NHF News Briefs

May 11 – May 17, 2018

This report includes selected news items from the past week on issues of concern to the bleeding disorders community. It is designed to help keep NHF national and local leadership and staff informed of the latest information from the news media. It will be distributed by email on Thursday of each week, covering important news items from the previous seven days. Subjects covered will include hemophilia, other bleeding disorders, gene therapy, hepatitis, HIV/AIDS, and others.

May 11, 2018
Raredr.com

16-Year Follow-Up Proves Weekly FVIII Prophylaxis Reduces Bleeding in Hemophilia A

By Mathew Shanley

Results from a study recently published in The Lancet Neurology describe in detail a 16-year follow up of patients with hemophilia A who were treated with frequency-escalated prophylaxis.

The study, "Tailored frequency-escalated primary prophylaxis for severe haemophilia A: results of the 16-year Canadian Hemophilia Prophylaxis Study longitudinal cohort," was conducted by Professor Brian M Feldman, MD of the Division of Rheumatology at The Hospital for Sick Children in Toronto, and colleagues. It was initially funded by grants from the Medical Research Council of Canada/Pharmaceutical Manufacturers Association of Canada Partnership Fund and the Bayer/Canadian Blood Services/Hema-Quebec Partnership Fund.

Hemophilia A is an X-linked bleeding disorder that results from mutations in the gene-encoding coagulation factor VIII (FVIII). Patients with severe hemophilia A are vulnerable to impulsive or triggered bleeding in joints and soft tissue, which can lead to excruciating and incapacitating arthropathy, poor quality of life (QOL), and escalated risks of intracranial hemorrhage and early death.

Commonly referred to as classic hemophilia, hemophilia A is a genetic disorder caused by missing of defective factor VIII. Approximately 1/3 of hemophilia A cases, however, are caused by a spontaneous genetic mutation.

The longitudinal study had 2 specific objectives: first, to estimate the incidence of target joint bleeding in patients with severe hemophilia A treated (for primary prophylaxis) with escalating dose prophylactic factor replacement. The second objective was obtaining accurate estimates of the direct and indirect costs associated with this protocol for use in a cost-effectiveness model, comparing escalating dose with standard prophylaxis and with intermittent therapy.

Fifty-six boys with severe hemophilia A and a factor level less than 2% were enrolled between June 26, 1997 and January 30, 2007. All were followed for a median of 10.2 years (to a maximum of 16.1 years) after they were treated with standard half-life recombinant factor VIII (SHL-rFVIII), beginning as once-weekly prophylaxis with 50 IU/kg and escalating in frequency (with accompanying dose adjustments) in response to breakthrough bleeding as determined by the protocol.

Joint health, as measured by the Colorado Child Physical Examination Scores (CCPES), served as the primary endpoint for the analysis and was evaluated at study end. All analyses were done by intention to treat. The median end-of-study CCPES physical examination score was 1 (IQR 1-3; range 0-12) for the left ankle and 1 (1-2; 0-12) for the right ankle, with all other joints having a median score of 0.

No treatment-related safety events were reported over the duration of the study, including central venous catheter infections. The median annualized index joint bleeding rate was 0.95 per year (IQR 0.44-1.35; range 0.00-13.43), but, at some point during the study, 17 (30%) patients had protocol-defined unacceptable breakthrough bleeding.

"Our study has shown that very good health outcomes within the WHO-ICF domains of body structures and functions, and activities and participation are possible with the use of tailored frequency-escalated prophylaxis, using less SHL-rFVIII than standard full-dose prophylaxis regimens," Dr. Feldman says in the study.

"Starting treatment with once weekly rather than more frequent infusions allowed most young boys to avoid the placement of a CVC.31 In addition, the use of less SHL-rFVIII has the potential to provide substantial cost savings16 as compared with standard treatment. However, because our tailored frequency-escalated approach was driven by bleeding events, some bleeding did occur that resulted in joint damage in some participants. Our primary outcomes of interest were long-term function and joint health, and we showed that despite some bleeding, our cohort had very good health at the end of the study."

References:

Feldman BM. Tailored frequency-escalated primary prophylaxis for severe haemophilia A: results of the 16-year Canadian Hemophilia Prophylaxis Study longitudinal cohort. *The Lancet Neurology*. 2018;PIIS2352-3026(18)30048-6. doi: 10.1016/ S2352-3026(18)30048-6

May 13, 2018
Newswiretoday.com

Genentech to Present New Phase III Data for HEMLIBRA in People with Hemophilia A at the World Federation of Hemophilia 2018 World Congress

• Data include results from HAVEN 3 study in people with hemophilia A without factor VIII inhibitors and HAVEN 4 study in people with hemophilia A with or without factor VIII inhibitors

• Ongoing HEMLIBRA clinical development program demonstrates commitment to advancing care for all people with hemophilia A.

Genentech, a member of the Roche Group, announced today that Phase III results for HEMLIBRA® (emicizumab-kxwh) will be presented for the first time during the World Federation of Hemophilia (WFH) 2018 World Congress (wfh.org) from May 20-24 in Glasgow, Scotland. The late-breaking presentations include positive results from the pivotal HAVEN 3 study of HEMLIBRA dosed every week or every two weeks in people with hemophilia A without factor VIII inhibitors and the pivotal HAVEN 4 study of HEMLIBRA dosed every four weeks in people with hemophilia A with or without factor VIII inhibitors. These data support the promising potential of HEMLIBRA for all people with hemophilia A.

"We look forward to sharing these new results from the HAVEN 3 and HAVEN 4 studies, which demonstrate the potential of HEMLIBRA to redefine treatment expectations for people with hemophilia A with and without inhibitors to factor VIII," said Sandra Horning, M.D., chief medical officer and head of Global Product Development. "We will also be sharing real-world data that provides new insight into the impact of hemophilia A treatment on daily life, as part of our ongoing commitment to advancing management and care for the global hemophilia community."

Data from the HAVEN 3 and HAVEN 4 studies will be presented for the first time in late-breaking oral presentations on Monday, May 21. The HAVEN 3 presentation will highlight new data on HEMLIBRA prophylaxis administered every week or every two weeks in people 12 years of age or older with hemophilia A without factor VIII inhibitors compared to no prophylaxis. The presentation will also include results from an intra-patient analysis comparing HEMLIBRA prophylaxis to prior treatment with factor VIII prophylaxis. The U.S. Food and Drug Administration (FDA) recently granted Breakthrough Therapy Designation for HEMLIBRA in people with hemophilia A without factor VIII inhibitors based on data from this study. The HAVEN 4 presentation will highlight primary data in people 12 years of age or older with hemophilia A with or without factor VIII inhibitors receiving HEMLIBRA prophylaxis every four weeks.

These presentations at WFH follow the announcement of positive top-line results from the HAVEN 3 study in November 2017 and positive top-line interim results from the HAVEN 4 study in December 2017. Data from both studies are being submitted to health authorities around the world for approval consideration.

Genentech will also present real-world data from a non-interventional study in adults with hemophilia A without factor VIII inhibitors and children with hemophilia A with factor VIII inhibitors. These data on health-related quality of life and health status will provide insights into challenges of living with and managing hemophilia A for patients and caregivers.

About HAVEN 3 (NCT02847637)

HAVEN 3 is a randomized, multicenter, open-label, Phase III study evaluating the efficacy, safety and pharmacokinetics of HEMLIBRA prophylaxis versus no prophylaxis (episodic/on-demand factor VIII treatment) in people with hemophilia A without factor VIII inhibitors. The study included 152 patients with hemophilia A (12 years of age or older) who were previously treated with factor VIII therapy either on-demand or for prophylaxis. Patients previously treated with on-demand factor VIII were randomized in a 2:2:1 fashion to receive subcutaneous HEMLIBRA prophylaxis at 3 mg/kg/wk for 4 weeks, followed by 1.5 mg/kg/wk until the end of study (Arm A), subcutaneous HEMLIBRA prophylaxis at 3 mg/kg/wk for 4 weeks, followed by 3 mg/kg/2wks for at least 24 weeks (Arm B), or no prophylaxis (Arm C). Patients previously treated with factor VIII prophylaxis received subcutaneous HEMLIBRA prophylaxis at 3 mg/kg/wk for 4 weeks, followed by 1.5 mg/kg/wk until the end of study (Arm D). Episodic treatment of breakthrough bleeds with factor VIII therapy was allowed per protocol.

About HAVEN 4 (NCT03020160)

HAVEN 4 is a single-arm, multicenter, open-label, Phase III study evaluating the efficacy, safety and pharmacokinetics (PK) of subcutaneous administration of HEMLIBRA dosed every four weeks. The study included 48 patients (12 years of age or older) with hemophilia A with or without factor VIII inhibitors who were previously treated with either factor VIII or bypassing agents, on-demand or as prophylaxis. The study was conducted in two parts: a PK run-in; and an expansion cohort. All patients in the PK run-in (n=7) were previously treated on-demand, and received subcutaneous HEMLIBRA at 6 mg/kg to fully characterize the PK profile after a single dose during four weeks, followed by 6 mg/kg every four weeks for at least 24 weeks. Patients in the expansion cohort (n=41) received subcutaneous HEMLIBRA prophylaxis at 3 mg/kg/wk for four weeks, followed by 6 mg/kg every four weeks for at least 24 weeks. Episodic treatment of breakthrough bleeds with factor VIII therapy or bypassing agents, depending on a patient's factor VIII inhibitor status, was allowed per study protocol.

About HEMLIBRA

HEMLIBRA is a bispecific factor IXa- and factor X-directed antibody. It is designed to bring together factor IXa and factor X, proteins required to activate the natural coagulation cascade and restore the blood clotting process for hemophilia A patients. HEMLIBRA is a prophylactic (preventative) treatment that can be administered by an injection of a ready-to-use solution under the skin (subcutaneously) once weekly. HEMLIBRA was created by Chugai Pharmaceutical Co., Ltd. and is being co-developed by Chugai, Roche and Genentech.

HEMLIBRA U.S. Indication

HEMLIBRA is a prescription medicine used for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adults and children with hemophilia A with factor VIII inhibitors.

Important Safety Information

What is the most important safety information to know about HEMLIBRA?
HEMLIBRA increases the potential for blood to clot. Discontinue prophylactic use of bypassing agents the day before starting HEMLIBRA prophylaxis. Carefully follow the healthcare provider's instructions regarding when to use an on-demand bypassing agent, and the dose and schedule one should use. Cases of thrombotic microangiopathy and thrombotic events were reported when on average a cumulative amount of >100 U/kg/24 hours of activated prothrombin complex concentrate (aPCC) was administered for 24 hours or more to patients receiving HEMLIBRA prophylaxis.

HEMLIBRA may cause the following serious side effects when used with aPCC (FEIBA®), including:

• Thrombotic microangiopathy (TMA). This is a condition involving blood clots and injury to small blood vessels that may cause harm to one's kidneys, brain, and other organs. Patients should get medical help right away if they have any of the following signs or symptoms during or after treatment with HEMLIBRA:
- confusion
- weakness
- swelling of arms and legs
- yellowing of skin and eyes
- stomach (abdomen) or back pain
- nausea or vomiting
- feeling sick
- decreased urination

• Blood clots (thrombotic events). Blood clots may form in blood vessels in one's arm, leg, lung or head. Patients should get medical help right away if they have any of these signs or symptoms of blood clots during or after treatment with HEMLIBRA:

- swelling in arms or legs
- pain or redness in the arms or legs
- shortness of breath
- chest pain or tightness
- fast heart rate
- cough up blood
- feel faint
- headache
- numbness in the face
- eye pain or swelling
- trouble seeing

If aPCC (FEIBA®) is needed, patients should talk to their healthcare provider in case they feel they need more than 100 U/kg of aPCC (FEIBA®) total.

Before using HEMLIBRA, patients should tell their healthcare provider about all of their medical conditions, including if they:

• are pregnant or plan to become pregnant. It is not known if HEMLIBRA may harm an unborn baby. Females who are able to become pregnant should use birth control (contraception) during treatment with HEMLIBRA.
• are breastfeeding or plan to breastfeed. It is not known if HEMLIBRA passes into breast milk.

What should patients know about lab monitoring?

HEMLIBRA may interfere with laboratory tests that measure how well blood is clotting and may cause a false reading. Patients should talk to their healthcare provider about how this may affect their care.

The most common side effects of HEMLIBRA include: redness, tenderness, warmth, or itching at the site of injection; headache; and joint pain.

These are not all of the possible side effects of HEMLIBRA. Patients should call their doctor for medical advice about side effects.

Side effects may be reported to the FDA at 800-FDA-1088 or fda.gov/medwatch. Side effects may also be reported to Genentech at 888-835-2555.

Please see the HEMLIBRA full Prescribing Information and the Medication Guide, including Serious Side Effects, for more important safety information.

About hemophilia A

Hemophilia A is an inherited, serious disorder in which a person's blood does not clot properly, leading to uncontrolled and often spontaneous bleeding. Hemophilia affects around 20,000 people in the United States, with hemophilia A being the most common form and approximately 50-60 percent of people living with a severe form of the disorder.

People with hemophilia A either lack or do not have enough of a clotting protein called factor VIII. In a healthy person, when a bleed occurs, factor VIII brings together the clotting factors IXa and X, which is a critical step in the formation of a blood clot to help stop bleeding. Depending on the severity of their disorder, people with hemophilia A can bleed frequently, especially into their joints or muscles. These bleeds can present a significant health concern as they often cause pain and can lead to chronic swelling, deformity, reduced mobility and long-term joint damage.

A serious complication of treatment is the development of inhibitors to factor VIII replacement therapies. Inhibitors are antibodies developed by the body's immune system that bind to and block the efficacy of replacement factor VIII, making it difficult, if not impossible, to obtain a level of factor VIII sufficient to control bleeding.

About Genentech in hemophilia

In 1984, Genentech scientists were the first to clone recombinant factor VIII in response to the contaminated hemophilia blood supply crisis of the early 1980s. For more than 20 years, Genentech (gene.com/hemophilia) has been developing medicines to bring innovative treatment options to people with diseases of the blood within oncology, and in hemophilia A. Genentech is committed to improving treatment and care in the hemophilia community by delivering meaningful science and clinical expertise.

About Genentech

Founded more than 40 years ago, Genentech (gene.com) is a leading biotechnology company that discovers, develops, manufactures and commercializes medicines to treat patients with serious and life-threatening medical conditions. The company, a member of the Roche Group, has headquarters in South San Francisco, California.

May 14, 2018
Businesswire.com

Bioverativ Will Highlight Commitment to Transforming Hemophilia Care at WFH 2018 World Congress

Late-breaking presentation to highlight preliminary Phase 1/2a data on BIVV001, a novel and potentially transformative investigational factor therapy for people with hemophilia A

Recent data show quality-of-life improvements for patients treated prophylactically with ELOCTATE® and ALPROLIX®, the leading extended half-life hemophilia therapies

Bioverativ Inc., a Sanofi company dedicated to transforming the lives of people with rare blood disorders, will present data at the World Federation of Hemophilia (WFH) 2018 World Congress, in Glasgow, Scotland, May 20-24, demonstrating the company's ongoing commitment to transforming the standard of care for people with hemophilia.

"We are committed to making a meaningful, positive impact for people with hemophilia by improving patient outcomes and advancing cutting-edge research," said Joachim Fruebis, Senior Vice President of Development at Bioverativ. "We look forward to sharing data on BIVV001, an investigational and potentially transformative von Willebrand factor independent therapy that has been developed to further extend protection from bleeds with prophylactic dosing of once weekly or longer for people with hemophilia A."

BIVV001 (rFVIIIFc-VWF-XTEN) is the first factor VIII therapy in clinical development that is designed to overcome the half-life ceiling imposed by von Willebrand factor, and it builds on the half-life extension provided by Fc fusion technology. Preliminary pharmacokinetic and safety data from a Phase 1/2a study of BIVV001 will be presented as an oral, late-breaking presentation.

Bioverativ will also present real-world data demonstrating improvements in quality-of-life measures, like physical activity and joint pain, in patients treated prophylactically with ELOCTATE® [Antihemophilic Factor (Recombinant), Fc Fusion Protein] for hemophilia A and ALPROLIX® [Coagulation Factor IX (Recombinant), Fc Fusion Protein], for hemophilia B, when compared to short-acting factor treatments. ELOCTATE and ALPROLIX are the leading extended half-life hemophilia therapies with well-established safety and efficacy profiles and the most real-world experience.

Bioverativ will present a total of six presentations, including a joint presentation with Sobi™.

Bioverativ Presentations

- BIVV001 – a novel, weekly dosing, VWF-independent, extended half-life FVIII therapy: first-in-human safety, tolerability, and pharmacokinetics: Monday, May 21, 10:15 – 11:45. Late-breaker

- Comparisons in physical activity and bleed rate among severe hemophilia A and B patients on prophylactic treatment with rFVIIIFc/rFIXFc vs conventional rFVIII/rFIX: Monday, May 21, 16:30-18:00. Poster #50

- Impact of pain on health-related quality of life in persons with hemophilia from the Hemophilia Utilization Group Studies Part VI (HUGS VI): USA Experience: Tuesday, May 22, 16:30-18:00. Oral presentation

- Distribution of rFIXFc and FIX using in vivo PET imaging analysis in non-human primates: Monday, May 21, 14:15-15:15. Oral presentation

- Allosteric activation of Factor IXa by an antibody binding to the protease domain: Monday, May 21, 16:30-18:00. Poster #36

Bioverativ and Sobi Joint Presentation

- Economic impact of recombinant factor VIII Fc fusion protein (rFVIIIFc) compared to conventional factor VIII for immune tolerance induction (ITI) of Hemophilia A patients with inhibitors: Monday, May 21, 16:30-18:00. Poster #77

All oral and poster presentations can be accessed at the WFH 2018 World Congress website here.

In addition, Bioverativ and Sobi will co-host two scientific symposia at the congress.

- Advances in Haemophilia: Factor-Based Therapies and Long-Term Evidence versus New Treatment Modalities. Monday, May 21, 18:15 – 19:45, Hall 3, Scottish Event Campus. The session will be chaired by K. John Pasi, Professor, MD, PhD, Barts and the London School of Medicine and Dentistry, London and will be open to healthcare practitioners only.

- Inhibitor Eradication: Clinician and Patient Perspectives on Safety Considerations and Long-Term Outcomes. Tuesday, May 22, 12:30-14:00, Hall 2, Scottish Event Campus. The session will be chaired by Victor Blanchette, MD, MA, MB, Pediatric Thrombosis and Hemostasis Program, The Hospital for Sick Children, Toronto and is open to all congress attendees.

About BIVV001

BIVV001(rFVIIIFc-VWF-XTEN) is a novel, investigational factor VIII therapy that is designed to extend protection from bleeds with prophylaxis dosing of once weekly or longer for people with hemophilia A. It is currently the only therapy in clinical development designed to overcome the von Willebrand factor ceiling, which is believed to impose a half-life limitation on current factor VIII therapies. BIVV001 builds on the Fc fusion technology by adding a region of von Willebrand factor and XTEN polypeptides to potentially extend its time in circulation. BIVV001 was granted orphan drug designation by the Food and Drug Administration in August 2017.

About ELOCTATE®

ELOCTATE® [Antihemophilic Factor (Recombinant), Fc Fusion Protein] is a recombinant clotting factor therapy developed for hemophilia A using Fc fusion technology to prolong circulation in the body. It is engineered by fusing factor VIII to the Fc portion of immunoglobulin G subclass 1, or IgG1 (a protein commonly found in the body), enabling ELOCTATE to use a naturally occurring pathway to extend the time the therapy remains in the body. While Fc fusion technology has been used for more than 15 years, Bioverativ and Swedish Orphan Biovitrum AB (publ) (Sobi) have optimized the

technology and are the first companies to utilize it in the treatment of hemophilia. ELOCTATE is manufactured using a human cell line in an environment free of animal and human additives.

ELOCTATE is approved and marketed by Bioverativ in the United States, Japan and Canada. It is also approved in Australia, New Zealand, Brazil and other countries, and Bioverativ has marketing rights in these regions. It is also approved as Elocta® in the European Union, Switzerland, Iceland, Liechtenstein, Norway and other countries where it is marketed by Sobi.

As with any factor replacement therapy, allergic-type hypersensitivity reactions and development of inhibitors may occur in the treatment of hemophilia A. Inhibitor development has been observed with ELOCTATE, including in previously untreated patients. For more information, please see the full U.S. prescribing information for ELOCTATE. Note that the indication for previously untreated patients is not included in the EU Product Information for Elocta.

About ALPROLIX®

ALPROLIX® [Coagulation Factor IX (Recombinant), Fc Fusion Protein] is a recombinant clotting factor therapy developed for hemophilia B using Fc fusion technology to prolong circulation in the body. It is engineered by fusing factor IX to the Fc portion of immunoglobulin G subclass 1, or IgG1 (a protein commonly found in the body), enabling ALPROLIX to use a naturally occurring pathway to extend the time the therapy remains in the body (half-life). While Fc fusion technology has been used for more than 15 years, Bioverativ and Sobi have optimized the technology and are the first companies to utilize it in the treatment of hemophilia. ALPROLIX is manufactured using a human cell line in an environment free of animal and human additives.

ALPROLIX is approved and marketed by Bioverativ for the treatment of hemophilia B in the United States, Japan and Canada. It is also approved in Australia, New Zealand, Brazil and other countries, and Bioverativ has marketing rights in these regions. It is also authorized in the European Union, Iceland, Liechtenstein, Norway and Switzerland, where it is marketed by Sobi.

Allergic-type hypersensitivity reactions and development of inhibitors have been observed with ALPROLIX in the treatment of hemophilia B, including in previously-untreated patients. For more information, please see the full U.S. prescribing information for ALPROLIX. Note that the indication for previously-untreated patients is not included in the EU Product Information.

About Hemophilia A and B

Hemophilia is a rare, genetic disorder in which the ability of a person's blood to clot is impaired. Hemophilia A occurs in about one in 5,000 male births annually, and more rarely in females. Hemophilia B occurs in about one in 25,000 male births annually, and more rarely in females. The World Federation of Hemophilia estimates that approximately 180,000 people are currently diagnosed with hemophilia A and B worldwide.1

People with hemophilia A or B experience bleeding episodes that can cause pain, irreversible joint damage and life-threatening hemorrhages. Prophylactic infusions of factor VIII or IX can temporarily replace the clotting factors that are needed to control bleeding and prevent new bleeding episodes.2 The World Federation of Hemophilia recommends prophylaxis as the optimal therapy as it can prevent bleedings and joint destruction.3

About Bioverativ, a Sanofi company

Bioverativ, a Sanofi company, is dedicated to transforming the lives of people with hemophilia and other rare blood disorders through world-class research, development, and commercialization of innovative therapies. Bioverativ is committed to actively working with the blood disorders community, and its hemophilia therapies when launched represented the first major advancements in hemophilia treatment in more than two decades. For more information, visit www.bioverativ.com or follow @bioverativ on Twitter.

About the Bioverativ and Sobi Collaboration

Bioverativ and Sobi collaborate on the development and commercialization of ALPROLIX and ELOCTATE®/Elocta® [Antihemophilic Factor (Recombinant), Fc Fusion Protein]. Bioverativ has final development and commercialization rights in North America and all other regions in the world excluding the Sobi territory, and has manufacturing responsibility for ELOCTATE and ALPROLIX. Sobi has final development and commercialization rights in the Sobi territory (essentially Europe, North Africa, Russia and most Middle Eastern markets). In September 2014, Sobi elected to add the rFVIIIFc-VWF-XTEN fusion molecule for the potential treatment of hemophilia A to its collaboration agreement with Bioverativ.

May 14, 2018
Raredr.com

Novel Gene Editing Treatment Strategy for Hemophilia B and Pediatric MMA

By Krista Rossi

This week at the annual meeting of the American Society of Gene & Cell Therapy (ASGCT) in Chicago from May 16-19, LogicBio Therapeutics Inc will present data regarding a number of abstracts, such as presentations on gene editing technologies in the rare diseases, hemophilia B and Methylmalonic Acidemia (MMA).

"Promoterless Targeting without Nucleases of Hyperactive Factor IX Corrects the Bleeding Diathesis in Hemophilia B Mice" will exhibit data from the study led by Adi Barzel, PhD, in which GeneRide AAV-based site-specific genome editing technology. was used with the intention to provide life-long benefits from a single injection neonatal phase in multiple disease models.

By being nucleus-free, specific hurdles, such as nuclease delivery, immunogenicity, off target cleavage, and on-target mutagenesis are avoided.

Additionally, the risk of oncogene activation by rare off-target integration is reduced since GeneRide vectors are promoterless and targeted by natural, error-free homologous recombinations (HRs), which are recombined into the Albumin locus. Essentially, the robust hepatic Albumin expression via a 2A peptide is linked to the expression of the therapeutic gene.

In the treatment of the hemophilia B mice, adult and neonatal mice were injected with an AAV-DJ GeneRide vector coding for a hyperactive variant of human F9. In both groups of mice, disease improvement was demonstrated at doses as low as 1.5E12 VG/kg. Treated mice also showed similarities in clotting time when compared to wild mice. The vectors were designed with synthetic mouse haplotypes baring analogous mutations; it was found that GeneRide was largely unaffected by this haplotype mismatch.

The study concluded that there is a need for either vector-borne promoters or the use of nucleases to induce integration and allow for safe and effective gene targeting for the improvement of hemophilia B in both infants and adults.

Additionally, "Promoterless Targeting without Nucleases of Hyperactive Factor IX Corrects the Bleeding Diathesis in Hemophilia B Mice" and "Generide™, a Novel AAV Strategy to Treat Pediatric Patients with Methylmalonic Acidemia" will provide data from the study led by Jing Liao, which utilized the same GeneRide technology, allowing the expansion of the utility of rAAV vectors to treat childhood diseases that require early intervention.

The study used a GeneRide vector to save neonatal murine models of MMA; the observations were then translated from the rodent model to human cells. A human specific GeneRide vector containing the human MUT coding and homology arm sequences was engineered in order to establish HR-mediated integration at the human ALBlocus. The site-specific integration and the consequent MUT expression was observed after application of the vector on both human cell lines and primary hepatocytes.

Based off of the study's results, it was concluded that GeneRide is able to mediate efficient genome editing of a therapeutic transgene into the ALB locus in human primary hepatocytes. In addition, it is paving the path for developing novel therapeutics for MMA patients as well as for other inborn metabolism errors.

May 14, 2018
Jsonline.com (Milwaukee)

Joan C. Gill Remembered as Advocate for Her Patients with Bleeding Disorders

By Don Behm

Joan Cox Gill was a doctor for children with hemophilia, a researcher of bleeding disorders who shed an early light on AIDS, a passionate advocate for her patients, lover of the arts and a master of crossword puzzles.

Gill died May 9 after a yearlong battle with cancer. She was 74.

Gill and her research team from the Medical College of Wisconsin were the first to identify immune abnormalities in hemophilia patients in the early 1980s that subsequently were recognized as AIDS, the immune deficiency disease caused by infection with HIV.

She led the clinical work on the first grant funded by the National Institutes of Health on AIDS in hemophilia, according to the Hemostasis and Thrombosis Research Society.

She was named one of the best doctors in America by her peers in pediatric hematology every year since 1996 and gained the recognition again this year, said her daughter, Gretchen Gill.

"She started medical school when I was in first grade," her daughter said. She was a single parent as she raised her daughter and worked to get through medical school. Gill graduated from the Medical College of Wisconsin in 1976.

"She paved the way for other women to follow," her daughter said. As a respected physician and researcher, she still found time to mentor other young female medical students and faculty.

"By 1978, she was deeply committed to a fellowship in pediatric hematology and began a lifelong love affair with the science and clinical management of bleeding and clotting disorders," said Lorilyn Jacobsen-Tews, executive director of the Hemostasis and Thrombosis Research Society.

"A favorite with young patients and their families, Joan's professional demeanor was soft-spoken and kind," Jacobsen-Tews said in a memorial tribute to Gill, one of the founders of the society in 1989.

In addition to hemophilia research, "her work was equally important in the diagnosis and treatment of von Willebrand Disease," Jacobsen-Tews said. That disease is a bleeding disorder caused by a deficiency of a protein that helps blood to clot.

Hemophilia is a lifelong disorder and Gill had patients who were with her over the course of a career spanning more than 30 years, her daughter said.

"She educated her patients about how to treat their disorders and that empowered the patients and their families," her daughter said.

The Hemostasis and Thrombosis Research Society has named an annual award for outstanding service in her honor.

In 2014, the Great Lakes Hemophilia Foundation put her name on the children's health lodge at its Camp Klotty Pine in Wautoma.

St. Norbert College awarded her the Distinguished Alumni Achievement Award in Natural Sciences in 2017. Gill graduated from the college in 1965.

At the time of her 2013 announcement that she would begin the gradual process of retirement, Gill was a professor of pediatrics, medicine and epidemiology at the Medical College of Wisconsin, medical director of the Hemophilia and Bleeding Disorders Center at Children's Hospital of Wisconsin, and an investigator and medical director of the Comprehensive Center for Bleeding Disorders at the BloodCenter of Wisconsin. She published more than 100 peer-reviewed articles, editorials and research abstracts.

Mother and daughter had a shared interest in the arts. "She supported my earlier performing career," said Gretchen Gill, who sang with the Milwaukee Symphony Orchestra chorus and performed at Renaissance Faires before returning to school for her own doctoral degree.

And mother and daughter were founding board members of RESCU (Renaissance Entertainers Services and Crafters United) Foundation.

"She was just ridiculous in putting puzzles together and she was the master of crossword puzzles," her daughter said.

Gill also enjoyed gardening at her home in Greendale.

In addition to her daughter, Gill is survived by two sisters and three brothers, ex-husband Gordon Gill of Sarasota, Fla., and nieces and nephews.

A celebration of her life will be held May 20 at Boerner Botanical Gardens in Hales Corners beginning with a 1 p.m. social gathering. A memorial service follows at 2:30 p.m.

May 15, 2018
Raredr.com

First Hemophilia A Patient in Phase 1/2 Study Dosed with Valoctocogene Roxaparvovec

By Krista Rossi

This morning, BioMarin Pharmaceutical Inc announced that the first patient has been dosed in its phase 1/2 study (BMN 270-203) that is evaluating the investigational gene therapy, valoctocogene roxaparvovec, in severe hemophilia A patients with pre-existing AAV5 antibodies.

Valoctocogene roxaparvovec is an AAV-factor VIII vector. In hemophilia A mouse models, valoctocogene roxaparvovec restored factor VIII plasma concentrations to levels deemed to be adequate for normal clotting in humans.
"Administration of valoctocogene roxaparvovec to this first patient seropositive for the AAV5 capsid is an important next step in our plan to expand the number and types of severe hemophilia A patients who may benefit from gene therapy and have antibodies to the vector," commented Hank Fuchs, MD, President, Worldwide Research and Development at BioMarin in a recent statement.

"The goal with this study is to determine if patients that already have antibodies to AAV5 can be effectively treated with valoctocogene roxaparvovec. Our objective is to develop a therapy with the potential to eliminate the need for chronic treatment in severe hemophilia A across all patient sub-groups," he added.

The study is evaluating the safety and efficacy of valoctocogene roxaparvovec in AAV5+ hemophilia A patients in an open-label, single-arm, titer-escalation trial. Eligibility criteria includes being an adult male with hemophilia A who has pre-existing AAV5 antibodies. Subjects are being enrolled into 2 titer cohorts that encompass the range of observed AAV5 antibody titer levels generally observed in the hemophilia population. They are also being treated with the 6e13 vg/kg dose of valoctocogene roxaparvovec.

There are 3 main primary outcome measures for the trial. First, investigators want to assess the impact of valoctocogene roxaparvovec, following a Patient Reported Outcome (PRO) questionnaire, Haemo-QoL-A, which is being measured in a time frame of 52 weeks. The questionnaire is a hemophilia-specific, health-related quality of life assessment for adults that measures on a scale of 0 to 5 with the lower value representing a better outcome.

Investigators also aim to evaluate the impact of valoctocogene roxaparvovec, according to the PRO questionnaire, EQ-5D-5L, which is also being measured in a time frame of 52 weeks. The general questionnaire measures health statuses on a scale of 0 to 100, with the higher value representing a better outcome.

The third outcome measure for the trial to determine the impact of valoctocogene roxaparvovec following PRO according to the Haemophilia Activities List (HAL), which is being measured in a time frame of 5 years. The questionnaire evaluates the difficulty of several activities for people with hemophilia A.

The primary endpoint of the study is to evaluate the drug's safety in the participating population. Secondary endpoints include assessments regarding FVIII activity levels, the frequency of required FVIII replacement therapies, and the number of bleeding episodes requiring treatment after therapy.

Additionally, the 6e13 vg/kg dose of valoctocogene roxaparvove is being evaluated in the GENEr8-1 study while a second valoctocogene roxaparvove dose of 4e13 vg/kg is being evaluated in the GENEr8-2 study. Both GENEr8-1 and GENEr8-2 are Phase 3 studies involving patients without pre-existing AAV5 antibodies.

Previously, the US Food and Drug Administration (FDA) granted Breakthrough Therapy Designation to valoctocogene roxaparvove. The European Medicines Agency (EMA) has also granted valoctocogene roxaparvovec access to its Priority Medicines (PRIME) regulatory initiative. Orphan drug designation has been granted by both the FDA and EMA for the treatment of severe hemophilia A.