Swimming exercise ameliorates pain, swelling and bone quality in a blood-induced joint damage animal model.

Fabio Souza, Liliam Takayama, Fernanda Roque, Gisele Picolo, Rosa Pereira, Edilamar Oliveira, Yara Cury, Clarice Tanaka, Suzana Mello

1Bone Metabolism Laboratory, Rheumatology Division, Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil, 2Laboratory of Biochemistry and Molecular Biology of the Exercise, School of Physical Education and Sport, University of São Paulo, São Paulo, Brazil, 3Laboratory of Pain and Signaling, Butantan Institute, São Paulo, Brazil, 4Department of Physiotherapy, Communication Science & Disorders, Occupational Therapy, Faculty of Medicine, University of São Paulo, São Paulo, Brazil, 5Rheumatology Division, Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil

Background: Arthropathy is one of the major complications in hemophilia, leading to functional limitations and poor quality of life. Exercise is recommended as being beneficial for people with hemophilia, yet a lack of exercise-related evidence using exercise and control groups exists in this population, compared to other joint pathologies (i.e. osteoarthritis). Objective: To evaluate effects of post-hemarthrosis exercise on: pain; swelling; bone density and joint damage, using an animal model. Methods: Twelve Wistar rats were divided into an Exercise Group (EG; n=6) and Control Group (CG; n=6). All rats received eight weekly intraarticular injections in their right knees with 0.1 mL autologous blood, and left knees with 0.1 mL saline solution. The EG performed an 8 wk swimming protocol (during the period of intraarticular injections) of 60 min (5x week) with 5% body weight attached on their tails. Pain status was assessed weekly with a static weight-bearing incapacitance test (SWIT). Joint diameters were measured post-protocol with a digital microcaliper. Bone mineral density was assessed using dual-energy X-ray absorptiometry (whole-body, tibia, femur and knee joint) pre and post-study. Following sacrifice, bilateral knee X-rays were taken and scored with Pettersson's score. Resting heart rate and heart weight were registered post-study, as markers of physical training. Results: CG manifested decreased weight-bearing with SWIT, compared to EG (p<0.001). EG presented reduced joint swelling, compared to CG (p=0.034). Significant increase in bone mineral density variation (BMDΔ) was observed at the tibia (p=0.016), and knee (p=0.018) of the EF compared to CG. The EG also showed a tendency of an increase in femoral BMDΔ compared to CG (p=0.09). Pettersson scores demonstrated increased bone destruction in the CG compared to EG (p=0.05). Conclusion: This is the first time that beneficial effects of a swimming exercise protocol on pain, swelling, bone density and radiologic changes have been shown in a blood-induced, joint damage animal model. Hopefully this data will provide clues for future study designs in this area.
Varying Regimens in Hemophilia A Patients Undergoing Immune Tolerance: Removing Barriers to Enhance Outcomes

Joan Couden, BSN, RN, Kirstin Schmidt, RN, Donna Haffler, BSN, RN, Elizabeth Hanlon, BSN, RN, Tami Bullock, BSN, RN

Walgreens Infusion Services, Deerfield IL, USA

Objective: Promote awareness of and an opportunity for dialogue regarding variability among prescribed regimens to enhance care for hemophilia A patients with inhibitors undergoing immune tolerance.

Methods: Retrospective chart review of all severe hemophilia A patients receiving interdisciplinary inhibitor management home infusion support between March of 2013 and March of 2015. Excluded mild patients developing inhibitors postoperatively and those for which insufficient titer information was provided/available from prescribers. 14 patients met the inclusion criteria. We attempted to further categorize these regimens into low and high dosing regimens as outlined in the International Immune Tolerance Study.

Summary: We identified 14 patients on 7 different ITI regimens, none of whom expressly followed the “low or high dose regimens” of 50 units per kg 3 times a week or 200 units per kg daily. They were on either recombinant FVIII products (11) or vWF containing products (3). The reviewed population was followed by 11 different HTC’s which included 13 different prescribers. We noted time to tolerization (when information available), bleed rate, as well as the interventions and support offered patients by the homecare inhibitor team. Although the sample was small, a notable increase in bleeds was seen in those patients on regimens below 100 units/kg/day. Time to tolerization was unavailable for 3 of the 14. Of the remaining 11, time to tolerization ranged from 1-45 months and there was no significant difference seen amongst regimens.

Conclusions: Seven different regimens for ITI were prescribed for 14 unique patients across the country. All achieved successful immune tolerance, but there was variability in the frequency of spontaneous bleeds and time to tolerance. Exact time to tolerance was limited by both the inability to obtain lab values (titers) from the prescriber or long periods between titer levels. Immune tolerance induction dosing regimens have been long debated and several studies continue to attempt to provide clarity and guidance. A missing component of the research published to date is the importance of patient adherence and the benefit of prescriber/pharmacist/payer collaboration. Economic influences further complicate this as many HTC’s perceive pharmacies as competitors, rather than collaborators in care. Additionally, payers may limit networks or implement other barriers to refills. The authors wish to work collaboratively to remove these barriers and enhance outcomes.
Pharmacist/Provider Collaboration needed to Optimize Dosing Regimens in Order to Reduce Bleed Rates in Hemophilia A Patients on Prophylaxis Regimens.

Joan Couden BSN, RN, Tina Dooley Pharm. D., Kim Milenski RPH

Walgreens Infusion Services, Deerfield IL, USA

Objective: Highlight the importance of collaboration in addition to dose, frequency, and PK data to personalize regimens in order to minimize bleed rates in Hemophilia A patients on prophylaxis.

Methods: Dose and bleed data was collected and reviewed from January 1, 2015 through March 31, 2015 for all moderate to severe hemophilia A patients on prophylaxis regimens with traditional acting products in 2 regional bleeding disorder hubs. Units per kilogram per dose, units per kilogram per week, and spontaneous bleed rate were calculated from data. If reporter was unsure of bleed origin, it was counted as a spontaneous bleed.

Results: Region X had 34 and Region Y had 40 patients that met the inclusion criteria for review. The average dispensed dose for Region X was 43.89 units per kg per dose. For Region Y, it was 35.47 units per kg per dose; a difference of 8.42 units per kg per dose. Due to varying frequency orders, regimens were further calculated in units per kg per week. Region X’s average was 121.38 units per kg per week and Region Y’s was 96.98; a difference of 24.4 units per kg per week. Patients in Region X reported zero spontaneous bleeds during the study period. Patients in Region Y reported 16 spontaneous bleeds from 12 unique patients. Of these patients, target joints were cited as contributing factors with 8 of the 16 bleeds. When appropriate, prescribers were notified and collaboration on regimen adjustments was made. Pharmacokinetic data was inconsistently available.

Conclusion: Zero spontaneous bleeds should be the goal for hemophilia A patients on prophylaxis. Small changes in dose or frequency can make significant changes in outcomes. Many variables impact bleed rates and doses vary widely. There is the potential for refining dosing algorithms based on a more personalized approach that includes close and careful monitoring of trough levels, patients activity level, bleed pattern and response to changes in treatment plans. This individualized approach would require collaboration between patients, prescribers, and pharmacies. Such an approach can have huge and long-term beneficial effects on pharmacoeconomic, clinical, and quality of life outcomes. Data collected from this study may further assist pharmacists with influencing prescribers to consider pharmacist obtained bleed data and/or obtain and provide PK data so they can assist with regimen adjustment recommendations based on their assessments. With increasing payer pressure and the introduction of longer acting products, this collaboration will become even more imperative.
Pediatric Venous Thrombosis Associated With Staphylococcal Infections: A single Institutional Experience

Divyaswathi C. Sridhar1, Ossama M. Maher2, Fernando Corrales-Medina4, Hatel R. Moonat3, Jorge Galvez Silva2, Trinh Nguyen2, Deborah Brown2, Nidra I. Rodriguez2

1Department of Pediatrics, The University of Texas Health Science Center, Houston, Texas, USA, 2Department of Pediatrics, Division of Hematology, The University of Texas Health Science Center, Houston, Texas, USA, 3Department of Pediatrics, The University of Texas MD Anderson Cancer Center, Houston, Texas, USA, 4Division of Pediatric Hematology and Oncology, University of Miami, Miller School of Medicine, Houston, Texas, USA

Introduction: Since the emergence of community-acquired methicillin-resistant S. aureus (MRSA), severe manifestations of infection are encountered more frequently. Venous thrombosis (VT) has been previously reported in children with S. aureus infections. This study reviews our institutional experience and outcomes of children with VT and staphylococcal infections. Methods: A retrospective analysis of 15 pediatric patients (≤ 18 years) treated for VT and staphylococcal infections at Children's Memorial Hermann Hospital between January 1, 2010 and December 31, 2014 was performed. Results: Fifteen patients were included (10 males, 5 females) with a median age at diagnosis of 8 years (range 2 mo-17yrs). Underlying infections included: osteomyelitis (n=7), soft tissue infection (n=3), aortitis (n=1), meningitis (n=1), septic arthritis (n=1), central line infection (n=1), septicemia (n=1). Primary presentation included: swelling (n=12), pain (n=11), tenderness (n= 8), and color changes (n=3). One patient had prior history of VT. Family history was positive for VT in one patient. Isolated organisms included: MRSA (n=9), MSSA (n=3), polymicrobial (n=2), and Staphylococcus non-aureus (n=1). Eight patients had central venous catheters (CVC) and 5 of them had thrombosis at the CVC site. VT sites identified by Doppler US (DUS) included: upper extremity (n= 5), lower extremity (n= 8), and neck (n=2). All thrombophilia work up was negative. The median D-dimer at diagnosis was 3 ug/ml (range: 0.31- 6.54 ug/ml). Median time elapsed between infection and VT diagnosis was 5.5 days (range: 0-35 days). All patients received anticoagulation using LMWH (1mg/kg/dose) except one who had superficial thrombophlebitis and was managed conservatively. Median time to achieve therapeutic anti-factor Xa level was 2.5 days (range 1- 6 days). Median duration of anticoagulation was 3 months. Three out of 13 patients (23%) had resolution of thrombosis within one week of anticoagulation. Four other patients had thrombus resolution by DUS at 3-6 months. Five patients did not have DUS at 3-6 months. None of the 15 patients required hospital re-admission for bleeding or thrombotic complications. Discussion: Staphylococcal infections may increase the risk of VT in children. Nine out of 15 patients (60%) with VT had a documented MRSA infection, which appears to confer an even higher risk for development of VT. Over half of the patients responded favorably to anticoagulation with resolution of VT within 6 months. Conclusions: A high index of suspicion for VT is warranted in children with Staphylococcal infections (particularly MRSA) to promptly diagnose and treat. This approach may improve outcomes and minimize complications including septic emboli and post-thrombotic syndrome. Prophylactic anticoagulation in presence of MRSA infection could be considered in future studies.

Keywords: Children, staphylococcal infection, venous thrombosis
Adherence influences annualized bleeding rate during prophylaxis with turoctocog alfa: results from the guardian™1 trial

Susan Lattimore¹, Tracy Peters², Nikola Tripkovic³, David Ungar⁴

¹Oregon Health & Science University, Portland, OR, USA, ²University of Iowa, Iowa City, IA, USA, ³Novo Nordisk Health Care AG, Zurich, Switzerland, ⁴Novo Nordisk Inc, Plainsboro, NJ, USA

Objective: Severe hemophilia is associated with bleeding into joints and the development of arthropathy. Prophylaxis with factor VIII (FVIII) is used to prevent bleeding and preserve joint function in patients with hemophilia A. However, for many reasons, including the inconvenience of treatment, not all patients adhere to standard prophylaxis schedules, which may influence long-term clinical outcomes. We explored the impact of treatment adherence on annualized bleeding rate (ABR), using data from guardian™1, a multinational, open-label, non-controlled phase 3 trial investigating safety and efficacy of turoctocog alfa (Novoeight®) in previously treated patients aged 12 years and older with severe hemophilia A [Lentz et al, Haemophilia 2013].

Methods: ABRs were determined following prophylaxis with turoctocog alfa and stratified by patient adherence. A patient was defined as less adherent to the prophylaxis treatment regimen if more than 20% of the prophylactic doses were outside the dose range (defined as less than 18 IU/kg and/or fewer than 3 prophylactic doses/week, taken for more than 20% of the weeks).

Results: A total of 150 patients (24 adolescents and 126 adults) with severe hemophilia A, at least 150 exposure days to any FVIII product, and no history of inhibitors, were enrolled in guardian™1; 146 patients (97%) completed the trial. All patients were prescribed prophylaxis with turoctocog alfa for approximately 6 months and had a mean of 85 exposure days during the trial. Overall, the level of prophylactic treatment adherence was high; 93% of patients adhered well to treatment, while 7% (all adults, ≥18 years) were less compliant. Consumption was slightly lower among patients who were less adherent to prophylactic treatment compared with patients who had good adherence (3412 IU/kg/year vs 3841 IU/kg/year, respectively). Patients who were less adherent to prophylaxis tended to have more bleeds vs patients who complied with treatment (estimated mean ABR 10.55 vs 6.18, respectively).

Conclusions: Patients who were less adherent to prophylaxis tended to have lower factor consumption and more bleeds vs patients who had good adherence to prophylaxis. These differences highlight the value of strategies to improve adherence to treatment regimens, thereby improving clinical outcomes for patients with hemophilia over the long term.
Interim results of the B-YOND study evaluating long-term safety and efficacy of recombinant factor IX Fc (rFIXFc) in children with severe hemophilia B

Carolyn Bennett1, Beatrice Nolan2, Roshni Kulkarni3, Kathelijn Fischer4, David Perry5, Christopher Barnes6, Huixing Yuan7, Alejandra Ramirez-Santiago7, Glenn F Pierce7, Baisong Mei1

1Emory University School of Medicine, Children’s Healthcare of Atlanta & the Aflac Cancer and Blood Disorders Center, Atlanta, GA, USA, 2Our Lady’s Children’s Hospital, Dublin, Ireland, 3Michigan State University, East Lansing, MI, USA, 4University Medical Center, Utrecht, The Netherlands, 5Addenbrookes Hospital, Cambridge, UK, 6Royal Children’s Hospital, Melbourne, Australia, 7Biogen, Cambridge, MA, USA

Objective: The ongoing rFIXFc extension study, B-YOND (clinicaltrials.gov #NCT01425723), evaluates the long-term safety and efficacy of rFIXFc for the treatment of severe hemophilia B. Here we report interim safety and efficacy data for children aged <12 yrs enrolled in B-YOND. Methods: Upon completing Kids B-LONG, eligible subjects could enroll in one of the 3 prophylactic treatment groups in B-YOND: weekly (20 to 100 IU/kg every 7 days), individualized (100 IU/kg every 8 to 16 days, or twice monthly), or modified (a prophylaxis regimen different from weekly or individualized prophylaxis). Subjects could change treatment groups at any point in the study. The primary endpoint was development of inhibitors. Secondary outcomes included annualized bleeding rate (ABR) and rFIXFc exposure days (EDs). Summary: At the time of the interim data cut (17 October 2014), 23 subjects had completed Kids B-LONG; all enrolled in B-YOND (<6 yrs of age cohort, n=9; 6 to <12 yrs of age cohort, n=14). As of the interim data cut, 2 subjects had completed and 21 subjects continued in B-YOND (median time on study: 47.7 weeks). From the start of Kids B-LONG to the B-YOND interim data cut, the median time on rFIXFc was 95.3 weeks, with a median of 94 cumulative rFIXFc EDs. All subjects were on weekly prophylaxis in Kids B-LONG; 5 subjects changed treatment groups at the start of or during B-YOND. In the weekly prophylaxis group, the median (IQR) average weekly prophylactic dose was 64 (52, 66) IU/kg and 63 (59, 64) IU/kg in the <6 yrs and 6 to <12 yrs of age cohorts, respectively. The median (IQR) dosing interval among subjects on individualized prophylaxis was 10 (10, 11) days. As of the interim data cut, no inhibitors were observed, there were no reports of anaphylaxis or serious hypersensitivity reactions associated with rFIXFc, and no thrombotic events. Adverse events were typical of the pediatric hemophilia B population; no subject discontinued the study due to an adverse event. Median ABRs were low in both age cohorts (Table). Overall, 95% of bleeding episodes were controlled with 1 or 2 infusions. Conclusions: Interim data in children with severe hemophilia B participating in B-YOND confirm the long-term safety of rFIXFc and the maintenance of a low ABR with extended-interval prophylactic dosing.

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>N</th>
<th>ABR, median (IQR)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Overall</td>
</tr>
<tr>
<td>&lt;6 years of age cohort</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weekly prophylaxis</td>
<td>9</td>
<td>0.00 (0.00, 1.30)</td>
</tr>
<tr>
<td>6 to &lt;12 years of age cohort</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weekly prophylaxis</td>
<td>10</td>
<td>2.65 (1.07, 3.21)</td>
</tr>
<tr>
<td>Individualized prophylaxis</td>
<td>5</td>
<td>2.37 (1.99, 6.28)</td>
</tr>
<tr>
<td>Modified prophylaxis</td>
<td>1</td>
<td>3.13</td>
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</tbody>
</table>
Long-term safety and efficacy of recombinant factor IX Fc (rFIXFc) in adults and adolescents with severe hemophilia B: interim results of the B-YOND study

Amy D Shapiro1, John Pasi2, Margaret Ragni3, Johnny Mahlangu4, Margareth Ozelo5, Johannes Oldenburg6, Tadashi Matsushita1, Ross I Baker8, Huixing Yuan9, Alejandra Ramirez-Santiago9, Glenn F Pierce9, Geoffrey Allen9, Baisong Mei9

1Indiana Hemophilia and Thrombosis Center, Indianapolis, IN, USA, 2Royal London Haemophilia Centre, Barts and the London School of Medicine and Dentistry, London, UK, 3Hemophilia Center of Western Pennsylvania, University of Pittsburgh, Pittsburgh, PA, USA, 4Haemophilia Comprehensive Care Centre, University of the Witwatersrand and NHLS, Johannesburg, South Africa, 5INCT do Sangue Hemocentro UNICAMP, University of Campinas, Campinas, Brazil, 6Institute of Experimental Haematology and Transfusion Medicine, University of Bonn, Bonn, Germany, 7Department of Transfusion Medicine, Nagoya University Hospital, Nagoya, Japan, 8Centre for Thrombosis and Haemophilia, Murdoch University, Royal Perth Hospital, Perth, WA, Australia, 9Biogen, Cambridge, MA, USA

Objective: The ongoing rFIXFc extension study, B-YOND (clinicaltrials.gov #NCT01425723), evaluates the long-term safety and efficacy of rFIXFc for the treatment of severe hemophilia B. Here we report interim safety and efficacy data for adults and adolescents enrolled in B-YOND.

Methods: Upon completing B-LONG, eligible subjects could enroll in one of 4 treatment groups in B-YOND: weekly prophylaxis (20 to 100 IU/kg every 7 days), individualized prophylaxis (100 IU/kg every 8 to 16 days, or twice monthly), modified prophylaxis (a prophylaxis regimen different from weekly or individualized prophylaxis), or episodic treatment. Subjects could change treatment groups at any point in the study. The primary endpoint was development of inhibitors. Secondary outcomes included annualized bleeding rate (ABR) and rFIXFc exposure days (EDs).

Summary: 93/115 subjects (80.9%) who completed B-LONG enrolled in B-YOND. As of the interim data cut (17 October 2014), 18 subjects had completed, 7 had discontinued, and 68 remained on study (median time on study, 119.9 weeks). From the start of B-LONG to the B-YOND interim data cut, the median time on rFIXFc was 171.6 weeks and 68 subjects (73%) had ≥100 cumulative rFIXFc EDs. 29/90 subjects (32%) from Arms 1-3 of B-LONG changed treatment groups at the start of or during B-YOND, including 9/19 subjects who changed from episodic to prophylactic treatment (1 subject changed back to episodic treatment before the interim data cut). In the weekly prophylaxis group, the median (IQR) average weekly prophylactic dose was 49.5 (21.0, 105.6) IU/kg. The median (IQR) average dosing intervals in the individualized and modified prophylaxis groups were 13.7 (10.1, 14.0) days and 6.9 (4.9, 7.0) days, respectively (a reduction in annual infusions of ~75% and ~50%, respectively, compared with twice-weekly administration of a standard half-life FIX product). As of the B-YOND interim data cut, no inhibitors were observed, and there were no reports of anaphylaxis or serious hypersensitivity reactions associated with rFIXFc, and no thrombotic events. Adverse events were generally typical of the hemophilia B population; no subject discontinued due to an adverse event. Median ABRs were low with rFIXFc prophylaxis (Table). 97.2% of bleeding episodes were controlled with 1 or 2 infusions.

Conclusions: Interim data from B-YOND confirm the long-term safety of rFIXFc and the maintenance of a low ABR with prophylactic dosing every 1 to 2 weeks.

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>N</th>
<th>Overall ABR (IQR)</th>
<th>Spontaneous ABR (IQR)</th>
<th>Total Joint ABR (IQR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weekly prophylaxis</td>
<td>50</td>
<td>2.28 (0.44, 3.76)</td>
<td>0.82 (0.00, 2.65)</td>
<td>0.86 (0.00, 3.01)</td>
</tr>
<tr>
<td>Individualized prophylaxis</td>
<td>30</td>
<td>2.25 (0.87, 4.47)</td>
<td>0.68 (0.00, 2.58)</td>
<td>1.58 (0.43, 4.47)</td>
</tr>
<tr>
<td>Modified prophylaxis</td>
<td>13</td>
<td>2.42 (1.26, 5.40)</td>
<td>0.41 (0.00, 1.84)</td>
<td>0.92 (0.42, 2.03)</td>
</tr>
<tr>
<td>Episodic treatment</td>
<td>15</td>
<td>11.27 (6.41, 19.62)</td>
<td>4.66 (1.17, 16.87)</td>
<td>8.95 (2.95, 16.14)</td>
</tr>
</tbody>
</table>
BAY 81-8973: Pharmacokinetic Parameters in Adolescents, Adults, and Children With Severe Hemophilia A

Anita Shah¹, Heinz Delesen², Thomas J. Humphries³

¹Bayer HealthCare Pharmaceuticals, Whippany, NJ, USA, ²Bayer Pharma AG, Wuppertal, Germany

Introduction: BAY 81-8973 is Bayer’s new full-length recombinant factor VIII product in development for the treatment of hemophilia A, with no human- or animal-derived raw materials added to the cell culture, purification, or formulation process. The pharmacokinetic (PK) properties of BAY 81-8973 were investigated in 3 studies in previously treated adults, adolescents, and children.

Methods: For all PK evaluations, a single dose of 50 IU/kg BAY 81-8973 was injected. Serial blood samples were collected over 48 hours in adults and 24 hours in children <12 years of age. PK samples in adolescents and adults were analyzed using one-stage and chromogenic assays. Limited samples were collected in children and were analyzed using only the chromogenic assay. Ethnic subgroups included Chinese, Japanese, and non-Asian patients.

Results: PK parameters using the chromogenic assay for children (aged <12 years), adolescents (aged 12–17 years), and adults (aged ≥18 years) are shown in Table 1.

Table 1. Pharmacokinetic Parameters Based on the Chromogenic Assay

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Children</th>
<th>Adolescents and Adults</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Aged 0 to &lt;6 y (n=5)</td>
<td>Aged 6 to &lt;12 y (n=10)</td>
</tr>
<tr>
<td>AUC, IU·h/dL</td>
<td>1334.3 (29.4)</td>
<td>1155.4 (34.7)</td>
</tr>
<tr>
<td>Cmax, IU/dL</td>
<td>74.2 (40.5)</td>
<td>79.8 (23.5)</td>
</tr>
<tr>
<td>t½, h</td>
<td>11.8 (27.0)*</td>
<td>11.9 (16.6)</td>
</tr>
<tr>
<td>CL, dL/h/kg</td>
<td>0.037 (25.1)*</td>
<td>0.043 (34.8)</td>
</tr>
<tr>
<td>MRTIV, h</td>
<td>17.3 (24.9)*</td>
<td>17.6 (15.5)</td>
</tr>
<tr>
<td>Vss, dL/kg</td>
<td>0.64 (20.6)*</td>
<td>0.76 (28.6)</td>
</tr>
</tbody>
</table>

All values are geometric mean (%CV).

AUC=area under the curve; CL=clearance; Cmax=maximum concentration; MRTIV=mean residence time after intravenous injection; t½=half-life; Vss=volume of distribution at steady state.

*n=4.

Conclusions: Analysis of PK across the different age groups showed that the values for maximum concentration (Cmax) and area under the curve (AUC) for adolescents were within the range of those seen for adults. PK values were slightly lower in children than in adults. There were no significant differences among the ethnic groups studied.
SPINART 3-Year Analyses: Patient- and Joint-Level Changes in Colorado Adult Joint Assessment Scale and Magnetic Resonance Imaging Scores With Bayer’s Sucrose-Formulated Recombinant Factor VIII (rFVIII-FS) in Adolescents and Adults

Sharon Funk\(^1\), Björn Lundin\(^2\), Walter Hong\(^3\)

\(^1\)University of Colorado Anschutz Medical Campus, Aurora, CO, USA, \(^2\)Lund University and Skåne University Hospital, Lund, Sweden, \(^3\)Bayer HealthCare Pharmaceuticals, Whippany, NJ, USA

Introduction: Efficacy and safety of routine prophylaxis vs on-demand treatment with Bayer’s sucrose-formulated recombinant factor VIII (rFVIII-FS) in patients with severe hemophilia A were evaluated in the randomized, controlled SPINART study.

Aim: Patient- and joint-level changes at year 3 in magnetic resonance imaging (MRI) and Colorado Adult Joint Assessment Scale (CAJAS) scores were compared to investigate if individual joint data revealed results that may have been obscured in previously reported patient-level analyses.

Methods: SPINART included males aged 12–50 years with severe hemophilia A, ≥150 exposure days to FVIII, no inhibitors, and no prophylaxis for >12 months in the past 5 years. Patients were randomized 1:1 to rFVIII-FS on demand or prophylaxis (25 IU/kg 3x/wk). Changes from baseline to year 3 were evaluated for 6 index joints (knees, ankles, elbows) using the Extended MRI (eMRI) scale and CAJAS. Percentages of patients or joints with improved, unchanged, or worsened scores were evaluated.

Summary: Of the 84 patients in SPINART, eMRI and CAJAS change from baseline data were available for 62 (prophylaxis, n=32; on demand, n=30) and 76 patients (n=39; n=37) and for 386 (n=197; n=189) and 446 joints (n=224; n=222), respectively. Categoric analysis of CAJAS data at year 3 showed a higher percentage of patients treated prophylactically vs on demand with improved scores (64.1% vs 43.2%) and a lower percentage with worsened scores (28.2% vs 51.4%); with eMRI, the percentage improved was smaller (12.5% vs 6.7% improved; 75.0% vs 73.3% worsened). At individual joints, improved, unchanged, and worsened CAJAS scores in patients treated with prophylaxis vs on demand were 46.0% vs 33.3%, 22.3% vs 24.3%, and 31.7% vs 42.3%; eMRI values were 8.1% vs 3.7%, 61.9% vs 69.8%, and 29.9% vs 26.5%.

Conclusions: These data suggest that in adults and adolescents with severe hemophilia A, joint function as measured by CAJAS is more likely to improve after 3 years of routine prophylaxis with rFVIII-FS than joint structure as measured by MRI.
NP0001

BAY 81-8973: The Effects of Routine Prophylaxis on Total, Joint, and Spontaneous Bleeding in Adolescents, Adults, and Children With Severe Hemophilia A

Sanjay Ahuja¹, Bryce Kerlin², Thomas J Humphries³, Olubunmi Afonja³, Monika Maas Enriquez⁴

¹University Hospital Case Medical Center, Cleveland, OH, USA, ²Nationwide Children’s Hospital, Columbus, OH, USA, ³Bayer HealthCare Pharmaceuticals, Whippany, NJ, USA, ⁴Bayer Pharma AG, Wuppertal, Germany

Introduction: BAY 81-8973 is Bayer’s new full-length recombinant factor VIII (FVIII) product for the treatment of hemophilia A, with no human- or animal-derived raw materials added to the cell culture, purification, or formulation process.

Methods: The safety and efficacy of BAY 81-8973 for routine prophylaxis in patients with severe hemophilia A (<1% FVIII) was evaluated in 3 clinical studies: 2 in adolescent and adult previously treated patients (PTPs; aged 12–65 years [Study 1 and Study 2]) and 1 in children aged ≤12 years (PTPs: completed [Study 3]; previously untreated patients: ongoing), enrolling a total of 204 patients. In Study 1, the prophylaxis regimen was 20–50 IU/kg 2x–3x/wk as determined by the investigator. In Study 2, patients were randomized to prophylaxis (20–30 IU/kg 2x/wk or 30–40 IU/kg 3x/wk) or on-demand treatment. In both 12-month studies, the primary efficacy variable was the annualized bleeding rate (ABR). In Study 3, the prophylaxis regimen was 20–50 IU/kg 2x–3x/wk or every other day, as determined by the investigator, for ≥50 exposure days (approximately 6–8 months). The primary efficacy variable was the ABR for total bleeds occurring within 48 hours of previous prophylaxis treatment; ABR was also analyzed independent of time of injection.

Results: A total of 193 patients treated with BAY 81-8973 were included in the analysis (Table 1). Sixteen (25.8%), 16 (27.1%), and 23 (45.1%) patients treated prophylactically had 0 bleeding episodes in Studies 1, 2, and 3, respectively.

Table 1. Annualized Bleeding Rates

<table>
<thead>
<tr>
<th>Study (n)</th>
<th>Study 1 (n=62)</th>
<th>Study 2 (n=80)</th>
<th>Study 3 (n=51)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prophylaxis (n=59)</td>
<td>Prophylaxis (n=21)</td>
<td>Dose ± 48h Overall</td>
<td></td>
</tr>
<tr>
<td>All bleeds</td>
<td>1.0 (0.0; 5.1)</td>
<td>2.0 (0.0; 7.0)</td>
<td>60 (41.7; 76.3)</td>
</tr>
<tr>
<td>Joint bleeds</td>
<td>1.0 (0.0; 3.0)</td>
<td>2.0 (0.0; 6.0)</td>
<td>38.8 (60.0)</td>
</tr>
<tr>
<td>Spontaneous bleeds</td>
<td>1.0 (0.0; 3.9)</td>
<td>1.0 (0.0; 4.0)</td>
<td>42.1 (61.3)</td>
</tr>
</tbody>
</table>

Data are median (quartile 1; quartile 3).

Conclusions: Study 1 and Study 2 demonstrated the efficacy and safety of routine prophylaxis treatment with BAY 81-8973 in adolescents and adults. Study 2 also demonstrated the superiority of prophylaxis over on-demand treatment during a one-year treatment period. An additional study in children aged ≤12 years showed low annualized rates for all bleeds, joint bleeds, and spontaneous bleeds within 48 hours after injection or later during routine prophylaxis.
Prevalence of high BMI in school age children with hemophilia

Ellen White, Alice J Cohen, Melinda Inzani

Newark Beth Israel Medical Center, Newark, NJ, USA

Background: Adults with hemophilia, prior to the use of primary prophylaxis with clotting factor concentrates to prevent hemarthrosis, suffered from significant arthropathy. This has led to decreased mobility and the ability to perform aerobic exercise. As a consequence, obesity and its secondary complications have occurred in this population. Children with hemophilia now receive primary prophylaxis and this has significantly reduced hemarthrosis and allowed children to participate in sports at a young age. Despite this, the rates of overweight and obesity among children with hemophilia are similar to those among the general population. This potentially, as reported by the CDC, has been strongly associated with joint mobility limitations. Additionally, these individuals, as they age, may become less compliant with clotting factor infusion for prophylaxis and possibly then have increased bleeding events.

Objective: Evaluate the effect prevalence of high body mass index (BMI) in school age children with hemophilia between the ages of 7-12 years who are followed at the Hemophilia Center at Newark Beth Israel Medical Center and Children Hospital of New Jersey and its impact on hemarthrosis, activity in sports and compliance with treatment.

Method: A chart review of 31 school age children with hemophilia (males) between the ages of 7-12 years was performed. Data was retrospectively reviewed over the prior 12 months. Type of hemophilia, severity of hemophilia, BMI, participation in sport activities was collected. Use of coagulation factor prophylaxis and compliance with treatment protocol was assessed and the frequency of bleeding events.

Results: Thirty one hemophilia patients between the ages of 7-12 years (10 y) were identified: 26 with Hemophilia A and 5 with Hemophilia B, 17 were Severe, 6 were Moderate and 8 were Mild. (Two boys had low titer inhibitors one factor VIII and one Factor IX), 15/17 patients with severe hemophilia were on primary prophylaxis, 1/17 on immune tolerance therapy and 1/17 had just arrived in the US and was awaiting insurance to begin therapy. 100% of patients on prophylaxis are compliant with treatment. 2/31(6%) and 1/31(3%) of these individuals were overweight (BMI 25-29.9) and obese (BMI >30) respectively. No hemarthrosis occurred during the study period. The 2 children who were overweight had severe hemophilia, had limited participation in sport activities, were on prophylaxis, had no chronic joint abnormalities, and no current breakthrough bleeding. The 1 child with obesity has mild hemophilia, does participate in sports, has family history of obesity, and no bleeding events.

Conclusion: The prevalence of high BMI in school age children with hemophilia at a single treatment center was low and unrelated to inactivity due to chronic arthropathy or bleeding events. With the use of prophylaxis to prevent hemarthrosis, the focus on weight control with diet and regular safe exercise should be the focus.
A Half-Life Extended Fusion Peptide Inhibitor of TFPI Improves Hemostasis in Preclinical Models of Hemophilia

Michael Dockal¹, Rudolf Hartmann¹, Thomas Polakowski², Erwin Panholzer¹, Willibald Kammlander¹, Frank Osterkamp², Ulrich Reineke², Alexandra Schiviz², Werner Hoellriegl¹, Friedrich Scheiflinger¹

¹Baxter Innovations GmbH, Vienna, Austria, ²3B Pharmaceuticals, Berlin, Germany

TFPI is a potent inhibitor of the tissue factor (TF)-induced extrinsic pathway of coagulation. Inhibition of TFPI with antibodies, aptamers, or peptide inhibitors improves hemostasis and may become an option for non-i.v. treatment of patients with hemophilia including those with inhibitors. We developed a TFPI inhibitory fusion peptide (FP) consisting of a linear and a cyclic peptide connected by an optimized linker. The two peptides bind to different epitopes on TFPI and synergistically inhibit TFPI. The FP was further improved by half-life extending (HL) non-covalent albumin binding. HL-FP was characterized for in vitro inhibition of TFPI, pharmacokinetics, and improvement of coagulation in animal models of hemophilia.

HL-FP bound to and efficiently inhibited TFPI in several in vitro test systems. The binding affinity of < 1nM correlated well with inhibition of TFPI in model assays, resulting in IC50s of ~0.7nM. HL-FP efficiently inhibited plasma TFPI, which improved all thrombin generation (TG) parameters in hemophilia A and B patient plasma (EC50s of 6 to 20nM). HL-FP increased peak thrombin levels of hemophilia plasma to a range established for individual normal plasma. Assays were also carried out at high TFPI concentrations up to 10nM, which is 40- to 50-fold above normal. Increased TFPI levels may occur locally upon platelet activation. HL-FP efficiently neutralized elevated TFPI, raising TG to levels observed for inhibition of physiologic TFPI concentrations. Non-covalent binding to albumin substantially increased the half-life to ~4 h with ~50% s.c. bioavailability in mice. The ex vivo procoagulant activity determined by TG correlated well with HL-FP plasma concentrations. In a repeated dose study, the HL-FP was well tolerated and did not accumulate TFPI, indicating that HL-FP did not interfere with TFPI clearance. HL-FP significantly reduced bleeding in the hemophilia mouse tail cut model at a dose as low as 40 nmol/kg. In marmoset monkeys, HL-FP efficiently improved ex vivo plasma TG, even at low peptide plasma concentrations (25-55nM).

To summarize, we developed a TFPI inhibitor composed of two TFPI antagonistic peptides that completely inhibits TFPI. Introduction of an entity non-covalently binding to albumin provides intermediate half-life extension and s.c. bioavailability. This HL-FP improved coagulation and hemostasis in animal models of hemophilia, did not interfere with TFPI clearance receptor interactions, and efficiently neutralized elevated TFPI. Our HL-FP appears to be useful in preventing bleeding in hemophilia, and provides a FVIII and FIX independent approach for non-i.v. treatment.
BAY 81-8973: Safety Observations in Clinical Trials in Adults, Adolescents, and Children With Severe Hemophilia A

Miguel Escobar\textsuperscript{1}, Dana Obzut\textsuperscript{2}, Thomas J Humphries\textsuperscript{3}, Olubunmi Afonja\textsuperscript{3}, Elke Detering\textsuperscript{4}

\textsuperscript{1}Gulf States Hemophilia and Thrombophilia Center, Houston, TX, USA, \textsuperscript{2}St. Joseph’s Hospital, Tampa, FL, USA, \textsuperscript{3}Bayer HealthCare Pharmaceuticals, Whippany, NJ, USA, \textsuperscript{4}Bayer Pharma AG, Berlin, Germany

**Introduction:** BAY 81-8973 is Bayer’s new full-length recombinant factor VIII (FVIII) product in development for the treatment of hemophilia A. BAY 81-8973 has no human- or animal-derived raw materials added to the cell culture, purification, or formulation processes.

**Objective:** To evaluate the safety profile of BAY 81-8973 as documented in clinical trials with BAY 81-8973.

**Methods:** The safety of BAY 81-8973 for prevention and treatment of bleeds in patients with severe hemophilia A (<1% FVIII) was evaluated in 3 clinical studies: 2 in adolescent and adult previously treated patients (PTPs; aged 12–65 years with ≥150 previous exposure days [EDs]) and 1 in pediatric PTPs (aged ≤12 years with ≥50 previous EDs). A total of 193 PTPs (including 51 pediatric patients) were included to assess the frequency of adverse reactions in the 3 phase 3 studies. The immunogenicity of BAY 81-8973 was also evaluated in PTPs. Adverse reactions were collected and analyzed throughout the studies.

**Results:** The frequency, type, and severity of adverse reactions in children were similar to those in adults. Adverse reactions in PTPs are listed in Table 1. In PTPs evaluated to date for immunogenicity, no inhibitors were detected.

Table 1. Adverse Reactions in Previously Treated Patients (N=193)

<table>
<thead>
<tr>
<th>Preferred Term(s)</th>
<th>Frequency of Each Adverse Reaction, \textsuperscript{*} n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>14 (7.3)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>8 (4.1)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>6 (3.1)</td>
</tr>
<tr>
<td>Injection site reactions, insomnia, rash</td>
<td>5 (2.6)</td>
</tr>
<tr>
<td>Abdominal pain, dyspepsia</td>
<td>4 (2.1)</td>
</tr>
<tr>
<td>Abdominal discomfort</td>
<td>3 (1.6)</td>
</tr>
<tr>
<td>Cardiac palpitation, chest discomfort, allergic dermatitis, dizziness, lymphadenopathy, sinus tachycardia</td>
<td>2 (1.0)</td>
</tr>
<tr>
<td>Dysgeusia, flushing, hypersensitivity, urticaria</td>
<td>1 (0.5)</td>
</tr>
</tbody>
</table>

\textsuperscript{*}Adverse reactions that occurred with the same frequency are listed together; the reported frequency corresponds to each individual adverse reaction.

**Conclusions:** The incidence of treatment-related adverse and serious adverse reactions in the BAY 81-8973 trials was low (<10%) and similar to those reported in the literature for other full-length FVIII products. No PTP developed a FVIII inhibitor.
Impact of FVIII CRM-positive status on the immunogenicity of FVIII in the hemophilia A mouse model

Jasmine Ito¹, Rylee Mercer¹, Brittany Chao², Michael Lenardo², John Healey¹, Hunter Baldwin¹, Shannon Meeks¹

¹Aflac Cancer and Blood Disorders Center, Emory University and Children's Healthcare of Atlanta, Atlanta, GA, USA; ²National Institutes of Health, Bethesda, MD, USA

Objective: Approximately 25-30% of patients with severe hemophilia A develop anti-FVIII antibodies (inhibitors). Over 50% of patients with severe hemophilia A are predicted to produce no detectable FVIII protein (CRM-negative) and thus are not immunologically tolerant to FVIII. The remaining patients are thought to produce some portion of the FVIII protein (CRM-positive). Studies have shown that mutation type is a major risk factor for inhibitor development with mutations predicted to cause a complete lack of endogenous FVIII protein having the highest rates. There is potential for CRM-positive patients to produce and present portions of the FVIII protein in the thymus, thus, acquiring some level of central tolerance to FVIII. The purpose of this study was to compare the immune response to FVIII in the commonly used E16 hemophilia A mouse model and a newly developed hemophilia A mouse model in which all coding exons have been removed (TKO). The E16 mice were previously reported to have very small amounts of circulating heavy chain and are thus CRM-positive.

Methods: We backcrossed E16 mice to greater than 95% C57BL/6 (E16-B6) for comparison to TKO mice which were made on a C57BL/6 background to minimize the known difference in immune responses among different strains of mice. Following a standard immunization regimen with human FVIII, plasma was collected and total anti-FVIII IgG titers were compared. To further evaluate the production of protein by E16 mice, we transfected BHK-M cells with plasmid containing the E16 FVIII gene minus the B-domain (tMSQ). Both secreted and intracellular levels of FVIII heavy chain expression were measured and compared to levels in BHK-M cells expressing mouse B-domain deleted FVIII (MSQ).

Summary: The immune response in E16-B6 mice showed a trend toward lower inhibitor levels with a median anti-FVIII IgG ELISA titer of 930 compared to 2760 for the TKO mice (p=0.51, Mann-Whitney). There was minimal secreted FVIII protein from BHK-M cells transfected with tMSQ, but intracellular levels were the similar for tMSQ and MSQ.

Conclusions: The CRM-positive E16-B6 mice had a lower immune response to human FVIII than TKO mice. This decrease may result from partial tolerance to portions of the murine FVIII produced by the E16-B6 mice. The availability of both CRM-positive and CRM-negative mouse models provides the opportunity for comparative immunology studies in severe hemophilia A mice.
Patient Satisfaction with US Hemophilia Treatment Centers 2015: National Results

Judith Baker¹, Karen Droze², Rick Shearer³, Kathryn McLaughlin⁴, Brenda Riske³

¹Center for Inherited Blood Disorders and UCLA, Orange, California, USA, ²Hemophilia of Georgia, Inc, Atlanta, Georgia, USA, ³Mountain States Hemophilia Network / Hemophilia & Thrombosis Center, Aurora, CO, USA, ⁴National Hemophilia Program MCHB/DSCSHN/Genetic Services Branch, Rockville, MD, USA

Objective: Patient satisfaction with healthcare services enhances patient experience, improves outcomes, and is increasingly mandated by public and private payers. While many US Hemophilia Treatment Centers (HTC) periodically assess patient satisfaction, the lack of a uniform survey hampered national measurement. To remedy this knowledge gap, the US HTC Network implemented a national patient satisfaction survey in 2015.

Methods: A Regional HTC Coordinator workgroup devised, piloted, and finalized a two-page survey for self-administration online, at clinic, or at home, in English or Spanish and mailed to households. Survey content and format were based on national health surveys to enhance comparability and scientific robustness, informed by legacy regional HTC surveys. Questions assessed patient demographics; satisfaction with services, team members, and care processes; and Healthy People 2020 adolescent transition objectives. Surveys included open ended questions to obtain qualitative data. Respondents were anonymous but identified with their respective HTCs. Participation was voluntary. Persons with genetic bleeding disorders who had HTC contact in 2014 were eligible. During February 2015, 124/130 HTCs sent surveys to 27,563 households. Parents completed surveys for children under age 15. No reminders were sent. Data were entered and analyzed at a central site and aggregated at national, regional and HTC levels.

Results: Over 4800 households (17.4%) returned surveys by April 30, 2015. National analyses on 4332 surveys reveal that 96.6% were ‘always’ or ‘usually’ satisfied with HTC care. Over 80% were ‘always’ satisfied with the core HTC team members. Three quarters of 12-17 year olds were ‘always’ satisfied with HTC encouragement regarding becoming more independent, and how the HTC discussed caring for a bleeding disorder upon reaching adulthood. Eighty–90% were ‘always’ or ‘usually’ satisfied with care processes, e.g. shared decision making, care coordination, ease of obtaining timely information and services, and being treated respectfully. Insurance and language were ‘always’ a problem for 20%. 29.0% of respondents were female and 10.3% Hispanic. 83.4% were Caucasian, 5.8 African-American, 3.1% Asian/Pacific Islander or Native Hawaiian, 4.3% Multiple races, and 4% Other. Over half had severe or moderate FVIII or FIX deficiency or VWD Type 3. Ages ranged from newborns to 96 years: 38% under 18, 20% age 18 – 34, and 42% over age 35.

Conclusions: Implementing a National Patient Satisfaction Survey for the US HTCN is feasible, and provides valuable information. Satisfaction with HTC services is high, but insurance and language ‘always’ pose problems for one fifth. Further analyses will examine regional differences.
Patients Treated with Recombinant Factor VIII Fc Fusion Protein (rFVIIIFc) Reported Increased or Maintained Physical Activity in the A-LONG and Kids A-LONG Studies

Doris Quon1, Robert Klamroth2, Roshni Kulkarni3, Amy Shapiro4, Ross Baker5, Giancarlo Castaman6, Bryce Kerlin7, Elisa Tsao8, Geoffrey Allen8

1Orthopaedic Hemophilia Treatment Center, Los Angeles, CA, USA, 2Zentrum fuer Gefaessmedizin/ Haemophiliezentrum, Vivantes Klinikum im Friedrichshain, Berlin, Germany, 3Michigan State University, East Lansing, MI, USA, 4Indiana Hemophilia & Thrombosis Center, Indianapolis, IN, USA, 5Western Australia Centre for Thrombosis and Haemostasis, Murdoch University, Perth, Australia, 6Center for Bleeding Disorders, Careggi University Hospital, Florence, Italy, 7Nationwide Children’s Hospital, Columbus, OH, USA, 8Biogen, Boston, MA, USA

Introduction and Objectives: In the phase 3 A-LONG and Kids A-LONG studies, subjects with severe hemophilia A receiving rFVIIIFc prophylaxis 1-2 times/week had low annualized bleeding rates (ABRs), with comparable pre-study and on-study weekly factor consumption for subjects previously on FVIII prophylaxis. This report evaluated the effect of rFVIIIFc on subjects’ physical activity across a variety of age groups using a subject-reported assessment.

Methods: Subjects eligible for A-LONG (≥12 y) and Kids A-LONG (<12 y) were previously treated males with severe hemophilia A (<1 IU/dL endogenous FVIII activity). Subjects in A-LONG were enrolled into 1 of 3 arms: Arm 1, individualized prophylaxis; Arm 2, weekly prophylaxis; or Arm 3, episodic treatment. All subjects in Kids A-LONG received rFVIIIFc prophylaxis. There were no restrictions regarding physical activity. Physical activity assessments were conducted at Weeks 7, 14, 28, 38, 52, and end of study (A-LONG) and Weeks 2, 7, 12, 17, 22, 26, and end of study (Kids A-LONG). At each visit after their first rFVIIIFc dose, subjects were asked to report any changes in their activity levels relative to their prior study visit as: more (or more intensive), fewer (or less intensive), or about the same amount of physical activities. To summarize each subject’s change in physical activity during the study compared to baseline, subjects’ reports were classified into four groups: less, the same, more, or undetermined.

Results: A total of 165 and 71 subjects enrolled in A-LONG and Kids A-LONG, respectively. Overall, the majority of subjects in A-LONG reported more or the same amount of physical activity, and few subjects reported less physical activity during the study (less, the same, more, undetermined in Arm 1 [n=117], 8%, 36%, 51%, 5%; Arm 2 [n=23], 9%, 48%, 39%, 4%; Arm 3 [n=23], 9%, 52%, 26%, 13%, respectively). Results were generally similar for subjects in Kids A-LONG (for subjects aged <6 y [n=35], 3%, 26%, 66%, 6%; for subjects aged 6 to <12 y [n=34], 9%, 26%, 56%, 9%).

Conclusions: The majority of subjects in A-LONG and Kids A-LONG reported similar or increased physical activity levels during the studies, while maintaining low ABRs. These self-reported data suggest that subjects across a variety of age groups with severe hemophilia A who are transitioning to rFVIIIFc may maintain or increase physical activity levels, while reducing infusion frequency and maintaining similar weekly factor consumption, without compromising efficacy.
Increase or Maintenance of Physical Activity in Patients Treated with Recombinant Factor IX Fc Fusion Protein (rFIXFc) in the B-LONG and Kids B-LONG Studies

Amy Shapiro¹, Roshni Kulkarni², Jerzy Windyga³, Margaret Ragni⁴, John Pasi⁵, Margareth Ozelo⁶, Elisa Tsao⁷, Geoffrey Allen¹, Baisong Mei⁷

¹Indiana Hemophilia & Thrombosis Center, Indianapolis, IN, USA, ²Michigan State University, East Lansing, MI, USA, ³Department of Disorders of Haemostasis and Internal Medicine, Institute of Haematology and Transfusion Medicine, Warsaw, Poland, ⁴University of Pittsburgh and Hemophilia Center of Western PA, Pittsburgh, PA, USA, ⁵Barts and The London School of Medicine and Dentistry, London, UK, ⁶INCT do Sangue Hemocentro UNICAMP, Campinas, Brazil, ⁷Biogen, Boston, MA, USA

Introduction and Objectives: In the phase 3 B-LONG and Kids B-LONG studies, subjects with severe hemophilia B receiving rFIXFc prophylaxis had low annualized bleeding rates (ABRs), with decreased weekly factor consumption and fewer infusions compared with pre-study FIX treatment. This report evaluated the effect of rFIXFc on subjects’ physical activity across a variety of age groups using a subject-reported assessment.

Methods: Eligible subjects for B-LONG (≥12 y) and Kids B-LONG (<12 y) were previously treated males with severe hemophilia B (≤2 IU/dL endogenous FIX activity). Subjects in B-LONG were enrolled into 1 of 4 treatment arms: Arm 1, weekly prophylaxis; Arm 2, individualized interval prophylaxis; Arm 3, episodic treatment; or Arm 4, perioperative management (not included in this analysis). All subjects in Kids B-LONG started on weekly prophylaxis. There were no restrictions regarding physical activity. Physical activity assessments were conducted at Weeks 4, 16, 26, 39, 52, and end of study (B-LONG) and Weeks 3, 12, 24, 36, 50, and end of study (Kids B-LONG). At each visit after their first rFIXFc dose, subjects were asked to rate their activity level relative to their prior study visit as: more (or more intensive), fewer (or less intensive), or about the same amount of physical activities. To summarize each subject’s change in physical activity over the course of the study compared to baseline, subjects’ reports were classified into four groups: less, the same, more, or undetermined.

Results: Overall, 123 and 30 subjects enrolled in B-LONG and Kids B-LONG, respectively. The majority of subjects in B-LONG reported more or the same amount of physical activity, and few subjects reported less physical activity during the study (less, the same, more, undetermined in Arm 1 [n=60], 7%, 42%, 35%, 17%; Arm 2 [n=25], 16%, 28%, 48%, 8%; Arm 3 [n=27], 15%, 26%, 30%, 30%, respectively). Results were generally similar for subjects in Kids B-LONG (for subjects aged <6 y [n=15], 13%, 27%, 47%, 13%; for subjects aged 6 to <12 y [n=15], 7%, 13%, 67%, 13%).

Conclusions: ABRs were low in B-LONG and Kids B-LONG despite similar or increased physical activity levels reported by the majority of subjects. These results suggest that people with severe hemophilia B across a variety of age groups may maintain or increase their physical activity levels with rFIXFc, while also reducing infusion frequency and weekly factor consumption, without compromising efficacy.
Long-term safety and efficacy of recombinant factor VIII Fc (rFVIIIFc) for the treatment of severe hemophilia A: United States subgroup interim analysis of the ASPIRE study

Doris Quon, Guy Young, Margaret Ragni, Barbara Konkle, Roshni Kulkarni, Amy Shapiro, Elisa Tsao, Lynda Cristiano, Geoffrey Allen

1Orthopaedic Hemophilia Treatment Center, Los Angeles, CA, USA, 2Children’s Hospital, Los Angeles, CA, USA, 3University of Pittsburgh and Hemophilia Center of Western PA, Pittsburgh, PA, USA, 4Puget Sound Blood Center, Seattle, WA, USA, 5Michigan State University, East Lansing, MI, USA, 6Indiana Hemophilia & Thrombosis Center, Indianapolis, IN, USA, 7Biogen, Boston, MA, USA

Objective: The ongoing rFVIIIFc extension study, ASPIRE (clinicaltrials.gov #NCT01454739), evaluates the long-term safety and efficacy of rFVIIIFc in adults, adolescents, and children with severe hemophilia A. Here we report interim outcomes for United States (US) subjects in ASPIRE. Methods: Eligible subjects could enroll in ASPIRE upon completing A-LONG or Kids A-LONG. There were 4 treatment groups: individualized prophylaxis (25-65 IU/kg every 3-5 days, or 20-65 IU/kg on D1, 40-65 IU/kg on D4 if twice weekly); weekly prophylaxis (65 IU/kg every 7 days); modified prophylaxis (to further personalize and optimize treatment when needed); or episodic treatment. Subjects could change treatment groups at any time. Subjects <12 yrs participated only in individualized and modified prophylaxis groups. Primary endpoint: development of inhibitors. Secondary outcomes included annualized bleeding rate (ABR) and rFVIIIFc exposure days (EDs). Summary: Sixty subjects (49 from A-LONG; 11 from Kids A-LONG) enrolled. As of the interim data cut (6 Jan 2014), the median time on ASPIRE was 80.37 (A-LONG) and 15.94 (Kids A-LONG) wks; 82% (A-LONG) and 27% (Kids A-LONG) of subjects had ≥100 cumulative rFVIIIFc EDs. 7/49 A-LONG subjects changed treatment groups upon enrollment into or during ASPIRE; 2 Kids A-LONG subjects switched from individualized to modified prophylaxis upon enrollment into ASPIRE. Median ABRs were low with rFVIIIFc prophylaxis (Table). Overall, most subjects treated prophylactically during the parent study did not experience changes to their total weekly prophylactic dose or dosing interval during ASPIRE. For subjects who enrolled from A-LONG and Kids A-LONG, 94% and 100% of all bleeding episodes during ASPIRE, respectively, were controlled with 1 infusion. In the overall study population, no inhibitors were observed during ASPIRE; adverse events were typical of the general adult and pediatric hemophilia A populations. Conclusion: Interim data from US subjects in ASPIRE are consistent with those of the phase 3 parent studies and the overall ASPIRE interim analysis. Results from ASPIRE confirm the longer-term safety of rFVIIIFc and the maintenance of a low ABR with extended interval prophylactic dosing in individuals with severe hemophilia A.

<table>
<thead>
<tr>
<th>ABR in US subjects during ASPIRE, by parent study</th>
<th>A-LONG</th>
<th>Kids A-LONG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Individualized prophylaxis</td>
<td>0.60 (0.00, 2.91) [39]</td>
<td>0.00 (0.00, 2.18) [9]</td>
</tr>
<tr>
<td>Weekly prophylaxis</td>
<td>1.79 (0.60, 4.39) [6]</td>
<td>--</td>
</tr>
<tr>
<td>Modified prophylaxis</td>
<td>0.96 (0.00, 3.81) [3]</td>
<td>3.28 (0.00, 6.55) [2]</td>
</tr>
<tr>
<td>Episodic</td>
<td>18.36 (14.23, 24.02) [6]</td>
<td>--</td>
</tr>
</tbody>
</table>
Associations Between Annual Bleeding Episodes and Financial Burden of Illness Among Persons with Hemophilia A and B in the United States

Christina Chen, Barbara Konkle, Xiaoli Niu, Judith Baker, Jeffrey Hord, Roshni Kulkarni, Megan Ullman, Duc Quang Tran, Joanne Wu, Amit Soni, Mimi Lou, Michael Nichol

1University of Southern California, Los Angeles, CA, USA, 2Puget Sound Blood Center, Seattle, WA, USA, 3Center for Inherited Blood Disorders, Orange, CA, USA, 4Akron Children’s Hospital Medical Center, Akron, OH, USA, 5Michigan State University, East Lansing, MI, USA, 6University of Texas Health Science Center at Houston, Gulf States Hemophilia and Thrombophilia Center, Houston, TX, USA, 7Emory University, Atlanta, GA, USA, 8Children’s Hospital of Orange County, Orange, CA, USA

Objective: To evaluate the effect of bleeding episodes on hemophilia patient burden of illness using observational data.

Methods: Between 2005-2007 and 2009-2012, the Hemophilia Utilization Group Studies Va and Vb, respectively, recruited patients from ten Hemophilia Treatment Centers (HTCs) in eleven states. Adult patients or parents of children with hemophilia A or B completed an initial survey assessing socio-demographics, clinical characteristics, and treatment regimen. Work absenteeism, underemployment due to hemophilia, and unpaid hemophilia-related caregiver time were recorded at regular intervals over two years to estimate indirect costs using the human capital approach. Direct costs were estimated using healthcare services utilization and drug dispensing records. All costs were annualized and converted to 2014 US dollars. Annual mean bleeding episodes were calculated from patient-reported number of bleeds recorded in follow-up interviews, and used to stratify patients into bleeding categories of 0, 1-3, 4-6, 7-9, and 10+ bleeds. Associations between bleeding episodes and healthcare utilization, work productivity losses, and total costs were analyzed in patient subgroups based on both severity and treatment regimen.

Results: Of 477 recruited patients, 352 with complete healthcare utilization and dispensing records and at least three months of follow-ups were included. A larger proportion of hemophilia A patients had severe disease and used prophylaxis compared to those with hemophilia B, but no socio-demographic variables differed significantly between the groups. Among severe patients, adults compared to children and episodic treatment compared to prophylaxis users had significantly more average annual bleeds [respective mean(standard deviation): 16.24(13.9) vs 5.54(9.47), p<0.0001 and 15.69(12.65) vs 8.39(11.1), p<0.0001]. Nearly two-thirds of the 82 severe patients using episodic treatment (63.4%) had 10 or more annual bleeds. Higher bleeding categories (more annual bleeds) were significantly associated with higher mean annual indirect costs for mild/moderate patients using episodic treatment [mean range across categories: $423-$21,434 (p=0.0003)] and severe patients on prophylaxis [$6,467-$14,890 (p=0.005]. Increased bleeding was also significantly associated with higher mean total costs in episodic treatment users with mild/moderate disease [$17,373-$136,552 (p<0.0001)] and severe disease [$83,957-$226,614 (p=0.008)]. Across all subgroups, increased bleeding was associated with more emergency room visits, outpatient procedures, and missed days of work, oftentimes reaching statistical significance.

Conclusions: A larger proportion of severe hemophilia patients treating episodically have poor bleed management compared to those on prophylaxis. Overall, higher bleeding frequency is associated with both higher direct and indirect costs for individuals with hemophilia A and B across disease severity and treatment regimen.
RELATIVE HEALTH STATUS OF YOUNG ADULTS IN THE HEMOPHILIA UTILIZATION GROUP STUDIES (HUGS)

Randall Curtis\textsuperscript{1}, Brenda Riske\textsuperscript{2}, Judith Baker\textsuperscript{3}, Megan Ullman\textsuperscript{4}, Xiaoli Niu\textsuperscript{5}, Kristi Norton\textsuperscript{2}, Marion Koerper\textsuperscript{6}, Mimi Lou\textsuperscript{5}, Michael Nichol\textsuperscript{6}

\textsuperscript{1}Factor VIII Computing, Berkeley, CA, USA, \textsuperscript{2}University of Colorado, Hemophilia and Thrombosis Center, Denver, CO, USA, \textsuperscript{3}The Center for Comprehensive Care & Diagnosis of Inherited Blood Disorders, and University of California, Los Angeles, Los Angeles, CA, USA, \textsuperscript{4}University of Texas Health Science Center at Houston, Gulf States Hemophilia and Thrombophilia Center, Houston, TX, USA, \textsuperscript{5}University of Southern California, Los Angeles, CA, USA, \textsuperscript{6}University of California, San Francisco, San Francisco, CA, USA

Introduction: Major advancements in care during the past 30 years should translate into improved health and quality of life among young persons with hemophilia in the U.S. However, few studies have examined the health status of this population.

Objective: To analyze the health status of young adults with hemophilia with regard to quality of life and comorbidities.

Methods: Adults with hemophilia type A or B, aged 18-34 years, reporting health status information to the Hemophilia Utilization Group Studies (HUGS) are compared to the general U.S. young adult population. National data reported in this study were drawn from the U.S. Census, Bureau of Labor Statistics, and various Centers for Disease Control surveys. A total of 477 adults were included in the HUGS hemophilia A/B studies, and 141 were aged 18-34 years at time of enrollment (63% had severe disease).

Results: When compared to the general US population of persons age 18 – 34, persons with hemophilia older than 18 years were: less likely to be married (42% HUGS vs. 58% national), more frequently unemployed (35% 18-34 years HUGS vs. 6% 20-34 years national), and less likely to have attained a high school education (62% 18-34 years HUGS vs. 86% 25-34 years national). Only 7.5% of persons with hemophilia reported having no insurance vs. 18.4% in the general population. 63% of the HUGS young adult population reported comorbidities (52% of the 18-24 age group, and 76% of the 25-34 age group). The most prevalent comorbidities included: liver disease (48%), arthritis (33%), and HIV (14%). This compares to the general US 18-44 population wherein <1% have liver disease, < 7% have arthritis, and HIV infection rates are less than 1/1,000th of a percent. Nearly a quarter of the HUGS population was reported as obese, and another 23% as overweight. The general US 18-44 population reports 26% obese and 31% overweight by comparison. Young adults in the HUGS population reported SF-12 physical component scores of 46.3±9.5, lower than the national norms of 54.0±7.0.

Conclusions: Young adults with hemophilia experience significantly higher comorbidity levels and significantly lower quality of life than young males in the general US population. Particularly disappointing is our finding that 24% of 18 to 24 year olds in the HUGS sample reported arthritis. Use of prophylaxis should result in healthier joints and less arthritis. Further studies are needed to identify potential interventions that could preserve society’s investment in this vulnerable population.
Long-term safety and prophylactic efficacy of once-weekly subcutaneous administration of ACE910 in Japanese hemophilia A patients with and without FVIII inhibitors: Interim results of the extension study of a phase I study

Midori Shima

Department of Pediatrics, Nara Medical University, Nara, Japan

Background: Current issues of Factor VIII (FVIII) replacement therapy for hemophilia A are development of FVIII inhibitors and requirement of frequent intravenous infusion which may lead prophylaxis to be ineffective. To overcome these issues, ACE910 has been developed, which is a humanized bispecific antibody that binds factors IXa and X, thereby mimicking the cofactor function of FVIII.

Methods: ACE910 has shown preferable safety and promising efficacy profiles in a first-in-patient phase 1 study. In the Phase I study, 18 Japanese hemophilia A patients received once-weekly subcutaneous ACE910 at one of the following dose levels for 12 weeks: 0.3, 1 and 3 mg/kg. These patients were offered to continue on the extension study, including the option to escalate the dose. The studies were approved by all local site Institutional Review Board. Informed consent was obtained from each patient.

Results: Interim data of the phase 1 and extension study combined are presented in this abstract, with a median follow-up of 9.5 months to-date. Age ranged from 12–58 years. The number of patients with FVIII inhibitors included was 4, 4 and 3 respectively for each dose level. A total of 16 patients participated in the extension study. The ACE910 dose was escalated in 2 patients from 0.3 to 1 mg/kg due to frequent bleeding.

Eighty adverse events (AEs) reported in 17 patients were mild or moderate. No thromboembolic AE was reported, even when FVIII or bypassing agents were given concomitantly as on-demand therapy. Anti-ACE910 antibodies screened by electrochemiluminescence immunoassay were developed in 2 patients, which did not affect ACE910 pharmacokinetics or pharmacodynamics.

The annualized bleeding rate (ABR) decreased compared to the ABR prior to ACE910 initiation for both patients with and without inhibitors. The median ABR was reduced from 32.5 to 2.0, 18.3 to 1.2, and 15.2 to 0.0 for the 0.3, 1 and 3 mg/kg dose levels, respectively.

Conclusion: The long-term safety and efficacy data show that ACE910 could be a groundbreaking treatment option for hemophilia A patients irrespective of the presence of FVIII inhibitors.
Pegylated full-length recombinant factor VIII (BAX 855) for prophylaxis in previously treated adolescent and adult patients with severe hemophilia A

Ralph Gruppo\(^1\), Brian Wicklund\(^2\), Barbara K. Konkle\(^3\), Oleksandra Stasyshn\(^4\), Pratima Chowdary\(^5\), Brigitte E. Abbuehl\(^6\), Werner Engl\(^6\), Lisa Patrone\(^7\), Bruce Ewenstein\(^7\)

\(^1\)Cincinnati Children’s Hospital, Cincinnati, OH 45229, USA, \(^2\)Children’s Mercy Hospitals & Clinics, Kansas City, MO, USA, \(^3\)Puget Sound Blood Center, Seattle, WA 98104, USA, \(^4\)Si Institute of Blood Pathology and Transfusion Medicine of NAMSU, 79044 Lviv, Ukraine, \(^5\)Royal Free NHS Foundation Trust, London NW3 2QG, UK, \(^6\)Baxalta Innovations GmbH, Vienna, 1221, Austria, \(^7\)Baxalta US Inc., Westlake Village, CA, USA

**Objective:** To assess the pharmacokinetics (PK) and efficacy of prophylactic treatment with BAX 855 - a novel polyethylene glycol (pegylated) full-length recombinant factor VIII, built on the rAHF-PFM (ADVATE) protein - by age group in previously-treated male patients with severe hemophilia A.

**Methods:** Adolescent (12 to <18 years) and adult (18 to 65 years) subjects received 45 ± 5 IU/kg BAX 855 twice weekly as prophylaxis for approximately 6 months. PK was assessed in a subgroup (n=25 planned, including ≥6 adolescents) for one ADVATE infusion, then for BAX 855 at the initial infusion and after ≥50 exposure days (EDs). Efficacy was assessed in all subjects.

**Summary:** Twenty-six subjects (8 adolescents, 18 adults) were included in the PK evaluation, and 121 (23 adolescents, 98 adults) were included in the efficacy analysis (all subjects assigned to treatment, i.e. full analysis set). The extended half-life (T\(_{1/2}\)) and mean residence time (MRT) of BAX 855 (initial dose) compared to ADVATE were demonstrated by fold increases in the means of 1.4 and 1.5, respectively in both adolescents and in adults, using the one-stage clotting assay. The initial and repeat PK assessments of BAX 855 showed similar results. Consistent trends were observed when PK was determined using the chromogenic assay. The arithmetic mean (SD) annualized bleeding rate (ABR) during prophylaxis with BAX 855 was higher in adolescents than in adults (6.2 [6.1] versus 3.2 [4.2]). ABRs for injury-related bleeding episodes (BEs) were higher in adolescents (arithmetic mean [SD]: 2.3 [3.2] versus 1.7 [3.1] in adults), thus contributing to the overall higher ABR in this group. Joint ABRs were lower in adolescents (arithmetic mean [SD]: 1.8 [2.5] versus 3.2 [8.8] in adults) with an inverse relationship for non-joint ABRs. Six adolescents (26.1%) and 39 adults (40.2%) had zero BEs. A total of 48 BEs occurred in adolescents (20 minor; 26 moderate; 2 severe); 182 occurred in adults (69 minor; 103 moderate; 10 severe). The hemostatic efficacy of BAX 855 was rated excellent or good at resolution for the majority of BEs in both age groups (93.8% in adolescents; 92.9% in adults).

**Conclusions:** Although fewer adolescents than adults were included in the study, the data suggest that BAX 855 is efficacious in both age groups for twice-weekly prophylaxis and control of BEs. As expected, joint ABR was higher in the adult group.
Reduced Polyethylene Glycol–Conjugated B-Domain–Deleted Factor VIII (PEG-BDD-FVIII) Clearance: Selective PEG Steric Modulation Without Affecting Potency

Eric Blasko, Lilley Leong, Derek Sim, Liang Tang, Jim Wu, Katalin Kauser, Babu Subramanyam

Bayer HealthCare Pharmaceuticals, US Innovation Center, San Francisco, CA, USA

Prophylactic factor VIII (FVIII) replacement therapy in hemophilia A requires frequent administration because of the short half-life of FVIII. Polyethylene glycol (PEG) conjugation is thought to extend FVIII half-life by decreasing hepatic clearance. BAY 94-9027 is a rationally designed B-domain–deleted (BDD) FVIII molecule with a 60-kDa PEG molecule attached to a specific amino acid (1804) to increase circulating half-life and reduce the exposure to epitopes reported to cause immunogenicity in the A3 domain while preserving full biological function. BAY 94-9027 is currently in clinical trials and has prolonged half-life and improved efficacy in animal models and humans.

To determine whether half-life extension with BAY 94-9027 is related to PEG steric hindrance, we first investigated whether PEG impacts BAY 94-9027 binding interactions. Direct binding of hybrid of kidney and B cells (HKB)11-derived FVIII, BAY 94-9027 or BDD-FVIII, was assessed by measuring the ability of a panel of immobilized monoclonal antibodies directed toward different FVIII domains to capture FVIII. Interactions with more physiologic partners were indirectly assessed by thrombin generation assay (TGA) and by an in vitro hepatocyte clearance assay.

Our results indicate that the presence of A3-directed PEG reduced BAY 94-9027 capture by immobilized antibodies directed toward FVIII regions at or near the site of conjugation. Capture by antibodies directed toward the A3 and C2 domains were most impacted, while those directed toward A1 and A2 still bound BAY 94-9027. The A3-specific C7F7 antibody showed ~50% lower capture of BAY 94-9027 vs BDD-FVIII at 20 ng/mL of FVIII. C7F7 capture of PEG-BDD-FVIII was further reduced when a di-PEG conjugate of BDD-FVIII was subjected to the same assay, again confirming that PEG sterically modulates PEG-BDD-FVIII reactivity to the antibody. To determine whether steric effects observed with PEG may impact FVIII function globally, TGA was performed with BAY 94-9027 spiked into FVIII-deficient plasma and subjected to 1 pM tissue factor initiation. By TGA, both BDD-FVIII and BAY 94-9027 generated comparable peak thrombin levels, with EC50 values of 3.9 and 3.2 nM for BDD-FVIII and BAY 94-9027, respectively. These results indicate that the PEG did not disrupt activated PEG-BDD-FVIII interactions with its partners in the factor Xase enzyme complex, consistent with published PEG-BDD-FVIII efficacy. By hepatocyte clearance assay, PEG-BDD-FVIII clearance was reduced ~30-40% compared with BDD-FVIII, regardless of whether von Willebrand factor was present. This reduction in hepatocyte clearance is likely to contribute to the prolonged plasma half-life reported for BAY 94-9027.
A Novel Anti-Tissue Factor Pathway Inhibitor Antibody, BAY 1093884, Prevents Bleeding in Hemophilia A Mice

Maria Koellnberger¹, Perry Liu², Derek Sim⁰

¹Bayer Pharma AG, Wuppertal, Germany, ²Bayer HealthCare Pharmaceuticals, US Innovation Center, San Francisco, CA, USA

Background: BAY 1093884 is a fully human monoclonal antibody against tissue factor pathway inhibitor (TFPI) developed as a bypass agent for hemophilia patients with inhibitors. It restores thrombin burst for stable clot formation in hemophilic conditions in vitro.

Aims: The goal of this study was to elucidate the in vivo prophylactic hemostatic potency of BAY 1093884.

Methods: The hemophilia A mouse tail vein transection model was used for this study to mimic the venous bleeding characteristics of severe hemophilia. Male hemophilia A mice (n=12/group) were treated prophylactically with escalating doses of BAY 1093884. All treatments were administered as single intravenous (IV) bolus at 4 different time courses prior to injury (1, 3, 5, and 7 days). Bleeding was induced by a 1.2-mm deep incision across the left lateral vein. Following injury, the animals were monitored hourly for moribundity for up to 9 hours and after 24 hours followed by euthanasia.

Results: Efficacious doses of BAY 1093884 providing 50% protection for survival (ED₅₀) for up to 6 days after IV bolus ranged from 0.6–2 mg/kg. In comparison, only 25% protection was achieved 6 days after the treatment with a very high dose of 1000 IU/kg of recombinant factor VIII (rFVIII). The effect of a single IV dose of 18 mg/kg BAY 1093884 providing 80%–90% survival was maintained over 8 days (ED₅₀ 6 mg/kg), whereas a single IV dose of rFVIII failed to provide protection over an 8-day period.

Conclusions: These studies demonstrate that BAY1093884 prevents bleeding and increases long-term survival to a greater degree than rFVIII in hemophilia A mice and may offer a convenient prophylactic treatment option for hemophilia patients with inhibitors.
Global Knowledge and Confidence Assessment of Hemophilia Clinical Practice Approaches Among Pediatricians

Emily Van Laar, Charlotte Warren, Neil Frick, Christine Kempton, Maria Elisa Mancuso, Steven Pipe

1Medscape LLC, New York, NY, USA, 2University of Michigan, Ann Arbor, MI, USA, 3Emory University School of Medicine, Atlanta, GA, USA, 4Università degli Studi di Milano, Milano, Italy, 5National Hemophilia Foundation, New York, NY, USA

Objective: Clinical knowledge gaps of hemophilia can affect patient outcomes through delayed diagnosis/referral as well as improper monitoring and interventions. A study was undertaken to identify and characterize clinical practice gaps and confidence levels in the management of hemophilia specific to pediatricians.

Methods: Building upon a previous assessment developed in 2014, an updated global, hemophilia-specific continuing medical education-accredited clinical practice assessment survey was developed utilizing current evidence-based consensus guidelines and best practices, including guidelines from the National Hemophilia Foundation and the World Federation of Hemophilia. The assessment included both knowledge- and case-based, multiple-choice questions that healthcare providers completed confidentially on-line between March 23, 2015 and April 9, 2015. Areas such as appropriate triggers for initiating prophylaxis and use of physical therapy were assessed. Responses from pediatric providers were de-identified and aggregated prior to analysis.

Summary: 660 pediatricians (30% of total respondents) completed the survey, from the following locales: North America (36%), Asia (23%), Europe (15%), Middle East (10%), Africa (7%), Central/South America (6%), and Australia (4%). Academic (31%), private practice (27%), community hospital (19%), community clinic (12%), and hemophilia treatment center (3%) practice settings were identified. Analysis of pediatricians who indicated professional interaction with hemophilia patients (87% of pediatrician respondents) demonstrated knowledge gaps including (% incorrect responses): classification of severity of hemophilia (37%); optimal use of prophylactic therapy, e.g., when to initiate (31%), at what dose (53%), prophylaxis in active patients (26%); likelihood of inhibitors (75%); using bypassing therapy (58%); comprehensive care model (61%); supporting overall joint health and quality of life (70%); and adherence (60%). A low level of confidence in the ability to identify when to use prophylaxis was reported among 31% of pediatricians. The top barriers to the administration of prophylaxis identified by the pediatric providers included lack of availability of FVIII or FIX concentrates, lack of venous access, and insurance coverage (29%, 22%, and 21% for respondents, respectively).

Conclusions: This study demonstrated gaps in knowledge and confidence about the assessment and optimal care of hemophilia for pediatricians, suggesting that further education specific to the needs of these providers is warranted.
The Effects of Hemophilia on Socialization

Aric Parnes1, Christine Mitchell1, Rachel Wentz1, Federico Campigotto2, Latoya Lashley3, Cathee Brunswick1, Donna Neuberg1, Judith Lin1

1Brigham and Women’s Hospital, Boston, MA, USA, 2Harvard Medical School, Boston, MA, USA, 3Boston Children’s Hospital, Boston, MA, USA

OBJECTIVE: Hemophilia is a congenital deficiency in a clotting factor resulting in a propensity for severe and disabling bleeds. Joint bleeds can lead to disabling arthropathy and past contamination of blood products resulted in an epidemic of HIV and hepatitis. We hypothesize that these issues may result in declines in quality of life, psychosocial well-being, and socialization (integration into society) and that socialization correlates with health-related quality of life (HR-QoL).

METHODS: We developed a socialization survey and interview for patients age >20 with hemophilia A (n=14) or B (n=4) and their spouses/significant others (SSOs) (n=9). The interviews were analyzed using PROMIS (patient-reported outcomes measurement information system-29) domains. Patients completed surveys in health-related quality of life measures including both A36 Hemofilia-QoL and WHOQOL-BREF. Patients were also scored according to the Colorado Joint Assessment Scale and Karnofsky Performance Scale. IRB approval and informed consent were obtained.

RESULTS: 19 patients were enrolled (ages 24-78), one withdrew. Nine patients had severe hemophilia, 5 had moderate disease, and 4 were mild. Four patients did not have SSOs (22%, 90% CI: [8%; 44%]); these included two severe and two moderate patients, one with HIV, and three with hepatitis C. Five SSOs declined participation. For the WHOQOL-BREF, patients reported overall quality of life in the physical domain an average score of 60 (range 13-94), 66 (31-100) in the psychological domain, 66 (31-100) in the social relationship domain, and 81 (44-100) in the environmental domain, all standardized 0-100. For the A36 Hemofilia-QoL, the median score was 94 (range 43-132) out of 144 (totaling physical health, daily activities, joint damage, pain, treatment satisfaction, treatment difficulties, emotional functioning, mental health, and relationships and social activities). Colorado Joint Assessment Scale-QOL provided scores of 6.1 out of 19 for ankles without gait and 8.3 out of 21 with gait, 4.2 for knees without gait, 6.3 with gait, and 3.6 for elbows. Analysis of interviews reflects social roles and social support as common domains in patients, whereas anxiety and anger predominated for SSOs.

CONCLUSIONS: This study employed established instruments as well as novel questionnaires and interview structures, although the latter have not been validated. Analysis points toward patient concerns regarding their social roles while SSOs expressed higher levels of anxiety and anger compared to patients. Both health-related-QoL and disease severity appear to be associated with social support domains of socialization. Patients with more severe disease may be less likely to have SSOs.
Kids B-LONG: Safety, Efficacy, and Pharmacokinetics of Long-Acting Recombinant Factor IX Fc Fusion Protein (rFIXFc) in Previously Treated Children with Hemophilia B.

Roshni Kulkarni1, Kathelijn Fischer2, Beatrice Nolan3, Johnny Mahlangu4, Savita Rangarajan5, Giulia Gambino6, Lei Diao6, Alejandra Ramirez-Santiago6, Glenn F Pierce6, Geoffery Allen6

1Michigan State University, East Lansing, MI, USA, 2University Medical Center, Utrecht, The Netherlands, 3Our Lady's Children's Hospital, Dublin, Ireland, 4Haemophilia Comprehensive Care Centre, University of the Witwatersrand and NHLS, Johannesburg, South Africa, 5Basingstoke and North Hampshire Hospital, Basingstoke, UK, 6Biogen, Cambridge, MA, USA

Objective: Kids B-LONG was an open-label phase 3 study that evaluated the safety, efficacy, and pharmacokinetics (PK) of rFIXFc in previously treated children (aged <12 years; ≥50 prior exposure days [EDs] to FIX) with severe hemophilia B (≤2 IU/dL endogenous FIX) and no history of FIX inhibitors.

Methods: Participants initiated prophylactic treatment with 50–60 IU/kg rFIXFc once-weekly; dose and interval adjustments were based upon PK data and bleeding frequency. The primary endpoint was development of inhibitors (neutralizing antibodies). Key secondary outcomes included PK and annualized bleeding rate (ABR).

Summary: The study enrolled 30 participants (<6 years of age, n=15; 6 to <12 years of age, n=15); 90% completed the study. Prestudy, all participants received FIX prophylaxis (23/30 were dosing ≥2×/week). The median time on study was 49.4 weeks; 24 participants had ≥50 rFIXFc EDs. No participant developed inhibitors to rFIXFc. The pattern of adverse events reported was typical of the population studied. There were no serious allergic reactions and no thrombotic events. No serious adverse events were assessed by the investigator as related to rFIXFc. The terminal half-life (geometric mean [95% CI]) of rFIXFc was 66.5 (55.9, 79.1) hours in the <6 years cohort (n=11) and 70.3 (61.0, 81.2) hours in the 6 to <12 years cohort (n=13). The geometric mean (95% CI) half-life of prestudy BeneFIX was 18.2 (15.5–21.3) hours in the <6 years cohort (n=11) and 19.2 (17.6–20.9) hours in the 6 to <12 years cohort (n=9). Median (IQR) ABR was 1.97 (0.00, 3.13) overall, and 0.00 (0.00, 1.16) for spontaneous bleeds; 33.3% of participants reported no bleeds on study. At study end, 97% of participants were dosing once weekly. The median (IQR) total weekly prophylactic dose with rFIXFc was 59.4 (53.0, 64.8) IU/kg and 57.8 (51.7, 65.0) IU/kg, in the <6 years and 6 to <12 years cohorts, respectively. The prestudy FIX median (IQR) total weekly prophylactic dose was 110.0 (58.0, 188.0) IU/kg and 100.0 (58.0, 120.0) IU/kg in the <6 years and 6 to <12 years cohorts, respectively. 75.0% of bleeding episodes were controlled with 1 infusion; 91.7% with 1 or 2 infusions (median average dose per infusion: 68.22 IU/kg).

Conclusions: rFIXFc was safe and effective for the prevention and treatment of bleeding in children with severe hemophilia B. Study participants achieved low bleeding rates with extended-interval rFIXFc prophylaxis, while reducing their weekly prophylactic factor consumption compared with their prior FIX regimen.
Recombinant von Willebrand factor in severe von Willebrand disease: a prospective clinical trial

Joan C. Gill¹, Giancarlo Castaman², Jerzy Windyga³, Peter Kouides⁴, Margaret Ragni⁵, Frank W.G. Leebeek⁶, Ortrun Obermann-Slupetzky⁷, Miranda Chapman⁷, Sandor Fritsch⁷, Borislava G. Pavlova⁷, Isabella Presch⁷, Bruce Ewenstein⁸

¹Blood Center of Wisconsin and University of Wisconsin, Milwaukee, WI, USA, ²San Bortolo Hospital, Department of Hematology and Center for Bleeding Disorders, University Hospital, Florence, Italy, ³Institute of Hematology and Transfusion Medicine, Warsaw, Poland, ⁴University of Rochester School of Medicine and Mary Gooley Hemophilia Center, Rochester, NY, USA, ⁵University of Pittsburgh and Hemophilia Center of Western Pennsylvania, Pittsburgh, PA, USA, ⁶Erasmus University Medical Center, Rotterdam, The Netherlands, ⁷Baxalta Innovations, GmbH, Vienna, Austria, ⁸Baxalta US Inc., Westlake Village, CA, USA

**Objectives**

This trial evaluated the hemostatic efficacy, pharmacokinetics, and safety of a recombinant VWF (rVWF) in adults with severe von Willebrand disease (VWD) (type 3 [VWF:Ag ≤ 3 IU/dL], severe type 1 [VWF:RCo< 20 IU/dL], 2A [VWF:RCo< 20 IU/dL], 2N [FVIII:C<10% ] , 2B, or 2M).

**Methods**

Bleeds were to be treated initially with rVWF and rFVIII (1.3:1 ratio), followed by rVWF alone (as long as FVIII:C >40%). Hemostatic efficacy was evaluated using a pre-defined 4-point rating scale (none=4, moderate=3, good=2, excellent=1). PK parameters for rVWF vs. rVWF:rFVIII were assessed in a randomized crossover design, and a 6-month repeated PK evaluation for rVWF alone.

**Summary**

Of 31 subjects assigned to bleed treatment, 22 (17 type 3, 4 type 2A and 1 type 2N) experienced 192 bleeding episodes (several in multiple locations) that were treated with rVWF: 106 occurred in mucosal tissue (including 32 menorrhagic, 42 nasopharyngeal, 26 mouth/oral bleeds), 59 joint bleeds, 6 gastrointestinal bleeds, and 37 in other locations. Treatment success (mean efficacy rating <2.5) was achieved in all 22 subjects (100%; Clopper-Pearson exact 90% confidence interval: 87.3 to 100.0). ‘Excellent’ ratings were given for 186/192 (96.9%) bleeds (119/122 minor, 59/61 moderate, 6/7 severe, 2/2 unknown severity) and the remaining 3.1% were ‘good’. One infusion was effective in 81.8% of bleeds (median [range]: 1 [1-4] overall; 2 [1-3] for severe bleeds). The subject’s own assessment of treatment efficacy (an exploratory endpoint), was ‘excellent’ within 8 hours after the first infusion for 125/134 (93.3%), ‘good’ for 8/134 (6.0%) and ‘moderate’ for 1/134 (0.7%) bleeding episodes. A substantial increase in FVIII:C and sustained stabilization (> 40% by 6 hours, rising to >80% 24 hours post-infusion) was observed after infusion with rVWF. PK parameters for VWF Ristocetin cofactor (VWF:RCo, a surrogate for the platelet-dependent function of rVWF) were similar when rVWF was infused alone (mean T½ 21.9 h vs. 19.6 h with rVWF:rFVIII). Eight adverse events (tachycardia, infusion site paraesthesia, ECG t wave inversion, dyseusia, generalized pruritis, hot flush, chest discomfort and increased heart rate) in 5 subjects were assessed as related to rVWF. No inhibitor or anti-VWF binding antibody development was observed, and there were no thrombotic events or severe allergic reactions.

**Conclusions**

rVWF was safe, well-tolerated and effective in the treatment of a variety of bleeding presentations in severe VWD. The sustained stabilization in FVIII:C after the initial infusion enables subsequent infusion of rVWF without rFVIII, when multiple infusions are required.
Quantitative research into people with hemophilia and caregiver perceptions of pre-filled diluent syringe (MixPro®)

Kate Khair1, Jim Munn2, Andrew Scott3, Robyn Shoemark4, Julia Spires1, Akin Akinwonmi5

1Haemophilia Centre, Great Ormond Street Hospital for Children NHS Trust, London, UK,
2University of Michigan Hemophilia and Coagulation Disorders Program, Ann Arbor, Michigan, USA,
3Phoenix Healthcare, London, UK,
4The Children’s Hospital at Westmead, Sydney, Australia,
5Novo Nordisk Health Care AG, Zürich, Switzerland

Objective: People with hemophilia (PWH) commonly self-infuse at home, and can provide valuable insights into device attributes. While Novo Nordisk initially launched recombinant activated FVII (NovoSeven® RT) with vial adaptors, these were replaced with prefilled diluent syringe (MixPro®) in 2013; rFVIII (NovoEight®) launched with MixPro® in the US in 2015. This market research study assessed PWH and caregiver perceptions and preferences between MixPro® and vial adaptors (original device).

Methods: A market research study was conducted in Fall 2014, comprising 30-minute face-to-face interviews. In total, 38 PWH (≥18 years) and 29 caregivers of children with hemophilia participated in the study, from Italy (n=20), Spain (n=20) and the US (n=27). Participants were eligible if they regularly home-infused replacement factor, and were excluded if they had ever used rFVIIa or were already familiar with MixPro®.

Summary: The mean age of participants was 27 years. Most had hemophilia A (84%) with the remainder having hemophilia B (16%), more received prophylaxis (73%) than on demand (27%), and most received rFVIII (73%). Other participants were treated with FIX or plasma-derived FVIII. One PWH had inhibitors and was treated with activated prothrombin complex concentrate. MixPro® was clearly and consistently preferred over vial adaptors, both overall and based on key criteria. Overall, 96% were confident that they could use the system correctly, 73% thought it was intuitive to use, and 93% thought it was easy to learn. When asked to rank 18 defined benefits in order of importance, ‘low contamination risk’ was deemed the most important; the only criteria where MixPro® was not superior were related to verifying mixed factor had been drawn into the syringe. MixPro® was most associated with being: quick, easy, and convenient to use; portable; and overall user friendly. Caregivers placed more emphasis on a device being suitable for a person with less strength, while PWH were more interested in portability and convenience. Results were generally consistent across sub-populations: PWH vs caregivers, and those treated on demand vs prophylaxis.

Conclusions: MixPro® demonstrated clear advantages over vial adaptors, based on feedback from PWH and caregivers, with respondents reporting it easy to learn and use, and confident they could use it correctly. The results affirm the importance of continuing to innovate on devices in collaboration with the hemophilia community.
Real-world dosing and patient characteristics of rFVIIIfc in hemophilia A patients

Brieana Buckley, Eric Hall, Ben Hagberg, Sangeeta Krishnan, Adi Eldar-Lissai

Biogen, Weston, MA, USA

Objective: To analyze real world rFVIIIfc patient characteristics and treatment interval patterns in patients with hemophilia A based on specialty pharmacy dispensing records.

Methods: A retrospective analysis was conducted using aggregate Specialty Pharmacy Provider (SPP) records from July 2014 through Mar 2015. SPP data included 63 different attributes for each prescription, including trade name, NDC, quantity shipped, prescribed infusion dose, days supplied, and dose frequency. Patients were considered eligible for the analysis if they received at least one shipment of rFVIIIfc for a prophylactic treatment regimen. Patients were excluded from the analysis if they were being treated episodically, for immune tolerance induction, or pharmacy records did not specify a prescribed infusion dose. Patients were categorized according to their age and dosing interval.

Summary: The analysis included 405 hemophilia A patients that received at least one shipment of rFVIIIfc with a median age of 23 (range: 2-68) and median weight of 70 kg (range: 10-154kg). Eight percent of dispensing records were for patients less than 6 years of age, 29% were between 6 and 17 years of age, and 63% were 18 years or greater. Pharmacy dispensing records represented 179 distinct prescribers across 40 states. Dosing frequency ranged from four times weekly to beyond once-weekly, with every four days as the most common dosing interval, representing 33% of patient records. The median infusion frequency was every four days. Fifty percent of all patients had a dosing frequency of four days or greater. Of the patients receiving rFVIIIfc that had previous rFVIII dispensing records, the most common rFVIII dosing frequency was three times per week. The majority of patients previously on prophylaxis regimen with a rFVIII dosing frequency of three times per week had a decreased number of prophylactic infusions per week on rFVIIIfc; 4% of patients reduced infusion frequency to every 3 days, 44% of patients reduced infusion frequency to twice weekly, 30% of patients reduced infusion frequency to every 4 days, 10% of patients reduced infusion frequency to every 5 days.

Conclusions: Current SPP dispensing records demonstrate that rFVIIIfc is being used in a broad patient population based on age range and geographical distribution. Patients with hemophilia A in the US may experience reductions in FVIII infusion frequency when they switch to rFVIIIfc, with conversion to an infusion frequency every four days as the most common treatment regimen and the recommended prophylaxis starting dose according to the US Prescribing Information.
Changes in Child and Parent Ratings of Health-Related Quality of Life Among Children With Hemophilia A in the KIDS A-LONG study

Nancy Young1, Mark Atkinson2, Ying Lu3, Shoshana Coleman2, Adi Eldar-Lissai3, Sangeeta Krishnan4, Geoffrey Allen3, Victor Blanchette4

1Laurentian University, Sudbury, ON, Canada, 2Covance, San Diego, CA, USA, 3Biogen, Cambridge, MA, USA, 4The Hospital For Sick Children, Toronto, ON, Canada

Objectives: The KIDS A-LONG study was a phase 3, open-label, single-arm study that demonstrated the safety and efficacy of prolonged half-life recombinant factor VIII Fc Fusion protein (rFVIIIFc) for prophylaxis in previously-treated pediatric subjects (<12 years of age) with severe hemophilia A. The Canadian Hemophilia Outcomes - Kids' Life Assessment Tool (CHO-KLAT) was used in this study to assess health-related quality of life (HRQoL) as rated by children ≥ 5 years of age and their parents. This post-hoc analysis examined the change in CHO-KLAT scores from baseline to the end of the study (week 26) and explored the relationship with clinical outcomes.

Methods: CHO-KLAT change scores were evaluated using a paired t-test and effect size estimates (Cohen's d). Pearson correlations were used to assess the association between child and parent ratings at baseline and 26 weeks. The correlation between clinical variables and change in CHO-KLAT scores was also explored.

Summary: Seventy-one children participated in the KIDS A-LONG study: the majority were Caucasian (70%). Nine (14%) were Black/African American, and 10 (16%) were ‘other’ races. Forty-five percent of subjects were from Europe, 30% from North America, and 25% from Asia/Africa. Forty-four of the boys were ≥ 5 years of age (mean 7.3 years, SD=2.0) thus, included in the current analyses. The mean baseline CHO-KLAT scores were 76.4 (SD=14.1) for children and 77.3 (SD=15.5) for their parents; these correlated well at both baseline (r=0.88) and at week 26 (r=0.72). Paired baseline and week 26 CHO-KLAT scores were available for 32 children and their parents. Over the 26 week study period, both child and parent CHO-KLAT scores significantly improved, gaining 4.6 points (SE=2.0; p=0.03; Cohen’s d=0.40) and 7.3 points (SE=1.8; p=0.0001; Cohen’s d=0.70), respectively. At baseline, the CHO-KLAT scores of parents (N=17) and children (N=15) with > 4 bleeds in the year prior to the study were significantly lower (indicative of more impairment) than for children with < 4 pre-trial bleeds [Child: 67.3 (SD=12.6) vs. 82.0 (SD=10.2), p=0.0001; Parent: 67.3 (SD=15.1) vs. 82.2 (SD=12.8), p=0.001]. Significant correlations (p<0.05) were observed between CHO-KLAT change scores and the following clinical variables: bleeding events, treatment regimen, and activity scores.

Conclusions: The KIDS-A-LONG study demonstrated significant improvement in children’s HRQoL with rFVIIIFc prophylaxis in a notably short duration of time. Further analyses of extension study data will be useful to determine if improvements of this degree persist over longer periods of time.
Personalization of Treatment Regimens for Physically Active Patients: A Comparison of Factor VIII and Extended Half-life Treatment Regimens

Elizabeth L Schwartz1, Yan Xiong1, Josh Epstein1, Bruce Ewenstein2, Leonard A. Valentino2

1Baxter Healthcare, Westlake Village, CA, USA, 2Baxter Healthcare, Deerfield, IL, USA

Objective: Personalizing FVIII treatment includes matching infusions with patient lifestyle. With new extended half-life (EHL) FVIII products, it is important to identify which patients may be most appropriate for treatment with different products and regimens. In the absence of real-world data to comparatively assess patient outcomes associated with different treatment options, a modeling exercise may be able to provide insight on how different regimens compare across different patient types. The objective of this research was to estimate the relative bleeding risk among prophylaxis regimens using recombinant FVIII (rFVIII) and BAX 855, an investigational EHL-rFVIII, among different patient physical activity profiles.

Methods: A literature-based model was developed with FVIII levels estimated from a one-compartment pharmacokinetic model (Collins 2010). Half-life and incremental recovery for rFVIII and EHL-rFVIII were taken from the BAX 855 pivotal trial. Three prophylaxis regimens were used: rFVIII 30IU/kg every other day (EOD), rFVIII 35IU/kg 3x/week, and BAX 855 45 IU/kg 2x/week. Activity categories from the NHF “Playing It Safe” brochure were used to develop different patient profiles. The three hypothetical activity profiles evaluated were: Consistently Active (M-Sun: Type 2), Regular Exerciser (M-F: Type 2, Sat-Sun: Type 1), and Weekend Warrior (M-F: Type 1, Sat-Sun: Type 3). Bleeding risk by activity category and FVIII was calculated using odds ratios from Broderick 2012. For each regimen, the infusion schedule with the lowest bleeding risk for the activity profile was used. The relative bleeding risks were compared between regimens.

Summary: For the Regular Exerciser, rVIII 3x/week was estimated to have a 2% and 8% lower relative bleeding risk than BAX 855 and EOD, respectively. For the Weekend Warrior, BAX855 was estimated to have a 12% and 13% lower relative bleeding risk relative to rFVIII 3x/week and EOD, respectively. For the Consistently Active patient, rFVIII EOD was estimated to have a 5% and 8% lower relative bleeding risk compared to rFVIII 3x/week and BAX 855, respectively.

Conclusion: The model suggests that different patient types may be better suited for rFVIII while others for BAX 855 2x/week. Physicians should consider personalizing treatment using different products and regimens to best accommodate patient types with different physical activity profiles.
Efficacy of a Recombinant Factor IX Investigational Product, IB1001 (trenonacog alfa) in Previously Treated Patients with Hemophilia B

Bojan Drobic1, Yi Hua1, Tim Babinchak1, Edward Gomperts2

1Emergent BioSolutions Inc., Winnipeg, Manitoba, Canada, 2Edward Gomperts Consultants Inc., Montrose, California, USA

Objective: To evaluate efficacy of IB1001 with respect to breakthrough bleeding during prophylaxis and with respect to control of hemorrhaging in prophylaxis and on-demand treatment regimens in previously treated patients (PTPs) with hemophilia B.

Methods: The efficacy of IB1001 has been evaluated in a prospective, open-label, uncontrolled multicenter international study in which a total of 68 male PTPs between 7 and 64 years of age received IB1001 either as prophylaxis or on-demand treatment. All subjects had severe or moderately severe (factor IX level ≤ 2 IU/dL) hemophilia B without inhibitors. There were 61 subjects who received prophylaxis [predominantly secondary or tertiary prophylaxis as defined by World Federation of Hemophilia (WFH) guidelines] and 12 were treated on-demand during the study conduct. Both, the subjects and the study investigators rated the efficacy of IB1001 in management of bleeding episodes.

Summary: The mean number of exposure days (ED) was 138.2 (median: 127.5 ED), including 55 subjects with ≥ 50 ED and 45 subjects with ≥ 100 ED. Subjects on prophylaxis received a mean intravenous dose of 55.0 ± 12.8 IU/kg IB1001 twice weekly, while subjects in the on-demand regimen received a mean dose of 60.0 ± 18.2 IU/kg IB1001. In the prophylaxis group, median annualized bleed rate (ABR) was 1.52, and in the on-demand group, median ABR was 16.39. There were 19/61 (31.1%) subjects on IB1001 prophylaxis who reported no bleeding episodes. A total of 508 bleeding episodes were treated with IB1001; 286 bleeds were recorded for patients on prophylaxis and 222 in the on-demand regimen. Majority of the bleeds (70.9%) resolved after a single IB1001 infusion, while 13% of the bleeds required two infusions. A minority of the bleeds (4.7%) required 5 or more infusions; these bleeds were predominantly related to trauma, target joints and/or muscle bleeds. Subjects rated efficacy of IB1001 as ‘excellent’ or ‘good’ in 84% of all treated bleeding episodes. Of 414 subject visits where the efficacy of IB1001 was evaluated by the study investigators, 92% were rated as ‘effective’ in prevention and treatment of bleeding by IB1001.

Conclusions: IB1001 is effective for the treatment of hemophilia B either as secondary or tertiary prophylaxis or on an episodic (on-demand) basis. Based on clinical trial data, IB1001 is effective in controlling breakthrough or episodic bleeding episodes.
Efficacy of a Recombinant Factor IX Investigational Product, IB1001 (trenonacog alfa) for Perioperative Management in Hemophilia B Patients

Bojan Drobic, Yi Hua, Tim Babinchak, Edward Gomperts

1Emergent BioSolutions Inc., Winnipeg, Manitoba, Canada, 2Edward Gomperts Consultants Inc., Montrose, California, USA

Objective: To evaluate efficacy of IB1001 for perioperative management of bleeding under surgical circumstances in hemophilia B patients.

Methods: The efficacy of IB1001 for perioperative management has been evaluated in a prospective, open-label, multicenter international study where 17 subjects (16 male PTPs and one female hemophilia B carrier) underwent 20 major surgical procedures. The PTPs were defined as patients with a minimum of 150 exposures to another factor IX preparation. The subjects had severe or moderately severe (factor IX level ≤ 2 IU/dL) hemophilia B without inhibitors, with exception of one mild hemophilia B female carrier. Efficacy of IB1001 was based on the surgeon’s assessment including estimation of blood loss as ‘less than expected’, ‘expected’, or ‘more than expected’ at the time of surgery and assessment of hemostasis at 12 and 24 hours post-surgery as ‘superior’, ‘adequate’, or ‘poorly controlled’. Transfusion requirements were also monitored.

Summary: Thirteen major procedures in 12 male subjects were managed by bolus regimen, and 6 major procedures in 4 male subjects were managed by continuous infusion regimen. Mean loading dose for 13 major procedures managed by bolus regimen was 120 ± 11.4 IU/kg and mean maintenance bolus dose (given every 12 hours) was 59.7 ± 12.2 IU/kg. During the 24 hours following surgery, factor IX levels were successfully maintained over 60%, as intended. Factor IX levels at pre-infusion were 59.7% ± 15.9% at 12 hours after surgery and 54.4% ± 16.5% at 24 hours after surgery. For a major procedure in one female carrier, the bolus dose was 110 IU/kg, while the mean maintenance dose was 44.9 ± 7.0 IU/kg. Mean loading dose for 6 major procedures managed by continuous infusion regimen was 95.4 ± 14.5 IU/kg and the mean maintenance infusions were 7.1 ± 4.0 IU/kg/hr. In all major procedures, blood loss at the time of surgery was ‘expected’ or ‘less than expected’ as assessed by the surgeon. IB1001 was rated by the surgeon as ‘superior’ or ‘adequate’ in controlling hemostasis post-surgery, including 8 knee arthroplasties, two elbow arthroplasties, one knee amputation, one percutaneous Achilles tendon lengthening, one open inguinal hernia repair, one tibiotalar fusion, two arthroscopic synovectomies, three debridements and one total hysterectomy/bilateral oopherectomy. There were no transfusions required perioperatively.

Conclusions: At the time of surgery, blood loss was expected or less than expected after IB1001 treatment, while post-surgery effective hemostasis control was achieved following IB1001 treatment in hemophilia B patients.
Cost of Treating Thrombotic Events in a US Population of von Willebrand Disease (vWD) Patients

Alexandra Khachatryan, Yan Xiong

Baxalta US Inc, Westlake Village, CA, USA

**Background:** Current available factor replacement therapy (FRT) for von Willebrand Disease (vWD) contains FVIII. Thromboembolic events (TEE) are a small but serious risk in patients with elevated FVIII levels as a result of accumulation from repeated doses of FRT (Manucci, 2004).

**Aim:** To assess the total medical cost incurred in one year of treating TEEs in vWD.

**Methods:** This retrospective database analysis utilized the Marketscan®Database, a US medical claims database, from Jan 2006 to Mar 2014. Patients with inpatient diagnosis for a TEE (ICD-9 code for venous thromboembolism [VTE], myocardial infarction [MI], ischemic stroke [IS], etc.) were identified, with the first inpatient TEE visit defined as the index date (ID). VWD diagnosis (286.4) was required prior to ID and ≥12 month continuous enrollment both prior and post ID. Direct medical costs of TEE management in the first year were estimated for inpatient and outpatient settings. The subset of VWD patients prescribed FRT prior to ID was also described. Costs were adjusted to 2013USD using the medical consumer price index.

**Results:** One hundred fifty-three vWD subjects were identified with an inpatient TEE. Mean age at the ID was 56 years (2–94 yrs) and 69.9% were female. Median annual cost and range associated with treatment of TEEs was $21,166 ($1,300–$867,710). VTE and IS were the most common TEEs (36.0% ≥1 VTE, $24,338 ($1,063–$235,090) and 32.7% ≥1 IS, $11,326 ($1,300–$368,550), respectively). Patients prescribed FRT (n=12) had a median annual cost of $64,648 ($4,690–$137,705) for TEE treatment.

**Conclusion:** This is the first study to estimate the total cost associated with management of TEEs in vWD. TEEs are a burden to the healthcare system and are potentially life-threatening. A vWD treatment option that can avoid the risk of FVIII accumulation may benefit vWD patients at risk for TEEs.
Description and Management of Pain and Functional Impairment in US Adults With Hemophilia: Initial Observations From the Pain, Functional Impairment, and Quality of Life (P-FiQ) Study

Michelle Witkop1, Kim Baumann2, Tyler Buckner3, Stacie Akins4, Sharon Funk3, Grace Hernandez5, Michael Recht6, Michael Wang3, Katharine Batt1, Christine Kempton7, David Cooper9

1Munson Medical Center, Traverse City, MI, USA, 2University of Minnesota Health Center for Bleeding and Clotting Disorders, Minneapolis, MN, USA, 3University of Colorado School of Medicine, Aurora, CO, USA, 4Indiana Hemophilia and Thrombosis Center, Indianapolis, IN, USA, 5The Center for Comprehensive Care and Diagnosis of Inherited Blood Disorders, Orange, CA, USA, 6Oregon Health & Science University, Portland, OR, USA, 7Wake Forest Baptist Medical Center, Winston-Salem, NC, USA, 8Emory University School of Medicine, Atlanta, GA, USA, 9Novo Nordisk Inc., Plainsboro, NJ, USA

Objective: Hemophilia is marked by frequent joint bleeding, resulting in acute and chronic pain and functional impairment. Surveys in US adults with hemophilia demonstrate suboptimal pain management and quality of life (QoL). The objective of P-FiQ was to methodologically assess QoL parameters, including functional impairment and pain, and pain management strategies.

Methods: Adult men with mild-severe hemophilia with a history of joint pain and/or bleeding completed a hemophilia/pain history and various patient-reported outcome assessments (completed twice in “retest” population of initially enrolled patients).

Summary: Of 164 adults with hemophilia (median age 34) in the “retest” population, more had hemophilia A (74%) than B (26%); 6% had inhibitors. Most had some college-or-above education (63%), 81% were employed, 61% were overweight/obese, and 61% self-reported arthritis/bone/joint problems. Current patient-reported treatment regimens were prophylaxis (42%), on-demand (39%), or mostly on-demand (19%; 25/31 using infusions ahead of activity). One-third (32.9%) reported unrestricted school/work/recreational activities in the prior 6 months; 6.2% reported needing assistance for school/work/self-care, or did not participate in recreational activities because of pain, loss of motion, and weakness. Some patients (31.3%) reported using a cane/crutches/walker (3.8% always) and 7.6% a wheelchair (1.3% always), and 47.0% reported a history of joint surgery (41 knee, 37 ankle, 29 elbow). Patients reported losing an average of 3.7 and 1.8 school/work days in the previous 6 months due to lower and upper extremity problems, respectively. Patients reported that during the prior 6 months they had experienced acute pain only (24%), chronic pain only (33%), or both (29%); 15% reported no pain. Acute pain was most frequently described as sharp (77%), aching (66%), shooting (57%), and throbbing (55%), and chronic pain as aching (74%), nagging (49%), throbbing (44%), and sharp (40%). Most common analgesics in the past 6 months for acute/chronic pain were acetaminophen (69%/58%), NSAIDs (40%/52%), hydrocodone-acetaminophen (29%/33%), oxycodone (12%/11%), and oxycodone-acetaminophen (9%/8%). Most common nonanalgesic treatment strategies reported for acute/chronic pain in the past 6 months were ice (73%/37%), rest (48%/34%), factor or bypassing agent (48%/24%), elevation (34%/28%), relaxation (31%/23%), compression (27%/21%), and heat (25%/15%); other reported strategies include medical marijuana (17%/9%), physical therapy (12%/9%), prayer (11%/8%), faith (9%/8%), alcohol (8%/7%), aquatherapy (5%/6%), illicit drugs (4%/2%), acupuncture (2%/1%), hypnosis (2%/1%), and biofeedback (1%/1%).

Conclusions: Initial data corroborate the high prevalence of pain and functional disability in adults with hemophilia and highlight opportunities to address clinical assessment, patient dialogue, and management strategies to improve outcomes.
Hospitalization for Acute Bleeding Events among Individuals with von Willebrand Disease (VWD) in the United States

Alexandra Khachatryan, Diane Ito

Baxalta US Inc, Westlake Village, CA, USA

**Background:** Individuals with von Willebrand Disease (VWD), the most common bleeding disorder, have defective, reduced, or absent von Willebrand factor leading to reduced hemostasis in response to bleeding episodes. People with VWD and severe bleeding episodes may require hospitalization for factor replacement therapy since serious bleeding may be associated with reduced health-related quality of life (HRQoL), particularly in physical and social functioning (de Wee EM, et al. 2010). Hospitalization due to severe bleeding may therefore impact a patient’s HRQoL, possibly due to missed days from work or school, limits on mobility, and in their ability to participate in daily and social activities.

**Objectives:** Determine length of stay (LOS) associated with acute bleeding events requiring hospitalization among VWD patients prescribed factor replacement therapy in the US.

**Methods:** Hospital stays from 2000 to 2013 were retrospectively analyzed using the US Premier Hospital database. Demographics, comorbidities, mortality and LOS were summarized for inpatient stays for adults (≥18 years) with VWD that met two criteria: the hospitalization was associated with a primary or secondary ICD-9 diagnosis of VWD (286.4) and the patient received factor replacement therapy (J-code J7187 or J7184/J7183 with Humate P or Wilate, respectively). VWD admissions were also analyzed by type of bleeding event using ICD-9 diagnosis.

**Results:** A total of 934 acute bleeding events in patients with VWD required hospitalization and treatment with factor replacement therapy. Patients were on average 52.0 years of age (range 18-89), predominately white (80.5%) and female (72.8%). The mean Charlson Comorbidity Index (CCI) score was 0.7, with the majority of patients having a CCI of 0 (61.3%). Hospitalized VWD patients prescribed factor had a median LOS of 4 days (range 1-70 days) and a mortality rate of 1.4%. Assessing hospital stays by bleeding location, 10.4% of VWD patients were admitted for gastrointestinal hemorrhage, 3.4% for menorrhagia, 1.8% for epistaxis, 1.1% for intracranial hemorrhage, 1.1% for joint bleedings, and 1.0% for mucosal bleeding which were associated with a median LOS of 5, 2, 4, 8, 3, and 4 days, respectively.

**Conclusion:** Results from this analysis suggest that a proportion of patients with VWD are treated in the inpatient setting for a variety of severe bleeding events requiring factor replacement therapy. Bleeding events associated with more difficult clinical management, particularly intracranial and gastrointestinal hemorrhage, are associated with longer LOS. Treatment that prevents hospitalizations or reduces LOS for acute bleeding episodes may translate into improved HRQoL for VWD patients.
The impact of missing one or two infusions per month: a comparison of rFVIII and rFVIIIFc regimens

Josh Epstein¹, Elizabeth L. Schwartz¹, Yan Xiong¹, Morgan Bron³, Jason Booth¹, Armin Reininger², Alessandro Gringeri²

¹Baxter Healthcare, Westlake Village, CA, USA, ²Baxter Innovations GmbH, Vienna, Austria, ³Baxter Healthcare, Deerfield, IL, USA

Objective: Because adherence is influenced by many factors, it is unknown how fewer infusions and the change in infusion days from week to week may or may not affect it. Non-adherence to treatment with missing or delaying an infusion may impact FVIII levels and bleed protection. Specifically, evidence demonstrates that time below 1% is associated with increased risk of having a bleed (Collins 2009). Therefore, it is important to understand the impact of adherence to rFVIII and rFVIIIFc regimens on FVIII levels. The objective of this research is to evaluate time above and below specific FVIII levels for patients missing 1 or 2 doses per month for rFVIII and rFVIIIFc prophylactic regimens.

Methods: A literature-based model was developed. Factor levels were estimated using a published pharmacokinetic model (Collins 2010). Half-life and incremental recovery were taken from a crossover study of rFVIII and rFVIIIFc (Young 2013). The following prophylaxis regimens were evaluated: 35IU/kg rFVIII, 3x/week; 50IU/kg rFVIIIFc, Q4D; and 50IU/kg rFVIIIFc, Q5D. The model ran for one month and simulated the impact of missing one or two doses per month on each regimen. Each scenario modeled was compared on the following metrics: time below 1% and 3% and time above 10% and 20% FVIII levels for the average week.

Summary: rFVIII provided more protection than rFVIIIFc under each scenario analyzed. Time spent below 1% and 3% and time spent above 10% and 20% is summarized for patients missing 1 or 2 doses for each regimen in Table 1.

Table 1: Hours per week below trough levels and above levels on rFVIII and rFVIIIFc

<table>
<thead>
<tr>
<th></th>
<th>Fewer hours below trough levels for rFVIII v rFVIIIFc</th>
<th>More hours above levels for rFVIII v rFVIIIFc</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Below 1%</td>
<td>Below 3%</td>
</tr>
<tr>
<td>rFVIIIFc every 4 days</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Missing 1 Dose/Month</td>
<td>11.6</td>
<td>2.9</td>
</tr>
<tr>
<td>Missing 2 Doses/Month</td>
<td>23.2</td>
<td>17.0</td>
</tr>
<tr>
<td>rFVIIIFc every 5 days</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Missing 1 Dose/Month</td>
<td>23.6</td>
<td>30.1</td>
</tr>
<tr>
<td>Missing 2 Doses/Month</td>
<td>47.2</td>
<td>46.1</td>
</tr>
</tbody>
</table>

Conclusion: This model suggests that a patient who is not fully adherent on rFVIII may have less FVIII protection on rFVIIIFc dosed every four or five days. Physicians and patients should consider this information when deciding if rFVIIIFc is the best option for a patient who is not fully adherent. Additionally, future research should assess fixed vs. variable infusion day schedules and how this may impact patient adherence.
Low Annualized Bleeding Rates in Phase 3 Studies of Recombinant Factor VIII Fc Fusion Protein (rFVIIIFc) in Subjects with Target Joints at Baseline

Michael Wang¹, Beatrice Nolan², Guy Young³, Savita Rangarajan⁴, Bryce Kerlin⁵, Roshni Kulkarni⁶, Margaret V. Ragni⁷, Ross I. Baker⁸, Elisa Tsao⁹, Desilu Glazebrook⁹, Glenn Pierce⁹, Geoffrey Allen⁹

¹University of Colorado, Aurora, CO, USA, ²Our Lady's Children's Hospital, Dublin, Ireland, ³Children's Hospital, Los Angeles, CA, USA, ⁴Basingstoke & North Hampshire Hospitals, Basingstoke, UK, ⁵Nationwide Children's Hospital, Columbus, OH, USA, ⁶Michigan State University, East Lansing, MI, USA, ⁷University of Pittsburgh and Hemophilia Center of Western PA, Pittsburgh, PA, USA, ⁸Western Australia Centre for Thrombosis and Haemostasis, Murdoch University, Perth, Australia, ⁹Biogen, Boston, MA, USA

Introduction and Objectives: The phase 3 A-LONG and Kids A-LONG studies demonstrated the safety and efficacy of rFVIIIFc for the control and prevention of bleeding episodes in subjects with severe hemophilia A. This subgroup analysis of A-LONG and Kids A-LONG examined bleeding frequency with rFVIIIFc prophylaxis in subjects with target joints at baseline.

Methods: A-LONG (≥12 y) and Kids A-LONG (<12 y) subjects with a history of target joints (a major joint with ≥3 bleeding episodes in a 6-month period) who were previously treated with FVIII and received on-study rFVIIIFc prophylaxis were identified. Self-reported pre-study 12-month bleeding history and on-study annualized bleeding rate (ABR) for all bleeds were evaluated.

Results: 93/141 subjects in A-LONG and 13/69 subjects in Kids A-LONG had target joints at baseline. The most prevalent locations of pre-study target joints identified at baseline among subjects in A-LONG were the elbow (61.7%) and ankle (59.6%). Similarly, in Kids A-LONG, these were the ankle (69.2%) and elbow (30.8%). A total of 59.7% and 52.4% of subjects receiving individualized (Arm 1) and weekly (Arm 2) rFVIIIFc prophylaxis in A-LONG, respectively, and 53.8% of subjects receiving rFVIIIFc prophylaxis in Kids A-LONG with target joints at baseline had no target joint bleeding episodes on-study. Median on-study ABRS with rFVIIIFc prophylaxis tended to be lower than pre-study bleeding rates in subjects with target joints at baseline (Table).

Conclusions: For subjects with severe hemophilia A who had target joints at baseline, rFVIIIFc prophylaxis lowered bleeding rates across age groups compared with pre-study FVIII treatment.

<table>
<thead>
<tr>
<th>Median (Interquartile Range) Pre-study and On-study Bleeding Rates in Subjects Receiving On-study rFVIIIFc Prophylaxis With Target Joints at Baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>A-LONG (Arm 1)</td>
</tr>
<tr>
<td>Pre-study regimen</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Episodic (n=26)</td>
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<tr>
<td>Pre-study bleeds (12 months prior)</td>
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<tr>
<td>On-study ABR</td>
</tr>
<tr>
<td>On-study spontaneous ABR</td>
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<tr>
<td>at target joint</td>
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</tbody>
</table>
A Novel Anti-Tissue Factor Pathway Inhibitor Antibody, BAY 1093884, Restores Hemostasis in Induced Hemophilia A Rabbits With Reduced Thrombogenic Potential

Maria Koellnberger¹, Axel Trabandt¹, Derek Sim², Volker Laux¹

¹Acute Care Research, Bayer Pharma AG, Wuppertal, Germany, ²Bayer HealthCare Pharmaceuticals, US Innovation Center, San Francisco, CA, USA

Background: BAY 1093884 is a fully human monoclonal antibody against tissue factor pathway inhibitor developed as a bypass agent for hemophilia patients with inhibitors. It restores thrombin burst, leading to stable clot formation in hemophilic conditions in vitro and effectively stops bleeding in vivo.

Aims: Efficacy and thrombogenic potential of BAY 1093884 were evaluated in bleeding models in acquired hemophilia A rabbits and the Wessler venous stasis model, respectively.

Methods: The efficacy of BAY 1093884 was tested in rabbit bleeding models. Anti-factor VIII antibodies rendered rabbits hemophilic, increasing bleeding time by ~3-fold (median 120–390 seconds) in an ear bleeding model and >7-fold (median 240–1800 seconds) in a saphenous vein bleeding model. In the Wessler model, thrombosis was induced by complete ligation of the jugular vein after administration of BAY 1093884, recombinant FVIIa (rFVIIa), or activated prothrombin complex concentrate (aPCC) to measure in vivo hypercoagulability.

Results: In both bleeding models, BAY 1093884 corrected bleeding time close to normal in a dose-dependent manner. A statistically significant reduction in saphenous vein bleeding was reached at 1 and 3 mg/kg BAY 1093884, reducing bleeding time to 330 and 240 seconds, respectively. In contrast, 1 mg/kg rFVIIa only slightly reduced bleeding time to a median of 1200 seconds. In the Wessler model, 1 mg/kg rFVIIa and 40 IU/kg aPCC resulted in thrombus formation, reaching full occlusion in rabbits with normal coagulation system. In contrast, BAY 1093884 up to 100 mg/kg did not fully occlude, and only showed a slight increase in localized clot formation over baseline, which could be completely prevented by an anticoagulant. In addition, no stasis-triggered thrombi were seen in hemophilia A rabbits treated with BAY 1093884, indicating reduced thrombogenicity risk for BAY 1093884 in patients with hemophilia.

Conclusions: These studies showed that BAY 1093884 potently controls bleeding in hemophilic rabbits while showing reduced thrombogenic risk compared with the current standard of care.
Leading an Active Lifestyle with Hemophilia B: Estimating the Bleeding Risk with Different FIX Treatment Regimens

Yan Xiong, Alexandra Khachatryan, Josh Epstein

Baxalta US Inc, Westlake Village, CA, USA

Background: Several studies have demonstrated the benefits of physical activity on overall health, well-being, and the preservation of joint health in persons living with hemophilia (Wittimier 2007, Gornis 2009, Harris 2006). Participating in differing types and levels of physical activity impose differing bleeding risk that may be greatly reduced with adequate factor levels (Broderick 2012). Understanding the optimal infusion schedules for FIX therapies that provide the greatest protection from bleeding during activity can help support active lifestyles for people with hemophilia.

Objective: To estimate the relative risk of bleeding among different patient physical activity profiles utilizing recombinant Factor IX (rFIX vs. rFIX-Fc) prophylaxis.

Methods: A mathematical model based on the available literature was developed. Factor levels were estimated using a two-compartment pharmacokinetic (PK) model for rFIX (Data on file, Wyndyga, 2014) and a three-compartment PK model for rFIX-Fc (Powell, 2014). Three prophylaxis regimens were evaluated: rFIX (50IU/kg 2x/week) and rFIX-Fc (50 IU/kg 1x/week and 100IU/kg every 10 days). Activities included in the model were classified as Type 1 (low risk), Type 2 (moderate risk), or Type 3 (high risk), according to the NHF "Playing It Safe Brochure" (Anderson 2005). Bleeding risk was calculated using odds ratio values from Broderick 2012 for each activity type and estimated factor level at time of activity. Three hypothetical physical activity profiles were evaluated: Regular Exerciser (M-F: Type 2 activities, Sat-Sun: Type 1 activities), Weekend Warrior (Sat: Type 3 activities, MWF: Type 2 activities, TThSun: Type 1 activities), and Weekly Sport (TF: Type 3 activities, MWF, Sat-Sun: Type 1 activities). For each activity profile, the relative bleeding risk of each prophylaxis regimen was evaluated.

Results: rFIX 50IU/kg 2x/week achieved the lowest bleeding risk across all four patient activity profiles. The risk of bleeding increased by 17% and 21% for the Weekly Sport, 4% and 10% for the Regular Exerciser, and by 7% and 11% for the Weekend Warrior patient prescribed rFIX-Fc 1x/week and every 10 days, respectively when compared to a patient prescribed rFIX 2x/week.

Conclusion: These results suggest that active patients with similar activity profiles may have reduced bleeding risk and better coverage with rFIX compared to extended half-life FIX-Fc dosing regimens evaluated in this analysis. Physicians should consider personalizing treatment using different products and regimens accounting for different patient types.
Development of a novel patient-centered outcome measure in hemophilia using Goal Attainment Scaling

Ellis Neufeld\textsuperscript{1}, James Munn\textsuperscript{2}, Debra Honig\textsuperscript{3}, Michael Denne\textsuperscript{4}, Sharon Richardson\textsuperscript{4}, Kenneth Rockwood\textsuperscript{5}

\textsuperscript{1}Boston Children’s Hospital, Harvard Medical School, Boston, MA, USA, \textsuperscript{2}University of Michigan, Ann Arbor, MI, USA, \textsuperscript{3}Rush University Medical Center, Chicago, IL, USA, \textsuperscript{4}Baxalta US, Inc., Deerfield, IL, USA, \textsuperscript{5}DGI Clinical, Halifax, Canada

Background and Objective: Standard outcome measures in hemophilia, such as the annual bleeding rate, have inherent limitations in both clinical practice and in research, including lack of both sensitivity and personalization. Goal attainment scaling (GAS) is a method for evaluating outcome that is patient-centered and sensitive to change in individuals and populations; collaborative goal setting may also be viewed through the biopsychosocial lens as a potential resource to strengthen disease-related coping. GAS has been used successfully in several disease areas. However, feasibility can be an issue. To address this, standardized goal attainment menus can be developed that preserve individualization, while allowing greater ease of use by non-experts. We initiated a process to develop a novel outcome measure in hemophilia, the GAS-Hem, by creating a goal attainment menu for patients living with hemophilia. Methods: We conducted 2 multidisciplinary workshops with participants from medicine, nursing, social work, and physical therapy (n=12). During the first workshop, we developed a list of goal areas, each with an associated set of descriptors of attainment levels. At the second workshop, a second group of experts (n=8) critically reviewed each goal to evaluate its importance and relevance for inclusion in the GAS-Hem. Summary: 28 goal areas with associated descriptors of attainment levels were developed, covering 3 broad categories: ability to manage hemophilia, ability to recognize and treat complications, and ability to cope with the impact of hemophilia on daily life. Descriptors incorporated several key parameters for each goal (eg. skill level, desire for change, utilization of available resources) (Table). Conclusions: We developed a novel, patient-centered outcome measure for patients with hemophilia. A comprehensive, preliminary list of goal areas and attainment levels was successfully created. The next step will be to incorporate feedback from patients and families, after which a feasibility study will be conducted to evaluate content and construct validity and overall ease of use.

<table>
<thead>
<tr>
<th>Descriptor Rank</th>
<th>GOAL AREA: Self Infusion</th>
<th>GOAL AREA: Attendance at Work</th>
<th>GOAL AREA: Attendance at School</th>
</tr>
</thead>
<tbody>
<tr>
<td>Highest</td>
<td>I am able to infuse independently and safely. I do not miss work due to hemophilia. I consistently engage in appropriate use of resources to assist in managing work attendance and challenges on the job. I consistently attend school with no more missed days than an average student. I take advantage of all resources and services provided to assist in this.</td>
<td>I occasionally miss a day due to hemophilia. I often engage in appropriate use of resources to assist in managing work attendance and challenges on the job. I attend school, but miss more days than the average student. I sometimes take advantage of resources and services provided to assist in this.</td>
<td></td>
</tr>
<tr>
<td>Midrange</td>
<td>I am sometimes able to self-infuse. I accept help with this when needed. I have some interest in improving this.</td>
<td>I have lost my job as a result of missed work due to hemophilia and difficulty making appropriate use of my resources.</td>
<td>I left school (or have been asked to leave school) due to absenteism.</td>
</tr>
<tr>
<td>Lowest</td>
<td>I am unable to self-infuse. I have little to no interest in improving this. I resist help.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table. Examples of Goal Areas and Descriptors
Objective: To assess pain and functional impairment through 5 patient-reported outcome (PRO) instruments in non-bleeding adults with hemophilia.

Methods: Adult men with hemophilia (mild-severe) with history of joint pain/bleeding completed a hemophilia/pain history and 5 PROs (EQ-5D-5L with visual analog scale [VAS], Brief Pain Inventory v2 [BPI-SF], International Physical Activity Questionnaire [IPAQ-SF], SF-36v2, and Hemophilia Activities List [HAL]) during routine visits. Initial patients were asked to complete the PROs again after their estimated 3-4 hour visit (retest population). PRO scores were calculated from published algorithms. Generally, higher scores indicate better health-related quality of life (HRQoL) and functional status, and greater pain severity/interference.

Summary: 381 Patients were enrolled between October 2013 and October 2014; 164 of the initial 187 completed the retest and are reported here. Median time for completion of the initial survey/PROs was 36.0 minutes and 21.0 minutes for the PRO retest. Most retest subjects had hemophilia A (74.4%) and were white-non-Hispanic (72.6%). Median (Q1, Q3) age was 33.9 (26.9, 46.0), 48.7% were married, 62.6% had some college or graduate education, 80.7% were employed, and 61.0% were overweight or obese. HCV (49.4%) was more common than HIV (16.5%); 61.0% self-reported arthritis/bone/joint problems. Median EQ-5D-5L VAS was 80.0 (0-100 scale), and EQ-5D-5L health index 0.80 (-0.11-1 scale); 61.6% reported any problems with mobility (29.3% reported moderate/severe problems), 55.8% with usual activities (18.4% moderate/severe), and 22.0% with self-care (4.3% moderate/severe). 73.2% reported pain-discomfort (43.3% moderate/severe), and 41.1% anxiety-depression (14.7% moderate/severe). For BPI, median pain severity was 3.0 (0-10 scale) and pain interference 2.9 (0-10 scale); median worst pain was 6.0, least pain 2.0, average pain 3.0, and current pain 2.0. Pain most impacted general activity, mood, walking ability, and normal work, and least impacted relations with other people. Ankles were the most frequently reported site of pain. Median IPAQ total activity was 693.0 MET/min/week; 49.3% reported no activity in the prior week. Median SF-36v2 scores (0-100 scale) were lower for physical health (39.6) than for mental health (51.6). Median overall HAL score was 76.1 (0-100 scale); complex lower extremity activities were the most impacted activity domain.

Conclusions: These 5 PRO instruments provide different levels of detail describing the impact of hemophilia on pain and function, and consequently, have varied burdens of administration. PRO data from the retest population demonstrate that most adults with hemophilia experience pain and functional impairment that impacts HRQoL, highlighting the importance of assessments and patient dialogue.
Pharmacokinetics, safety, and efficacy of pdFX, a new high-purity factor X concentrate: a phase 3 study in patients with moderate or severe hereditary factor X deficiency

Steven Austin¹, Miranda Norton²

¹St. George’s Haemophilia Centre, St. George’s Hospital, London, UK, ²Bio Products Laboratory Ltd, Elstree, UK

Objective: To assess the pharmacokinetics (PK), safety, and efficacy of the first high-purity, plasma-derived factor X concentrate (pdFX) for on-demand treatment of bleeding episodes in a prospective, open-label, multicenter, nonrandomized phase 3 study in subjects with hereditary moderate or severe factor X (FX) deficiency (basal plasma FX activity <5 IU/dL).

Methods: Included subjects were aged ≥12 years who required treatment with replacement therapy for ≥1 spontaneous or menorrhagic bleed in the past 12 months. Subjects received 25 IU/kg of pdFX on-demand for specific bleeds or as preventative use for 6 months to 2 years. PK was assessed following a single dose at baseline and after ≥6 months. Each bleed was categorized as major or minor, and subjects assessed efficacy for each bleed as “excellent,” “good,” “poor,” or “unassessable”; hospital-treated bleeds were also assessed by investigators. At study end, each investigator assessed the overall efficacy of pdFX. Safety assessments were adverse events (AEs), inhibitor development, viral seroconversions, and changes in laboratory parameters.

Summary: The study enrolled 16 subjects (aged 12-58 years [mean 27.1 years], 62.5% female) with moderate (n=2) and severe (n=14) FX deficiency. PK parameters did not differ between baseline and repeat assessment visits, with overall mean (median, interquartile range [IQR]) incremental recovery of 2.00 (2.12, 1.79-2.37) IU/dL per IU/kg and half-life of 29.4 (28.6, 25.8-33.1) hours. In total, 468 pdFX infusions were administered; 187 bleeds treated with pdFX were analyzed for efficacy (98 major and 88 minor), of which 155 (82.9%) were treated with one pdFX infusion. A mean (standard deviation) of 1.2 (0.5) infusions per bleed were administered, with a median (IQR) dose of 25.0 (24.4-26.7) IU/kg. Efficacy of pdFX was rated as excellent in 90.9% of bleeds, good in 7.5%, and poor in 1.1%. For the 15 subjects who completed the study, investigators rated overall pdFX efficacy as excellent in 12 (80%) and good in 3 subjects (20%). Six mild/moderate AEs were observed, no serious AEs were considered by investigators to be possibly related to study drug, and no hypersensitivity reactions or clinically significant trends in any laboratory safety parameters were observed.

Conclusions: In this study, pdFX was safe and efficacious in on-demand treatment of bleeds and short-term preventative therapy in subjects with moderate or severe FX deficiency at a nominal dose of 25 IU/kg. PK results supported these observed hemostatic effects.
Patient Preferences for FVIII and BAX 855: Results from the BAX 855 Pivotal Trial

Josh Epstein¹, Elizabeth L. Schwartz¹, Morgan Bron², Jason Booth¹, Bruce Ewenstein², Brigitt E. Abbuehl³

¹Baxter Healthcare, Westlake Village, CA, USA, ²Baxter Healthcare, Deerfield, IL, USA, ³Baxter Innovations GmbH, Vienna, Austria

Objective: BAX 855 is an extended half-life recombinant Factor VIII based on ADVATE. It was developed as an option to further personalize care and improve outcomes in people with hemophilia A. As a new therapy, it is important to understand patient satisfaction and preferences relative to their prior treatment. The objective of this research was to describe patient satisfaction with and preference for their prior FVIII therapy and BAX 855 as reported in the pivotal trial.

Methods: BAX 855 was studied in a 6-month, phase 2/3, multi-center, open label study. Subjects in Arm A received 45 ± 5 IU/kg of BAX 855 twice weekly while subjects in Arm B infused BAX 855 on-demand. Patient preference and satisfaction were included as exploratory endpoints. Patient satisfaction was captured with the following options describing their treatment: very satisfied, satisfied, neither satisfied nor dissatisfied, or very dissatisfied at baseline for their prior FVIII therapy and at follow-up for BAX 855. Patient preference for BAX 855 or their prior FVIII therapy was captured at follow-up. Ethics approval and informed consent were obtained. The percent of very satisfied and satisfied patients were combined for this analysis. Results were reported for all patients and by treatment arm.

Summary: 138 patients were in the intent to treat (ITT) sample. The majority of patients in the ITT sample completed the satisfaction questionnaire, however the number varied slightly by question and visit. While 79.4% (100 of 126) of patients were satisfied with their prior FVIII at baseline, satisfaction increased to 90.1% (109 of 121) with BAX 855 and 84.7% (100 of 118) preferred BAX 855 over their prior FVIII. Of the 85 patients in Arm A previously on prophylaxis, 18 patients in Arm A previously on-demand, and 15 patients in Arm B previously on-demand, 83.5%, 88.9% and 86.7% preferred BAX 855 over their prior FVIII, respectively.

Conclusion: Notably, patients enrolled in the BAX 855 trial had a high degree of satisfaction with their prior FVIII therapy. Nonetheless, treatment with BAX 855 was successful in further improving patient satisfaction with the majority of patients preferring it over their prior FVIII product.
Efficacy and safety of pdFX, a new high-purity factor X concentrate, in patients with mild to severe hereditary factor X deficiency undergoing surgery

Miguel Escobar1, Günter Auerswald2, Austin Steven3, Huang James N4, Miranda Norton5, Carolyn Millar6

1Gulf States Hemophilia and Thrombophilia Center, Houston, Texas, USA, 2Klinikum Bremen-Mitte, Professor-Hess-Kinderklinik, Bremen, Germany, 3St. George’s Haemophilia Centre, St. George’s University Hospitals NHS Foundation Trust, London, UK, 4UCSF Benioff Children’s Hospital, San Francisco, CA, USA, 5Bio Products Laboratory Ltd, Elstree, UK, 6Imperial College Healthcare NHS Trust, Hammersmith Hospital, London, UK

Objective: To assess the safety and efficacy of treatment with the first high-purity plasma-derived factor X concentrate (pdFX) in 2 prospective, multicenter, open-label, nonrandomized phase 3 studies in subjects with hereditary mild to severe mild factor X (FX) deficiency (basal plasma FX activity [FX:C] <20 IU/dL) undergoing surgery.

Methods: Subjects aged ≥12 years received pdFX preoperatively to raise plasma FX:C to 70-90 IU/dL and postoperatively as necessary to maintain levels at ≥50 IU/dL until they were no longer at risk of bleeding due to surgery. Efficacy assessments included blood loss during surgery, requirement for blood transfusion, postoperative bleeding, and changes in hemoglobin levels. Following treatment, efficacy of pdFX in the control of bleeding was assessed as “excellent,” “good,” “poor,” or “unassessable.” Safety outcomes included adverse events (AEs), inhibitor development, viral seroconversions, and other clinically significant changes in laboratory parameters.

Summary: Five subjects (aged 14-59 years) underwent 7 surgical procedures (major procedures: 2 knee replacements, 1 coronary artery bypass graft, and 1 extraction of 6 teeth; minor procedures: 2 extractions of 1 tooth each and 1 extraction of 2 teeth). Median pdFX exposure was 181 IU/kg (over 13 infusions) for major procedures and 89 IU/kg (over 2.5 infusions) for minor procedures. A median dose of 48.85 (range, 30.88–54.41) IU/kg was administered preoperatively, resulting in plasma FX:C levels of 0.77-1.32 IU/mL, and a median FX incremental recovery of 2.21 (range, 1.67-2.34) IU/dL per IU/kg was observed. For all procedures, bleeding control was rated by investigators as “excellent,” no blood transfusions were required, and no clinically significant changes in hemoglobin levels were observed. Blood loss was rated as “as expected” in 5 procedures and “less than expected” in 2 procedures compared with a similar patient without a coagulation disorder undergoing the same surgery. The most common AEs were constipation and dyspepsia (3 cases each). No treatment-related AEs, thrombotic events or evidence of thrombogenicity, viral seroconversions, or inhibitor development were observed.

Conclusions: These results show that pdFX was safe and efficacious as replacement therapy for 5 subjects with mild to severe FX deficiency undergoing a variety of surgical procedures on 7 occasions. Based on these findings, dosing should be tailored to the severity of the surgical procedure and the patient’s concomitant medical issues, and continual assessment of plasma FX levels in the perioperative period is recommended.
My Life, Our Future: A “Genetics Day” to Facilitate Efficient Enrollment

Julie Smith, Nancy Hatcher, Frances Patterson, Ruthrolen Martinez, Vinod Balasa

Valley Children’s Hospital, Madera, CA, USA

Objectives

My Life, Our Future (MLOF) is a collaboration between American Thrombosis and Hemostasis Network, National Hemophilia Foundation, Bloodworks Northwest (formerly Puget Sound Blood Center) and Biogen that offers free genotype analysis for patients with hemophilia A and B in the U.S. through hemophilia treatment centers (HTCs). Additionally, participants have the option to contribute to a research repository of blood samples and genetic data to support future research. At one partner HTC, a “Genetics Day” was implemented with the following goals: 1) Educate patients and families about MLOF; 2) Create a sense of community impetus for participating; and 3) Efficiently conduct the genetic testing of patients.

Methods

In January 2015, the Valley Children’s Hospital (VCH, formerly Children’s Hospital of Central California) HTC conducted a “Genetics Day” on a Sunday when the clinic was closed. Letters were sent to all HTC families informing them of the event and emphasizing that only the first 35 respondents would be eligible to participate. At clinic appointments, families were informed further about the event, and consent to participate was obtained in advance when possible. On the days prior to the “Genetics Day,” each family was called to remind them of their appointment. Patients were scheduled at 10-minute intervals between 10am and 2pm. VCH administration paid the salaries and overtime of 8 employees staffing the event; 2 others volunteered their time. A Spanish interpreter was present to translate, as needed. MLOF educational materials were available.

Summary

Thirty-four persons were enrolled and had a blood sample drawn in a 4-hour period, boosting enrollment significantly; thus the event met the primary objectives. Families were very enthusiastic about the opportunity to participate in research and to have their blood drawn in a short time. The following key lessons learned will help inform future events: 1) Match staff to expected capacity, including at least 2 nurses to answer patient and family questions; 2) Have lab personnel available to handle the increase in blood draws and sample processing volume that day; and 3) Patients and families appeared to benefit from knowing that other patients and families were willing to participate.

Conclusion

A “Genetics Day” was found to be a good way to educate and enroll a significant number of patients into MLOF in a short period of time. Appropriate preparation and planning of logistical requirements in advance and adequate staffing on-site are needed to ensure that the event achieves its objectives.
Hemophilia B Patients Who Switch From rFIX to Extended Half-Life rFIX-Fc: A Retrospective Analysis of Cost using US Specialty Pharmacy Dispensing Data

Yan Xiong, Josh Epstein, Morgan Bron, Alexandra Khachatryan

Baxalta US Inc., Deerfield, IL, USA

Background: Until recently, the hemophilia B community has only had standard Factor IX (FIX-Fc) products as treatment choices. With the availability of additional standard rFIX products and extended half-life (EHL) rFIX-Fc, there has been much debate (1-4) regarding clinical and cost expectations, balanced with optimizing use in patients. To level the debate, an understanding of real-world prescription costs of patients who switch to EHL FIX-Fc products is warranted.

Objectives: 1) To characterize patients who switch from rFIX to EHL rFIX-Fc, and 2) to understand their change in factor costs.

Methods: Retrospective analysis using national US specialty pharmacy dispensing databases from Jan 1, 2013-Apr 25, 2015 of Hemophilia B (ICD-9 code 286.1) individuals who switched from rFIX to rFIX-Fc. Descriptive statistics summarized patient characteristics. Patients who had at least 90 days of prescription coverage on both products were included. Utilization was averaged on a monthly basis pre and post switch. Costs were calculated by multiplying the units by the wholesale acquisition prices for each product (Red Book) and the percentage change in cost from rFIX to EHL-rFIX was compared. This analysis studied patients who switched but stayed on similar regimens. Cohorts were characterized as prophylaxis to prophylaxis (P to P), or on-demand to on-demand (OD to OD).

Results: Sixteen switchers were included in the study. Hemophilia severity was reported as 62.5% severe, 12.5% moderate, 6.25% mild, and 18.75% of unknown severity. The P to P cohort comprised of the majority of patients at 87.5% (n=14) while OD to OD were smaller at 11% (n=2). The median ages for these cohorts were similar. The P to P median age was 15 (range: 5-51) and OD to OD was 14 (range: 13-15) years old. Median prescription costs increased in the P to P cohort by 40% (range: -56% to 181%), while OD to OD increased by 173% (range: 1% to 348%).

Conclusion: While the availability of EHL rFIX-Fc allows hemophilia B patients an option with less frequent infusions, our findings demonstrate that for those who initially switched from prophylaxis to prophylaxis or from on-demand to on-demand regimens, costs increased for the majority of patients. This analysis provides initial real-world cost data for those who have switched to EHL and may be helpful in decision makers’ understanding of the value of EHL rFIX-Fc in hemophilia B.
Table 1. Summary of nonacog alfa studies that were included in this pooled analysis

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>N</th>
<th>Objective</th>
<th>Patient Population</th>
<th>Inclusion Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>300</td>
<td>Open-label, nonrandomized, multicenter</td>
<td>67</td>
<td>Evaluate the efficacy and safety of standard-of-care treatment (on-demand, routine prophylaxis, and surgical prophylaxis)</td>
<td>Treatment-naive infants/children with moderately severe or severe hemophilia B</td>
<td>FIX:C ≤ 3 IU/dL; FIX inhibitor undetectable</td>
</tr>
<tr>
<td>301</td>
<td>Open-label, nonrandomized, multicenter</td>
<td>25</td>
<td>Evaluate the efficacy and safety in the treatment of acute bleeding episodes, prophylaxis, and/or surgery</td>
<td>Children aged ≤ 6 years with severe hemophilia B</td>
<td>FIX:C ≤ 1%</td>
</tr>
<tr>
<td>Study Number</td>
<td>Study Design</td>
<td>Study Purpose</td>
<td>Age Group</td>
<td>FIX:C Level</td>
<td>Exposure Days</td>
</tr>
<tr>
<td>--------------</td>
<td>--------------</td>
<td>---------------</td>
<td>-----------</td>
<td>-------------</td>
<td>---------------</td>
</tr>
<tr>
<td>302&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Open-label, nonrandomized, multinational</td>
<td>Evaluate the efficacy and safety of standard-of-care treatment (on-demand, prophylaxis, and surgical prophylaxis)</td>
<td>PTPs aged 6–65 years with moderately severe or severe hemophilia B</td>
<td>FIX:C ≤2%</td>
<td>≤150 exposure days</td>
</tr>
<tr>
<td>304 [27]</td>
<td>Double-blind, randomized, crossover, PK study followed by a 6- to 12-month open-label, on-demand treatment extension</td>
<td>Determine bioequivalence of new formulation to reference formulation; evaluate efficacy and safety of new formulation</td>
<td>PTPs aged 6–65 years with moderately severe or severe hemophilia B</td>
<td>FIX:C ≤2%</td>
<td>≤150 exposure days</td>
</tr>
<tr>
<td>400 [33]</td>
<td>Open-label, randomized, 4-period, crossover</td>
<td>Evaluate the efficacy and safety of prophylaxis regimens vs. on-demand treatment</td>
<td>PTPs aged 6–65 years with moderately severe or severe hemophilia B</td>
<td>FIX:C ≤2%</td>
<td>≤12 bleeding episodes (6 of which were joint bleeding events) in the 12 months before screening</td>
</tr>
</tbody>
</table>
Prospective, open-label, multicenter, noninterventional, observational, cohort, registry

Evaluate safety with usual use

Patients with hemophilia B Scheduled to begin or already receiving nonacog alfa

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FIX, factor IX activity; PK, pharmacokinetic; PTPs, previously treated patients.

*Results have not been published.

**Table 2. Baseline demographics and characteristics**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Pooled Safety Population (N=412)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>23 (19.8)</td>
</tr>
<tr>
<td>Median (min–max)</td>
<td>21 (0–79)</td>
</tr>
<tr>
<td>Aged &lt;1 year, n (%)</td>
<td>50 (12.1)</td>
</tr>
<tr>
<td>0–27 days</td>
<td>3 (0.7)</td>
</tr>
<tr>
<td>28 days to &lt;1 year</td>
<td>47 (11.4)</td>
</tr>
<tr>
<td>Sex, n (%)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>396 (96.1)</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td></td>
</tr>
<tr>
<td>----------------------</td>
<td>-------</td>
</tr>
<tr>
<td>White</td>
<td>366 (88.8)</td>
</tr>
<tr>
<td>Black</td>
<td>20 (4.9)</td>
</tr>
<tr>
<td>Asian</td>
<td>7 (1.7)</td>
</tr>
<tr>
<td>Other</td>
<td>19 (4.6)</td>
</tr>
</tbody>
</table>

| Prior treatment, n (%) | 274 (66.5) |

<table>
<thead>
<tr>
<th>Lifetime exposure to factor replacement, b days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (SD)</td>
</tr>
<tr>
<td>Median (min-max)</td>
</tr>
</tbody>
</table>

| 225 (312.5)                                    |
| 136 (0-2400)                                   |

<table>
<thead>
<tr>
<th>Family history, n (%)</th>
</tr>
</thead>
</table>

| Hemophilia B                                 |
| 202 (49.0)                                   |

| Inhibitors                                    |
| 2 (0.5)                                       |

| Allergy to FIX product                        |
| 3 (0.7)                                       |

---

*a Received nonacog alfa in Study 101039 (n=15) [34] or in Study 300 (n=1) for FIX deficiency or were hemophilia carriers.

*b n=215.

FIX, factor IX.
Table 3. Pooled disposition and nonacog alfa consumption

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enrolled, n</td>
<td>415</td>
</tr>
<tr>
<td>Received ≥1 dose of nonacog alfa, n</td>
<td>412</td>
</tr>
<tr>
<td>Completed study, n (%)</td>
<td>255 (61.9)</td>
</tr>
<tr>
<td>Discontinued, n (%)</td>
<td>160 (38.8)</td>
</tr>
<tr>
<td>withdrew consent</td>
<td>14 (3.4)</td>
</tr>
<tr>
<td>Protocol violation</td>
<td>12 (2.9)</td>
</tr>
<tr>
<td>Due to AEs</td>
<td>7 (1.7)</td>
</tr>
<tr>
<td>Patient or investigator request</td>
<td>5 (1.2)</td>
</tr>
<tr>
<td>Lost to follow-up</td>
<td>4 (1.0)</td>
</tr>
<tr>
<td>Death</td>
<td>4 (1.0)</td>
</tr>
<tr>
<td>Other*</td>
<td>114 (27.7)</td>
</tr>
</tbody>
</table>
Reformulated nonacog alfa 411 consumption, n

Total number of infusions given 11,933

Infusions per patient, mean (SD) 29.2 (46.3)

Dose per infusion, IU/kg, mean (SD) 64.9 (42.8)

Total number of exposure days 11,588

EDs per patient, mean (SD) 28.2 (44.5)

aIncludes investigator withdrawal, failure of patient to provide consent, noncompliance, sponsor request/decision, liver transplantation, patient moved to another country, and inhibitor development.
bOne patient in Study 304 did not receive reformulated nonacog alfa and thus was not included [27].

AE, adverse event; ED, exposure days; SD, standard deviation.

Table 4. Adverse events occurring in ≥3% of patients
<table>
<thead>
<tr>
<th>Event, n (%)</th>
<th>Pooled Safety Population (N=412)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any AE</td>
<td>220 (53.4)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>63 (15.3)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>53 (12.9)</td>
</tr>
<tr>
<td>Cough</td>
<td>52 (12.6)</td>
</tr>
<tr>
<td>Headache</td>
<td>36 (8.7)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>31 (7.5)</td>
</tr>
<tr>
<td>Otitis media</td>
<td>29 (7.0)</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>28 (6.8)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>27 (6.6)</td>
</tr>
<tr>
<td>Ear infection</td>
<td>25 (6.1)</td>
</tr>
<tr>
<td>Nasal congestion</td>
<td>25 (6.1)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>22 (5.3)</td>
</tr>
<tr>
<td>Rash</td>
<td>22 (5.3)</td>
</tr>
<tr>
<td>Influenza</td>
<td>22 (5.3)</td>
</tr>
<tr>
<td>Pain in extremity</td>
<td>18 (4.4)</td>
</tr>
<tr>
<td>Rhinorrhea</td>
<td>18 (4.4)</td>
</tr>
<tr>
<td>Event</td>
<td>Pooled Safety Population (N=412)</td>
</tr>
<tr>
<td>-----------------------</td>
<td>---------------------------------</td>
</tr>
<tr>
<td><strong>Treatment-Related AEs</strong></td>
<td></td>
</tr>
<tr>
<td>Any treatment-related AE</td>
<td>48 (11.7)</td>
</tr>
<tr>
<td>Urticaria</td>
<td>6 (1.5)</td>
</tr>
<tr>
<td>Hypersensitivity</td>
<td>6 (1.5)</td>
</tr>
<tr>
<td>FIX inhibition</td>
<td>5 (1.2)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>4 (1.0)</td>
</tr>
<tr>
<td><strong>Serious AEs</strong></td>
<td></td>
</tr>
<tr>
<td>Any serious AE</td>
<td>74 (18.0)</td>
</tr>
<tr>
<td>Condition</td>
<td>Count (Percent)</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>-----------------</td>
</tr>
<tr>
<td>Hemarthrosis</td>
<td>6 (1.5)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>6 (1.5)</td>
</tr>
<tr>
<td>FIX inhibition</td>
<td>5 (1.2)</td>
</tr>
<tr>
<td>Device-related infection</td>
<td>4 (1.0)</td>
</tr>
<tr>
<td>Hematoma</td>
<td>4 (1.0)</td>
</tr>
<tr>
<td>Arthropathy</td>
<td>4 (1.0)</td>
</tr>
</tbody>
</table>

### AEs of Special Interest

<table>
<thead>
<tr>
<th>Condition</th>
<th>Count (Percent)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any AE of special interest</td>
<td>31 (7.5)</td>
</tr>
<tr>
<td>Allergic-type manifestations</td>
<td>15 (3.6)</td>
</tr>
<tr>
<td>Lack of effect</td>
<td>8 (1.9)</td>
</tr>
<tr>
<td>Red blood cell agglutination</td>
<td>7 (1.7)</td>
</tr>
<tr>
<td>Inhibitor development</td>
<td>5 (1.2)</td>
</tr>
<tr>
<td>Thrombogenicity</td>
<td>2 (0.5)</td>
</tr>
</tbody>
</table>

*Patients may have reported more than 1 AE.

AE, adverse event; FIX, factor IX.
QLOR06

SPACE (Study of Prophylaxis ACtivity, and Effectiveness): An interim descriptive analysis of patient activity levels and participation

Barbara Konkle\(^3\), Michael Recht\(^4\), Maggie Moore\(^3\), Susan Lattimore\(^4\), Elizabeth L Schwartz\(^1\), Diane Ito\(^1\), Josh Epstein\(^1\), Iliana Leony-Lasso\(^1\), Sharon A Richardson\(^2\)

\(^1\)Baxter Healthcare, Westlake Village, CA, USA, \(^2\)Baxter Healthcare, Deerfield, IL, USA, \(^3\)Bloodworks Northwest, Seattle, WA, USA, \(^4\)Oregon Health & Science University, Portland, OR, USA

Objective: Personalizing treatment to a patient’s lifestyle and promoting overall health and wellness in persons with hemophilia (PWH) is essential to optimizing outcomes. There is limited evidence that correlates how activity and infusions impact bleeding episodes and further data on this relationship is needed. The research objective of SPACE is to prospectively explore the association between activity level, timing of infusion, and occurrence of a bleeding episode in PWH using novel technology.

Methods: This six-month prospective, observational study includes PWH A or B in the United States currently receiving ADVATE or RIXUBIS between the ages of 13 and 65 years. Enrolled PWH use a smartphone eDiary application to log information on activities, infusions, and bleeding episodes. As an additional measurement of activity, enrollees are given a FitBit, a consumer-based activity tracker that measures steps taken and calories burned. Activity types are assessed based on their level of perceived risk for collision, according to the NHF “Playing It Safe” brochure. We report here current study status and descriptive analysis of baseline data.

Results: The interim analysis included 15 patients with a median age of 19 (Range: 13 to 47). At baseline, 87% of patients were on prophylaxis and 13% treated on-demand treatment. Fifty-three percent of patients had 0 target joints at baseline. Eighty-seven percent of patients indicated that they had discussed activity participation with their physician. Sixty-seven percent of patients considered themselves ‘very satisfied’ or ‘satisfied’ with their level of activity. Data collected from the FitBit indicated that patients in SPACE walked on average 7,367 (SD: 3250) steps per day and burned 979 (SD: 398) calories from their activity. For patients on prophylaxis, the mean number of days per week doing mild, moderate and strenuous activity were 3.57, 2.64, and 1.5 respectively. Of the data reported on bleeding episodes, 40% of patients reported no bleeds at the time of the interim analysis. Forty percent of patients did not report having a bleed at the time of the interim analysis. Of all bleeds reported, 34% were associated with physical activity.

Conclusions: Current data from SPACE demonstrates that subjects are active and participating in various activities. Continued data will provide better understanding of the types of activities and infusion schedules that may be associated with risk as well as protective effects on bleeding episodes by infusing prior to activity. A personalized approach to treatment based on physical activity levels may minimize bleeding risk in PWH.
Increased physical activity levels and improvement in treatment outcomes in patients who switch from on-demand to prophylaxis with BAX 855

Barbara A Konkle2, Elizabeth L Schwartz1, Josh Epstein1, Andrea Hafeman1, Leonard A. Valentino4, Brigitt E. Abbuehl3

1Baxter Healthcare, Westlake Village, CA, USA, 2Bloodworks Northwest, Seattle, WA, USA, 3Baxter Innovations GmbH, Vienna, Austria, 4Baxter Healthcare, Deerfield, IL, USA

Objective: The treatment benefits of FVIII prophylaxis include benefits in clinical and patient reported outcomes such as a significant reduction in bleeding episodes, slowing the progression of arthropathy, improving mobility, and improvements in physical health-related quality of life (HRQoL) (Lee 2007, Manco-Johnson 2007, Royal et al 2002, Valentino et al. 2012). Although there is evidence supporting improvements in physical function, limited evidence exists on how prophylaxis facilitates changes in a patient’s activity and lifestyle. The objective of this descriptive analysis was to summarize the changes in physical activity levels and in treatment outcomes for patients previously on-demand who switched to prophylaxis in the BAX 855 pivotal trial.

Methods: This post hoc analysis of the pivotal trial included those patients previously on-demand who received prophylaxis with BAX 855 in the pivotal trial. Details on study design and outcome measurements were specified elsewhere (Konkle et al. EAHAD 2015). Descriptive data on target joint status, HRQoL measured by SF-36 domain and component scores, and days of physical activity level (defined by at least 15 minutes doing mild, moderate or strenuous activity) per week were reported.

Summary: There were 18 patients who were previously on-demand and switched to prophylaxis with BAX 855 in the study. This group had a median age of 31.5 (IQR: 18.5). All patients had at least one target joint with a median of 3 target joints (IQR: 1.75). The following change in domain and component scores for the SF-36 met thresholds for a minimally important difference and could be considered clinically meaningful improvements: Role Physical (3.27), Bodily Pain (4.51), and Physical Component Score (3.48). Mean physical activity level participation for patients previously on-demand who switched to prophylaxis with BAX 855 increased by 3.06 days (SD: 5.90) per week.

Conclusions: Subjects in the PROLONG-ATE trial who were previously on-demand and switched to prophylactic treatment with BAX 855 reported increases in their physical activity levels as well as their physical health-related quality of life. To the authors’ knowledge, this is the first evidence to demonstrate an increase in physical activity levels for patients who switch to prophylaxis treatment. With these outcome improvements, patients could to live more full/active lifestyles.
An Evaluation of the Switch from Standard Factor VIII Prophylaxis to Prophylaxis with an Extended Half-Life, Pegylated, Full-length Recombinant Factor VIII (BAX 855)

Oleksandra Stasyshyn, Ralph Gruppo, Barbara Konkle, Tung Wynn, Marilyn Manco-Johnson, Pratima Chowdary, Vladimir Komrská, Laimonas Griskevičius, Elaine Eyster, Krzysztof Chojnowski, Werner Engl, Lisa Patrone, Brigitt Abbuehl

Objective: This report assesses the changes in bleeding patterns as previously treated severe hemophilia A patients were switched from their pre-study standard factor VIII (FVIII) prophylactic treatment regimen to prophylaxis with BAX 855 - an extended half-life, pegylated, full-length recombinant FVIII built on ADVATE - during their participation in the pivotal trial.

Methods: Patients’ informed consent and appropriate ethics committee approvals were obtained. At baseline, eligible patients reported their pre-study treatment regimen and average annualized bleeding rate (ABR) for the previous 3-6 months. Patients assigned to the prophylactic arm were to receive 45±5 IU/kg of BAX 855 twice weekly for ≥50 exposure days or approximately 6 months. This per-protocol analysis included 101 treated patients in the prophylactic arm.

Summary: The overall mean (SD) ABR for these treated patients was 3.7 (4.7), which was lower than the ABR for the 17 patients treated on-demand during the study (40.8 [16.3] - who were all treated on-demand pre-study). Of the 101 subjects in BAX 855 prophylactic arm, 82 were treated on prophylaxis and 19 were treated on-demand during the pre-study period. The BAX 855 prophylactic dosing frequency was reduced by a mean (SD) of 26.7% (27.9) compared to the frequency reported in the pre-study period, which is approximately equivalent to one less prophylactic infusion per week when using BAX 855 for prophylaxis. The mean dose per prophylactic infusion was higher for the BAX 855 treatment regimen compared to pre-study (44.53 vs 38.12 IU/kg), but FVIII consumption per week was lower during the study compared to pre-study (83.96 vs 97.79 IU/kg/week). More patients treated on BAX 855 prophylaxis during the study treatment period had zero bleeding episodes compared to during their pre-study period: 37.8% vs 23.2%. The mean ABR was lower for subjects on BAX 855 prophylaxis compared to pre-study: 4.13 vs 9.74.

As expected, the 19 patients treated on-demand pre-study had a higher mean ABR (31.53) and all experienced bleeding (ie, none had zero hemarthroses during the pre-study period) compared to during their BAX 855 prophylactic treatment period (mean ABR of 1.68 and 47.4% had zero bleeding episodes).

Conclusions: These results further demonstrate the benefit of BAX 855 prophylaxis (45±5 IU/kg twice weekly) and support its efficacy profile for the prevention of bleeding when used twice weekly, which suggests that fewer infusions may be needed to maintain prophylactic efficacy.
Update on a phase 1/2 open-label trial of BAX 335, an adeno-associated virus 8 (AAV8) vector-based gene therapy program for hemophilia B

Paul E. Monahan¹, Christopher E. Walsh², Barbara A. Konkle³, Jerry S. Powell⁴, Neil C. Josephson⁵, Miguel A. Escobar⁶, Scott W. McPhee⁷, Boyan Litchev⁸, Michael Cecerle⁹, Bruce Ewenstein¹⁰, Hanspeter Rottensteiner⁹, Maurus De la Rosa⁹, Birgit M. Reipert⁹, R. Jude Samulski¹, Anne Prener¹⁰, Friedrich Scheifflinger⁹

¹Gene Therapy Center, University of North Carolina, Chapel Hill, NC, USA, ²Mount Sinai School of Medicine, New York, NY, USA, ³BloodworksNW and the University of Washington School of Medicine, Seattle, WA, USA, ⁴Division of Hematology and Oncology, University of California Davis Medical Center, Sacramento, CA, USA, ⁵Seattle Genetics, Bothell, WA, USA, ⁶University of Texas Health Science Center at Houston, Houston, TX, USA, ⁷Asklepios BioPharmaceutical, Chapel Hill, NC, USA, ⁸Baxalta US, Inc., Westlake Village, CA, USA, ⁹Baxalta Innovations GmbH, Vienna, Austria, ¹⁰Baxalta US, Inc., Cambridge, MA, USA

Background: Gene therapy, by enabling persistent endogenous production of FIX, may provide long-term benefit in Hemophilia B with a single administration. Non-integrating adeno-associated viral (AAV) vectors have shown to induce stable transgene expression with an excellent safety profile. Baxter Healthcare has developed a gene therapy product BAX 335 (AAV8.sc-TTR-FIXR338Lopt): a codon optimized hyperactive F9 transgene (FIXR338Lopt), driven by the liver-specific transthyretin (TTR) promoter in an AAV8 capsid.

Aims: Evaluate plasma FIX activity and its relationship to vector dose; determine dose to achieve stable plasma FIX activity between 10% and 40% of normal; evaluate systemic immune responses to FIXR338Lopt and the AAV8 capsid.

Methods: Up to 16 male adults with severe hemophilia B are to be given a single intravenous dose of BAX 335 in up to 4 sequentially ascending dose cohorts. Pharmacodynamic (e.g. plasma FIX activity) and safety data (e.g. immune response, adverse events [AEs]) are to be collected.

Results: We report data available from the first 7 subjects dosed with BAX 335: 2 at 2x10¹¹ vg/kg (Cohort 1), 3 at 1x10¹² vg/kg (Cohort 2), and 2 at 3x10¹² vg/kg (Cohort 3), with follow-up ranging from 2 weeks to more than 2 years. None of the subjects developed FIX inhibitors. A dose-dependent immune response with variable neutralizing antibody titters to the AAV8 capsid was observed 2 weeks post gene transfer in all subjects. No severe product-related AEs were reported. Therapeutic FIX levels of up to 3% were achieved in Cohort 1, sustained levels up to 20 to 25% were observed 9 months post dosing in Cohort 2. In Cohort 3 peak FIX expression exceeded 50%; subsequently, declining FIX activity prompted corticosteroid therapy to support the maintenance of FIX expression.

Summary: BAX 335 appears to be well-tolerated in the 7 subjects dosed to date and hemostatically effective plasma FIX levels were achieved in three dosing cohorts.

Maura Padula¹, Stacy Croteau², Ellis Neufeld², Loren D'Angelo¹, Kate Quint¹

¹Boston Children’s Hospital, Boston, MA, USA, ²Boston Hemophilia Center, Boston, MA, USA

Attainment of self-management skills, disease knowledge, and a documented transition plan are key elements for smooth transfer from pediatric to adult care for patients with chronic disease. Our hemophilia center had no standardized approach for assessing key patient competencies or independence readiness. In the last quarter of 2014, our team undertook a quality improvement project; we developed a transition tool with the goals of consistently assessing self-efficacy skills at a sustained rate of 90% during annual comprehensive visits; and developing patient-centric skill-building plans based on these assessments.

We previously reported that after four PDSA ramps of tool utilization, 31 patients, age 2-21 years, had been seen in hemophilia comprehensive clinic during the 3 month period studied. Utilizing the newly developed tool, 97% had a global assessment of competency with respect to their current age group; 93% had transition or progress plans documented. This demonstrated significant improvement compared with retrospective data from the three month period prior to implementation of the tool.

Since this previous report, we have continued to utilize the tool during hemophilia comprehensive clinic. In the proposed poster, we will demonstrate sustainability of the tool through analysis and presentation of Hemo-milestone data from the first half of 2015. Further, based on these results we will propose additional areas of study inspired by the transition tool, with the aim of continued improvement of the skill-building and transition process. These include improved utilization of educational materials based on identified learning needs; evaluation of documented, planned interventions; the development of collaborative educational events with our partner adult HTC; and retrospective, patient-centered evaluation of the transition process after the transition to adult hemophilia care.
Effect of Hemophilia Treatment Center digital monitoring on bleeding rates

Marc Lara¹, Natalie Duncan², Raquel Andres³, John Chapin⁴, Catherine McGuinn⁴

¹MicroHealth, New York, NY, USA, ²Indiana Hemophilia and Thrombosis Center, Indianapolis, Indiana, USA, ³Independent, New York, NY, USA, ⁴Weill Cornell Medical Center, New York, NY, USA

Objective: To assess the effect of digital monitoring on bleeding rates in patients with hemophilia A using prophylaxis.

Methods: A total of 294 eligible patients with hemophilia A were included in our observational study. Eligible patients used clotting factor concentrates and had no active inhibitors. Patients used a digital health tool powered by MicroHealth to log bleeds and infusions via smartphone, texting, or online. The study observational period was August 2014 to January 2015. Patients using the tool could choose to invite their care professionals for monitoring. For each patient, Hemophilia Treatment Center (HTC) monitoring was defined as having at least one HTC professional: 1. Linked to the patient and with online access to the infusion logs; 2. Receiving notifications when the patient had bleeds and/or had adherence below a threshold, and; 3. Having two or more patients under monitoring. There were a total of 35 and 259 patients in the monitoring and non-monitoring groups, respectively.

We conducted Bayesian analysis using linear mixed models and a negative binomial distribution to compare the relative risk of bleeding rates for patients with and without HTC monitoring.

Summary: Patients using HTC monitoring had a relative bleeding rate of 0.60 vs. patients without monitoring, which is equivalent to a 40% reduction in bleeding rates for monitored patients (95% credible interval: 0.38—0.96).

Patients on the monitoring and no monitoring groups were comparable except that the monitoring group had 23% more pediatric patients (p<0.001). However, bleeding rates between pediatric and adults were comparable (p=0.500). Subgroup analysis showed no differences in the reductions of bleeding rates due to monitoring between pediatric-only and adult-only subgroups (p=0.353).

Conclusions: The use of digital tools for chronic care monitoring is a growing global trend. A reduction in the annualized bleeding rate of 40% (~2 bleeds a year) is both statistically and clinically significant and may have a cumulative protective impact on patients’ long-term outcomes. Observational studies are subject to sample bias, however, patients in both groups were technologically savvy and motivated enough to track their condition using a digital health tool. Given that this intervention is free, safe, and fits the accountable care model, we encourage clinicians to explore its adoption. Confirmatory studies on this topic are encouraged.
Assessment of motor proficiency in people with bleeding disorders using the Bruininks-Oseretsky Test of Motor Proficiency, Second Edition (BOT-2™)

Bethany Sloane, PT, DPT, Brittany Gurgel, PT, DPT, Nancy Durben, MSPT, PCS, Paul Sochacki, MS, David Oleson, PT, PCS, Michael Recht, MD, PhD

Oregon Health & Science University, Portland, OR, USA, 2Laboratory Statistical Solutions, LLC, Portland, OR, USA

Background: Activity limiting joint disease has greatly decreased with the introduction of prophylactic treatment for people with severe bleeding disorders. Previous research using the Bruininks-Oseretsky Test of Motor Proficiency, Second Edition (BOT-2™), a standardized, normative, age and sex matched test of motor development, suggested motor development of males aged 4-21 years with bleeding disorders may be lower than age-matched peers.

Objective: The primary purpose of this study was to compare the gross motor proficiency of boys with hemophilia ages 4-21 years followed at the Hemophilia Center at Oregon Health & Science University utilizing the BOT-2. Secondarily, we examined the relationship between joint health and gross motor proficiency.

Methods:

a) Participants and setting: Thirty-four subjects with either hemophilia A or B were recruited from our center. Data collection occurred during clinic visits or at the patients’ homes.

b) Design and Procedures: A prospective, cross-sectional study design was used. The Upper Limb Coordination, Bilateral Coordination, Balance, Running Speed and Agility, and Strength subtests of the BOT-2 were administered. Body composition, range of motion, presence of an inhibitor, and use of prophylaxis were collected at the time of testing or from chart review.

c) Analyses: Analysis of variance (ANOVA) modeling was used to compare BOT-2 scores of PWH with baseline BOT-2 scores estimated from the general population of comparable age.

Summary: Mean Running Speed & Agility scores were greater among boys with hemophilia compared to the control population (p=0.0026). Agility scores were similar between boys with hemophilia A and B (p>0.60), and significantly greater compared to the control group (p=0.0153). No other significant differences were found comparing boys with hemophilia to the control group. Within the boys with hemophilia cohort, age-adjusted ANOVA found no significant differences in BOT-2 scores between subjects of different severities, treatment regimen (prophylaxis or episodic), or diagnoses (Hemophilia A or B).

Conclusion: Boys with hemophilia have the same or better gross motor proficiency as age matched peers.
Adopting and Piloting the Patient Safety and Clinical Pharmacy Services Collaborative (PSPC) breakthrough model to transform and significantly improve adherence, improve health status and bring patients under control in the Hemophilia Community.

Mary Pham, Segundo Gallo, Diane Nugent, Amit Soni

Center for Inherited Blood Disorders, Orange, CA, USA

Introduction

The delivery and integration of medication therapy management services in the hemophilia community changes how health care is being delivered. Through integration of clinical pharmacists within the Hemophilia Treatment Center (HTC) core team, the PSPC model serves to go beyond the traditional health care system. PSPC data for other conditions (e.g. asthma, diabetes) have demonstrated 35% to 43% improved patient outcomes and the reduction of unnecessary healthcare costs. A four month pilot project was performed where HTC specific metrics were designed.

Summary

The clinical pharmacist serves as an integral member of the HTC core team to provide medication specific education, monitoring and communication with the patient outside of their regular scheduled care. Activities include: medication reconciliation, adverse drug event (ADR), potential ADR monitoring and patient specific adherence data review.

HTC’s routinely schedules patients to be seen every 6-12 months for multidisciplinary care and as needed for injury, pre/post-operative procedures, or following hospitalization. Clinical Pharmacist direct interaction with patients can decrease negative outcomes related to intermittent compliance, delayed treatment of breakthrough bleeds, which can result in long term joint damage.

Our goals is: (1) to attain a reduction of bleeding events in the prophylaxis hemophilia population and (2) to optimize medication therapy to improve better health outcomes.

Methods

Baseline adherence data was compiled using 2 years of retrospective pharmacy claims data. Subjects included: patients with severe hemophilia A and B on prophylaxis and enrolled in the 340B program. Exclusion: patients with inhibitors, patients on demand only and those with additional comorbidities (e.g. HIV/Hepatitis C). Prospective review of adherence and monitoring of interventions and bleeding events are tracked monthly. Once all patients have completed a full two year analysis, a regression analysis model will be used as one of the statistical tests.

Conclusions

Baseline adherence was measured at 58.45%. After four months of implementation, a 66.67% result improvement in adherence. Baseline annual bleed rate (ABR) was assessed at 7 events. A 14% reduction of ABR to 6 events over a period of 4 months was measured. Further analysis of the current data estimates that patient medication adherence will improve and an impact of up to 43% improvement in ABR can be achieved over a period of one year. Thus, statistically significant reduction of bleeding events in the prophylaxis community with an increase in adherence and improved overall control within the hemophilia population can be achieved with this pilot.
Hemophilia is a rare bleeding disorder in which the blood doesn't clot normally. (National Heart, Lung, and Blood Institute, 2013). It mostly affects males. (Raabe, 2008).

For parents hearing that their new baby has hemophilia can be stressful and worrying. Babies do not realize what is happening around therefore parents often tend to be overprotective. As the boys grow up, they are capable of seeing the cause and effect of situations on their own and they realize that they cannot do the same things like their friends. When the adolescence come, teenagers worry about what society thinks, so having hemophilia may make them feel different. (Hemophilia Federation of America, 2015). Hemophilia is not an illness, it's just a “life style” which people have to live with.

Within psychological intervention is important to address the emotional aspect of patients and family’s support patient handling of his illness, personal life and surroundings.

Objective: Describe intervention strategies in the summer camp “Ceiba” of “Tabasqueña de Hemofilia A.C.” in order to promote the social integration in patients with hemophilia.

Materials: Intervention programs carried out in the camp were used to realize an analysis of the strategies, which were provided by "Tabasqueña de Hemofilia A.C."

During the last eight years, eight camps were realized, the average of assistants every year was 80, 60 patients (between 6 and 24 years old) and 20 additional people in medical field. The objective of the camps is to learn, enjoy, bring all their everyday life experiences and have a better quality of life. (Tabasqueña de Hemofilia, 2007).

The interventions were directed to: accept and make awareness of patient’s life style, learn about hemophilia, live in cooperation, socialize and integrate, improve communication, express himself, team work, experience the freedom, become independent, self-esteem and have a better quality of life.

Each intervention was related to a specific activity; 3 workshops (Psychologist, hematology and nursing), parents and relatives letters, hydrokinesitherapy, talent show, treasure hunt and visits to entertainment and cultural places.

Camps have a great significant learning in their lives and teach children and teenagers valuable life skills through education, activities and games; socialization is achieved, independence, and sense of individual responsibility and group.

Having this camps around the world and taking this interventions will be excellent, because its an interactive way to achieve self- realization and learn to live with the disease, knowing others with the same "life’s style".
Building ‘Zoris in the Sand’ – Best Practice for Bleeding Disorder Capacity Building in the Underserved US Commonwealth of the Northern Mariana Islands

Tiffany F. Lin, Pam Carhill, Judith Baker, James N. Huang

Objective: The Commonwealth of the Northern Mariana Islands (CNMI), an isolated United States territory in the North Pacific, is home to an underserved bleeding disorders population. Historically, patient diagnoses were uncertain and health care providers had limited knowledge about symptoms, treatment, and morbidities. Regional efforts to establish modern hemophilia care in the mid-1990’s engaged a local physical therapist champion, but workforce shortages and economic problems stymied comprehensive care implementation. After a pediatric hematology/oncology fellow from University of California San Francisco relocated to CNMI in 2014 the fellow, Physical Therapist champion, and Regional Hemophilia Coordinator developed an island-wide strategy to provide hemophilia education, assess patient/family needs, and build team based bleeding disorders care.

Methods: In the summer of 2014, the hematology fellow identified potential patients via chart reviews, polling local providers, and a community outreach event. In the fall of 2014, patient diagnoses and medication response was confirmed with supplemental testing. We then partnered with the local Marianas Health and Los Angeles Orthopedic Institute for Children to design and conduct CNMI’s first weeklong bleeding disorder conference series for health care providers, educators, patients and their community in December 2014. The CNMI Department of Public Health and Biogen co-sponsored.

Results: Case finding and testing confirmed eleven CNMI residents have bleeding disorders including severe hemophilia A and B, von Willebrand’s types 2A, 2B, and 2N. All patients had clarifications or completely new diagnostics required for formal diagnosis. Two hundred participants attended discipline specific seminars: physicians, nurses, therapists, pharmacists, dentists, athletic coaches, and health education teachers. Pre/Post test evaluations documented the conference’s effectiveness: 99% enjoyed attending, >90% reported knowledge gains in all domains, and 90-100% from all disciplines reported learning something new. All patients/families completed a modified version of the HRSA National HTC Patient Needs assessment, providing a baseline and identifying priority information and services needs.

Conclusion: Local hematology expertise and leadership is critical to confirm patient diagnoses, initiate appropriate therapies, and catalyze hemophilia care team building. In resource limited areas, correct diagnoses are essential for accurate education and resource allocation. A concentrated weeklong education series should be considered - over one-shot approaches - to raise rare disorder awareness, knowledge, and capacity in isolated and/or under-resourced areas. Regional rare disorder network infrastructure can provide strategic expertise in program planning and evaluation, referrals to funders and mentors, and links to national assessment tools.
Access to Dental Care for People with Bleeding Disorders: Survey Results of Hemophilia Treatment Centers in the United States

Rona Bodman\textsuperscript{1,} Rebecca Schaffer\textsuperscript{2,} Denise Frances\textsuperscript{1,} Mai-Ly Duong\textsuperscript{2}

\textsuperscript{1}NYU/Lutheran Medical Center, Brooklyn, NY, USA, \textsuperscript{2}Arizona School of Dentistry & Oral Health - A.T. Still University, Mesa, AZ, USA

Aim: The goal of this project was to gather data and identify factors affecting access to dental care for people with bleeding disorders in the United States.

Methods: The Arizona School of Dentistry and Oral Health and the National Hemophilia Foundation conducted a joint survey. The survey was completed by 102 of the 147 hemophilia treatment centers (HTC) in the USA. This represents 69\% of the HTC's in the country. Each HTC provided specific information concerning the dental services and education provided for patients.

Summary: Survey results revealed inconsistent levels of oral health services available to patients. Major factors limiting access to care include finances, patient anxiety and a lack of providers with the skills to treat this population.

Conclusion: Improvement in oral health for persons with bleeding disorders requires appropriate education for providers, patients and families. Additionally, both public and private health funding must be re-evaluated as it relates to people with bleeding disorders.