare metal stents are preferred to drug eluting stents; e) Anticoagulants should only be used in PwH after replacement therapy; f) Minimum trough levels should not fall below 5-15% in PwH on dual antiplatelet therapy; g) The duration of dual antiplatelet therapy after ACS and PCI should be limited to a minimum; h) PwH receiving antiplatelet therapy should be offered gastric protection; i) The use of GPIIb-IIIa inhibitors is not recommended in PwH other than in exceptional circumstances; j) The use of fibrinolysis may be justified in PwH when primary PCI (within 90 minutes) is not available ideally under adequate clotting factor management.

Conclusion: It is hoped that the results of this initiative will help to guide optimal management of ACS in PwH.
Atrial Fibrillation in People with Hemophilia: a Cross-Sectional Evaluation in Europe by the ADVANCE Working Group

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Objective: With increasing life expectancy of people with hemophilia (PWH) in developed countries, the number of PWH affected with age-related diseases is also increasing. Atrial fibrillation is a common health problem in the general population, but in PWH, evidence-based guidelines for the management of AF are lacking.

The aim of this cross-sectional pan-European study is to analyze the prevalence of AF and risk factors for stroke in our adult hemophilia population and to document current anticoagulation practice.

Methods: The ADVANCE Working Group consists of members from 14 European hemophilia centers. Each center retrieved data on the number of PWH with AF in their hemophilia population, as well as their total number of adult PWH. For each person with AF, a case report form was completed.

Summary: In total, 29 PWH with AF were documented. The mean age was 68.2 years (IQR 62-75.5). Hemophilia was severe in 6 (20.6%), moderate in 6 (20.6%) and mild in 17 (58.6%) patients. The prevalence in the total studied hemophilia population was 0.94% (29/3094) and increased with age; in patients >40 years it was 1.7% (29/1723) and in patients >60 years 3.6% (23/635). The mean CHA2DS2-Vasc score was 1.3 (IQR 0-2). Hypertension was reported in 12 patients (41.4%), diabetes in 3 (10.3%), previous stroke or TIA in 1 (3.4%), peripheral vascular disease in 4 (13.8%). In 11 patients (37.9%), anticoagulation was started of whom 9 low dose aspirin and 2 vitamin K antagonists. Of these 11 patients, 9 had mild hemophilia, 1 moderate and 1 severe with FVIII prophylaxis. During follow-up after diagnosis (mean follow-up 52.9 months), there were no thrombotic events reported, nor increases in bleeding severity.

Conclusions: In this largest cohort of PWH with AF so far, the prevalence of AF in hemophilia increases with age and is predominantly present in mild hemophilia. Based on the population based CHA2DS2-Vasc risk scores, PWH have a low stroke risk that might be even lower considering the hypocoagulable state. Hemophilia doctors prescribe anticoagulation therapy approximately in half of their mild hemophilia patients and very few in moderate and severe.
Relationship of quality of life, pain, and self-reported arthritis with age, employment, bleed rate, and utilization of hemophilia treatment center and healthcare provider services: US results from adult patients with hemophilia in the HERO study

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Objective: Examine potential relationships between health-related quality of life (QoL), pain interference and self-reported arthritis and age, employment, activity, bleed frequency, and hemophilia treatment center (HTC) and healthcare professional utilization within the HERO psychosocial assessment study.

Methods: In HERO, adults with hemophilia (≥18 years) from 10 countries completed a 5-point Likert scale on pain interference over the prior 4 weeks, EQ-5D-3L (mobility, usual activities, self-care, pain/discomfort, anxiety/depression) and EQ-5D health-related visual analog scale (VAS, 0-100, coded as an 11-point categorical response). US responses are considered below.

Summary: Of 675 adults, 189 (90 with self-reported arthritis) respondents were from the US. Adults with arthritis were older; median age also increased with progressive disability and worsening pain. The percentages reporting full-time, part-time, or self-employment and the percentage reporting “good” EQ-5D VAS scores of 80-90-100 declined with increasing disability and pain interference. Median number of annual bleeds increased with increasing disability, pain interference, and arthritis. There was little difference in the median number of HTC visits per year in those reporting pain or arthritis. The percentage of adults reporting a lot/extreme pain interference was higher in those with more disability and with arthritis. Adults with increasing pain interference and arthritis were more likely to report social worker and nurse involvement. Physiotherapist utilization decreased with increasing disability and arthritis.

Conclusions: In the US, increased disability and pain were associated with increased age, lower employment, higher reported bleed frequency, and lower QoL. Adults who reported experiencing more pain were more likely to report suffering from arthritis and more issues with mobility.
Outcomes of Total Knee and Hip Arthroplasty for Hemophilic Arthropathy

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Objective: To assess subjective and objective outcomes of total joint arthroplasty (TJA) as a treatment for hemophilic arthropathy, and to assess the safety and efficacy of perioperative pharmacologic thromboprophylaxis as a means to prevent venous thromboembolism in this population.

Methods: We performed a retrospective chart review to identify patients with congenital bleeding disorders who underwent TJA between 1987 and 2012. We collected data on range of motion (ROM) and pain before and after surgery and on early and late complications (bleeding, infection, thrombosis). Data are presented descriptively using median values and ranges where appropriate.

Summary: We identified 38 procedures (29 knees (TKA) and 9 hips (THA) in 28 patients (26 male, 2 female) with hemophilia A (n = 21), hemophilia B (n = 4), factor 11 deficiency (n = 1) and von Willebrand disease (n = 2). Median age at operation was 42 years (range, 17 – 74) for TKA and 45 years (range, 18 – 71) for THA. Inhibitors were present in one patient with hemophilia A (1.5 B.U.) and one patient with factor 11 deficiency (0.5 B.U.). All patients were treated with hemostatic agents appropriate to their disorders for up to 4 to 6 weeks post-operatively. Complete data at 2 months post-operatively are available for 27 TKA patients, of whom, 7 (23%), demonstrated improvement in ROM (median 15 degrees, range 5 – 25). At 1.5 years post-operatively, 17/29 (59%) TKA patients showed improvement in ROM (median 15 degrees, range 4 - 58) and 100% reported decreased knee pain. All 9 THA patients demonstrated improved ROM at 2 months post-operatively. Eight (89%) demonstrated gains in internal rotation (median, 45 degrees, range 15 – 45), 9 (100%) in external rotation (median 30 degrees, range 15 – 45), 5 (56%) in flexion (median 35 degrees, range 27 – 55), 7 (78%) in extension (median 15 degrees, range 3 – 95), and 7 (78%) in abduction (median 15 degrees, range 10 – 25).

We were able to contact 22 of 28 study subjects (79%), accounting for 31 of 38 (82%) procedures. Patients who underwent 25 of the 29 TKAs (86%) and 6 of the 9 THAs (67%) agreed to provide answers to yes/no questions about their experience with TJA. 25 of 25 (100%) TKA subjects reported improvement in pain and stated that if given the opportunity to go back and revisit their decision, would make the same decision to have the surgery. 24 of 25 (96%) TKA subjects reported improvement in their joint function after the surgery. 6 of the 6 THA subjects we contacted stated that they experienced improvement in joint pain and function as a result of the surgery, and 5 of 6 (83%) stated that they would choose to have the surgery if they had to choose again.

Low molecular weight heparin was administered post-operatively in 29 of 38 procedures (76%). Thromboprophylaxis was discontinued in 3 patients for non-joint bleeding (one hematuria, two cases of hypotension and anemia). There were no symptomatic VTE. Early complications included 5 cases of cellulitis and 2 hemarthroses in patients not receiving thromboprophylaxis. Late complications included two patients with aseptic loosening in prosthetic knees leading to TKA revisions, one with a subsequent joint infection requiring surgical debridement and one patient with a worsening flexion contracture requiring TKA revision.
Conclusions: While there are risks associated with TJA in patients with bleeding disorders, our data suggest they are outweighed by the benefits manifesting as decreased pain and improved function. Pharmacologic thromboprophylaxis appears safe in this population; whether it is necessary is unknown and should be a subject of future trials.
A Phase I Study of Safety and Pharmacokinetics (PK) of BAX 855, a Longer Acting PEGylated Full-Length Recombinant Factor VIII (PEG-rFVIII), in Patients with Severe Hemophilia A

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Objectives: BAX 855 is a PEG-rFVIII designed to prolong the half-life of ADVATE (octocog alfa) through the covalent binding of polyethylene glycol (PEG) moieties, while maintaining the strong safety and efficacy profile demonstrated for the base molecule. The primary objective of this prospective, open-label study was to assess safety and tolerability of a single dose of BAX 855 in previously treated patients with severe hemophilia A. Secondary objectives included pharmacokinetic comparisons between BAX 855 and ADVATE at the same dose level.

Methods: Severe hemophilia A patients with ≥150 FVIII exposure days, no history of inhibitors to FVIII, and no significant renal or hepatic disease were enrolled to receive either 30 IU/kg (cohort 1) or 60 IU/kg (cohort 2) of BAX 855. Patients were initially treated with octocog alfa and underwent PK evaluation. A washout period preceded infusion of BAX 855 at the same dose, followed by a 7-day PK evaluation. FVIII measurements were obtained at pre-infusion, 0.5, 1, 4, 9, 12, 24, and 48 h post-infusion for both octocog and BAX 855, and at 56, 72, 80 h and 4, 5, 6 and 7 days post-infusion of BAX 855. Patients were followed for 4 weeks after BAX 855 infusion for safety assessments, including adverse events (AEs), changes in vital signs (VS) and laboratories, and immunogenicity (FVIII inhibitors, binding antibodies (BA) to FVIII, BAX 855 and PEG).

Summary: A total of 24 patients were enrolled, 19 of whom completed the study (9 in Cohort 1 and 10 in Cohort 2, including 2 patients in Japan). Mean T₁₂ was 1.4 and 1.5-fold higher for BAX 855 than for octocog alfa for Cohorts 1 and 2, respectively. Measurement of thrombin generation in platelet-poor-plasma showed that mean peak thrombin is increased above baseline for >120 hours after infusion of 60 IU/kg BAX 855. Other PK parameters were comparable to or better than octocog alfa. No serious or treatment related AEs occurred during the study and no patients developed FVIII inhibitors. There were no deaths, thrombotic or allergic events, or significant changes in VS or laboratory measurements.

Conclusions: This phase I clinical trial suggests BAX 855 remained in circulation longer than its base molecule ADVATE, while demonstrating comparable safety and efficacy. Therefore, less frequent dosing regimens may be possible with BAX 855 in the prophylactic treatment of patients with hemophilia A.
The PROLONG-ATE Study: A Phase 2/3 Study to Evaluate Efficacy and Safety of BAX 855, a Longer-Acting Pegylated Full-Length Recombinant Factor VIII (PEG-rFVIII), for Prophylaxis and Treatment of Bleeding in Severe Hemophilia A

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Objective: BAX 855 is a PEGylated recombinant factor VIII based on full-length ADVATE (octocog alfa). The new molecule was designed to prolong its half-life while maintaining the strong safety and efficacy profile demonstrated by the base molecule. The goal of extending the half-life of a rFVIII product is to provide therapeutic efficacy using fewer infusions and potentially increase patient adherence to prophylaxis. Preclinical studies of BAX 855 have confirmed a safety and efficacy profile comparable to octocog alfa with an improved pharmacokinetic profile. Furthermore, the association of BAX 855 and von Willebrand factor (VWF) has been shown to be comparable to that of octocog alfa and VWF. A recent phase I study suggested the mean half-life of BAX 855 was higher than its parent molecule.

Methods: The PROLONG-ATE study is a Phase 2/3 study for evaluating efficacy and safety of BAX 855 during prophylaxis and treatment of bleeding episodes in patients with severe hemophilia A. The primary objective of the PROLONG-ATE study is to compare annualized bleeding rate (ABR) between participants receiving BAX 855 during prophylaxis or on-demand treatment regimens. Secondary objectives include evaluating the control of bleeding episodes, weight adjusted consumption of BAX 855, immunogenicity, safety, pharmacokinetics, and patient reported outcomes. Evaluable participants will be treated with BAX 855 during prophylaxis for ≥ 50 exposure days (EDs) or as on-demand therapy. Subjects who meet the following criteria are eligible: age 12-65 y, male with severe hemophilia A (<1% FVIII) with no history of inhibitors, ≥150 EDs to FVIII, currently receiving FVIII treatment, good performance status, no severe hepatic and renal dysfunction, no other bleeding disorder and no hypersensitivity to mouse or hamster proteins, PEG or Polysorbate 80.

Summary: This global study will enroll approximately 146 patients at over 100 hemophilia centers and has started in early 2013. Primary outcome of ABR will be supported by secondary outcomes in efficacy, safety and patient-reported outcomes as well as pharmacokinetic profile of BAX855 as compared to ADVATE.

Conclusions: BAX855 is a PEGylated rFVIII based on the full-length ADVATE molecule and produced using the same plasma/albumin-free manufacturing platform. The PROLONG-ATE Study will provide prospective, clinical trial data in patients with severe hemophilia A with regards to the anticipated longer half-life as compared to the base molecule, and the safety and efficacy profiles of this product in development.
FEIBA PROOF: A Prospective, open-label, randomized, parallel study with FEIBA NF to evaluate the efficacy and safety of prophylactic versus on-demand treatment in haemophilia A or B subjects with inhibitors

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Objectives: Treatment with FEIBA NF is a key therapeutic option for controlling acute and difficult to treat bleeds in hemophilia A and B patients with inhibitors. Prevention of hemorrhages with prophylactic therapy reduces morbidity and improves quality of life. FEIBA PROOF study evaluated the safety and efficacy of prophylaxis compared to on-demand treatment. The primary objective of this study was to demonstrate a reduction in annualized bleed rate (ABR) in subjects receiving FEIBA prophylactically compared to on-demand therapy. The study also evaluated the safety of prophylaxis compared to on-demand treatment.

Methods: This prospective, randomized study had two arms: prophylaxis and on-demand regimens for duration of 12 months ± 14 days. Thirty-six hemophilia A or B subjects with inhibitors refractory to FVIII or FIX treatment were enrolled across 17 sites globally. Seventeen subjects randomized to the prophylaxis arm, received FEIBA at a dose of 85 ± 15 U/kg every other day. Nineteen subjects randomized to the on-demand arm received FEIBA for control of acute bleeding episodes at dosages per their treating physician. Median age of the subjects was 23.5 years. The study was approved by each institutional ethics committee and all subjects signed informed consent.

Summary: The median ABR for subjects in the prophylaxis arm (7.9) was significantly lower than subjects in the on-demand arm (28.7). For both intent-to-treat (ITT) and per-protocol (PP) efficacy analysis sets, the differences in mean transformed ABRs between prophylaxis and on-demand were statistically significant (p = 0.0003 and p = 0.0006, respectively). Occurrence of new target joints was substantially lower in the prophylaxis arm (7 in 5/17 subjects) compared to the on-demand arm (23 in 11/19 subjects). Median ABR for new target joints was higher in the on-demand arm (5.9) than in the prophylaxis arm (0); the difference was statistically significant (p = 0.027).

Of the 104 AEs reported, 30 were serious and 74 non-serious. Twenty-seven AEs (26.0%) in 8 (22.2%) subjects were deemed related to FEIBA; of these 3 were serious. There was one unrelated death and one subject discontinued the study due to a non-serious hypersensitivity reaction. There were no thromboembolic events reported.

Conclusions: FEIBA prophylaxis significantly reduced (72.5%) all types of bleeds as compared to on-demand therapy. Zero bleeding episodes were achieved in 2 prophylaxis subjects who were in the study for 12 months. The safety and efficacy of prophylaxis was comparable to on-demand therapy. Prophylaxis with recurrent dosing of FEIBA was safe.
Patient Caregiver, and Nurse Satisfaction with BAXJECT III, a Next-Generation Reconstitution System for AHF-rFVIII (ADVATE®)

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Objective: BAXJECT III is an all-in-one, next generation reconstitution system currently being developed for reconstituting Antihemophilic Factor (Recombinant), Plasma/Albumin-Free Method (ADVATE). The primary advancement of BAXJECT III is that it does not require users to cleanse and attach the FVIII vials and sterile water to the reconstitution system. Elimination of these steps allows faster reconstitution and reduction of potential touch contamination. This study evaluated satisfaction and preferences for BAXJECT III and assessed the potential for improved adherence using this new system.

Methods: Hemophilia patients, caregivers of pediatric hemophilia patients, hemophilia nurses and members of the general public were recruited to participate in an evaluation of the usability/safety of BAXJECT III and a comparative time and motion study with BAXJECT II. After the time and motion study was completed, a paper-based survey was administered to all participants to assess satisfaction with and preference for BAXJECT II and BAXJECT III and the potential for improved adherence to their treatment regimen with BAXJECT III.

Summary: Overall, there were 44 respondents, of these 25 (57%) were either adult hemophilia patients or caregivers of pediatric patients, 14 (32%) were hemophilia nurses and 5 (11%) were naïve participants never exposed to hemophilia products. 39 (89%) respondents reported that it was ‘very easy’ to learn to use BAXJECT III and felt comfortable with it after a median of 2 minutes. The vast majority of participants indicated being ‘very satisfied’ with various attributes of BAXJECT III compared to BAXJECT II, including, the number of steps involved (83% v 11%), time to reconstitute (73% v 21%), total time to prepare infusions (78% v 13%), ease of use (76% v 13%), safety/sterility (89% v 33%) and overall satisfaction (86% v 19%) (all p<0.0001). Satisfaction regarding the size of the kit (50% v 25%) and portability of the kit (50% v 28%) was higher for BAXJECT III compared to BAXJECT II (both p<0.05). Overall, 96% of respondents preferred BAXJECT III over BAXJECT II. While approximately 28% of patient/caregivers indicated being ‘somewhat’ or ‘not adherent’ to their current treatment regimen, the majority of patients/caregivers (75%) and hemophilia nurses (93%) indicated that BAXJECT III may help improve adherence to treatment.

Conclusions: Hemophilia patients/caregivers and hemophilia nurses were highly satisfied with BAXJECT III, preferring it over BAXJECT II, with most feeling that it may help improve patient adherence to their treatment regimen.