Factor Nine News

The Coalition for Hemophilia B Fall 2011

Topics in Hemophilia

Save the Date!

5th Annual Fundraising Dinner

Friday, March 16, 2012

Live entertainment and raffle drawings!
Monies raised will benefit the William N. Drohan Scholarship Fund in addition to our Educational Programs.

Water's Edge Restaurant

401 44th Drive; Long Island City, New York; 718-482-0033
(2.6 miles away just over the Queens midtown tunnel.
An 8 minute ride from the Grand Hyatt Hotel)

See details online at www.coalitionforhemophiliab.org

6th Annual Symposium

Saturday, March 17, 2012

Educational sessions, guest speakers,
exhibitor booths and more!

Grand Hyatt New York

109 East 42nd Street; New York, New York
Park Avenue at Grand Central Station
Call for special room rate of $195 per night: 646-213-6817

Registration and Exhibit Registration Forms available online at www.coalitionforhemophiliab.org

FACTOR FORWARD

We are Biogen Idec Hemophilia,

and we're exploring ways to make factor last longer. Backed by 30 years of biotechnology leadership, our goal is to make progress for the hemophilia community. As we blaze a new trail of scientific discovery toward long-lasting factor, we're also creating programs and resources with the potential to change lives. **Join us as we move hemophilia treatment forward.**

Sign up for updates on our progress.

www.BiogenIdecHemophilia.com

We are currently enrolling patients in our clinical trials.

biogen idec
HEMOPHILIA

New Products for Treatment of Hemophilia B

By Dr. David Clark

After a period in the late 1990s and early 2000s during which there was little action on new treatments for hemophilia B, the last several years have seen a huge increase in development of new products. The following are brief snapshots of the known efforts currently in progress. There may even be more since some companies are fairly secretive about their plans until they begin clinical studies.

Remember that no product is definite until it is actually licensed and on the market. Products have stalled during the licensure process, and a few have even been licensed but never produced because of unforeseen manufacturing issues or company financial troubles. The licensure process in the U.S. can take two years or more, although a few happen more quickly.

Note that in several cases theoretical advantages or disadvantages of the various technologies behind the products are mentioned. However, these are only theoretical until a product is finally in use in a large number of patients and its actual performance is seen. Researchers are always surprised by "sure things" that don't work out, and by "that'll never work" products that do.

Matrix Health

Dedicated to Making a Difference!
in the lives of people with Hemophilia,
von Willebrand Disease and other Bleeding Disorders

A specialized pharmacy with homecare services that go beyond the ordinary...

Experience the Difference!

877-337-3002
www.matrixhealthgroup.com

Near Term Factor IX Products

There are two new recombinant factor IX products that will probably be available in the U.S. in the next few years. Inspiration Biopharmaceuticals has completed European clinical trials and submitted a European license application for their recombinant factor IX product. Phase 3 clinical trials for U.S. licensure are still ongoing. Inspiration's product, currently termed IB1001, could provide a second recombinant product for the U.S. market. Inspiration's patented technologies provide more efficient production of recombinant proteins, which they expect will reduce product cost and increase availability. With lower-cost products, they hope to be able to serve worldwide markets that cannot afford the recombinant or even plasma-derived products currently available.

Biogen Idec has a longer-acting recombinant factor IX in Phase 3 clinical trials that are expected to be completed in 2012. The product, currently termed rFIXFc, is a recombinant factor IX molecule linked to the Fc portion of a human antibody molecule. This gives it a longer lifetime in the bloodstream, which should reduce the frequency of infusions for prophylactic treatment.

Conventional Factor IX Products

Baxter is developing a recombinant factor IX product, BAX 326, which is currently in Phase 3 studies. In spite of a history as one of the first manufacturers of factor IX concentrates, Baxter has been largely out of the factor IX market in recent years, but they now have several factor IX products under study, as well as products for hemophilia A, von Willebrand Disease and inhibitor treatment.

GTC Biotherapeutics is developing a recombinant factor IX produced in the milk of transgenic goats. Transgenic animals can produce large quantities of proteins, thus potentially reducing the overall cost of production. GTC also manufactures ATryn, a recombinant antithrombin product that is the first transgenic product licensed in the U.S.

Octapharma is developing a recombinant factor IX in Europe. Few additional details are available. They are also developing a recombinant factor VIII product that would be the first product ever made in a human cell line. That should give it identical post-translational modifications as native factor VIII. If the same technology were applied to recombinant factor IX, that should resolve the issues seen, for instance, with the lower recovery and shortened half-life of BeneFIX.

Pharmstandard, a Russian company, is developing a recombinant factor IX that is reportedly in clinical studies, but few details are available.

Factor IX Products with Modified Activities

Catalyst Biosciences is investigating modified recombinant factor IX molecules that have higher activities, longer half-lives and/or other improved features. Their Alterase technology produces large groups of modified proteins that can then be screened to select ones with improved properties. They are also working on a modified recombinant factor VIIa product with Pfizer and a recombinant factor X.

AlphaNine® SD

Coagulation Factor IX (Human)

Packaged with Mix2Vial® Filter Transfer Set

Available in the following potencies and color coded assay ranges

Potency	Diluent Size
500 IU FIX Range	10 mL
1000 IU FIX Range	10 mL
1500 IU FIX Range	10 mL

For further information call: **Grifols USA, LLC** Professional Service: 888-GRIFOLS (888 474 3657)
Customer Service: 888 325 8579; Fax: 323 441 7968 **www.grifols.com**

Grifols Biologicals Inc.
5555 Valley Boulevard, Los Angeles, California 90032, USA

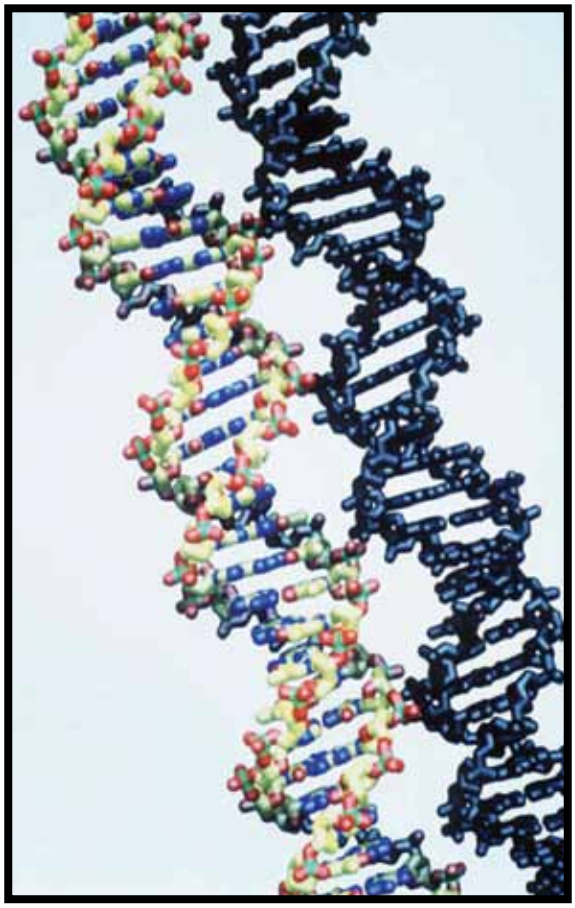
GRIFOLS

A9U14-17-US-10

Longer-Acting Factor IX Products

Baxter is developing a longer-acting factor IX in collaboration with Nektar Therapeutics. This will be a PEGylated product in which the factor IX molecule is coupled to polyethylene glycol (PEG) chains to increase its lifetime in the circulation.

Baxter is also investigating another method to increase the half-life of factor IX in collaboration with Xenetic Biosciences (formerly Lipoxen) using their PolyXen technology. PolyXen links polysialic acid molecules to proteins like factor IX to extend the half life. Many proteins have side chains that end with a sialic acid group, and when the sialic acid breaks off, the liver knows that the molecule is "old" and removes it from circulation. Having a long chain of sialic acids attached to a molecule would increase its lifetime because when one breaks off, another is still there at the end of the chain.



In addition to their FIXFc product mentioned above, Biogen Idec is also collaborating with Amunix to use their XTEN method to fuse proteins like factor IX to long unstructured hydrophilic amino acid sequences as another method of extending the half life.

CSL-Behring is developing a recombinant factor IX linked to albumin to increase its half-life in circulation. Termed CSL654, it is currently starting Phase 1 clinical studies. They are also working on albumin-linked factor VIIa and factor VIII products.

Novo Nordisk is developing a longer-acting recombinant factor IX product, which is currently in Phase 3 clinical studies. The product, termed NN7999, is glycopegylated. The glycopegylation technology was originally developed by Neose Technologies, which has since gone out of business. It specifically attaches the PEG molecules to the side chains of a protein where they are less likely to interfere with the activity of the protein than in conventional pegylation, which attaches the PEG to amino acids on the main backbone of the protein.

Prolor Biotech is developing a longer-acting recombinant product, Factor IX-CTP, in which factor IX is linked to the CTP portion of human chorionic gonadotropin (hCG) hormone. The CTP group gives hCG a longer half-life in circulation and has been shown to do the same for factor IX in pre-clinical studies in mice.
Wyeth had been working with Nautilus Biotech to develop longer-acting recombinant factor IX proteins, but it is not clear whether that has continued under Pfizer.

Alternative Treatments for Hemophilia

There are a number of treatments under study for both hemophilia A and B that do not involve factor VIII or factor IX. Many activate the clotting system in other ways, somewhat analogous to activation of the clotting system by NovoSeven or FEIBA, which are used to treat hemophilia patients with inhibitors. Many of these might work for both major types of hemophilia.

One challenge in any method of this kind is to maintain control of the clotting process to prevent thrombosis—too much clotting and/or clotting in the wrong place. As mentioned in the accompanying article in this issue, factor IX complex products are no longer used for hemophilia treatment because they

Coram Hemophilia Services

Together Forward

A Customized-Care Approach For **Managing Bleeding Disorders**

- **Over 30 years of experience**
- **In-home training and education**
- **24/7 clinical support**
- **Experienced hemophilia nurse educators**
- **Consumer advocacy program**
- **College scholarship program**
- **Spanish language services**
- **Travel support from our nationwide locations**
- ***96% Patient Satisfaction***

2010 Press Ganey, Inc. Independent Survey Results

Call or click today!

888.699.7440 | coramhemophilia.com

CORAM
specialty infusion services
An Apria Healthcare Company

have a tendency to produce serious sometimes-fatal thrombosis.

One other product below aims to overcome certain gene mutations that prevent factor IX and other proteins from being produced correctly.

Alnylam Pharmaceuticals uses a method called RNA interference (RNAi) to reduce the amounts of various proteins that are produced by cells. They have recently begun a program to look at reducing levels of Protein C, an anticoagulant that inhibits thrombin, and thus inhibits clotting.

Baxter is continuing research on a TFPI inhibitor that was started by Archemix, a company whose hemophilia technology they bought in 2010. The product, BAX 499, currently in Phase 1 clinical trials, is an inhibitor of an inhibitor. Tissue Factor Pathway Inhibitor (TFPI) regulates the clotting process by inhibiting part of the clotting system. BAX 499, which may be a subcutaneous (under the skin) rather than an intravenous product, would inhibit TFPI and thus increasing activation of clotting.

Catalyst Biosciences is investigating modified recombinant factor X and factor Xa (activated factor X) molecules that could be used to bypass the factor IX step in the coagulation cascade. Normal factor X is thrombogenic at high doses, but the modified versions appear to not have that problem.

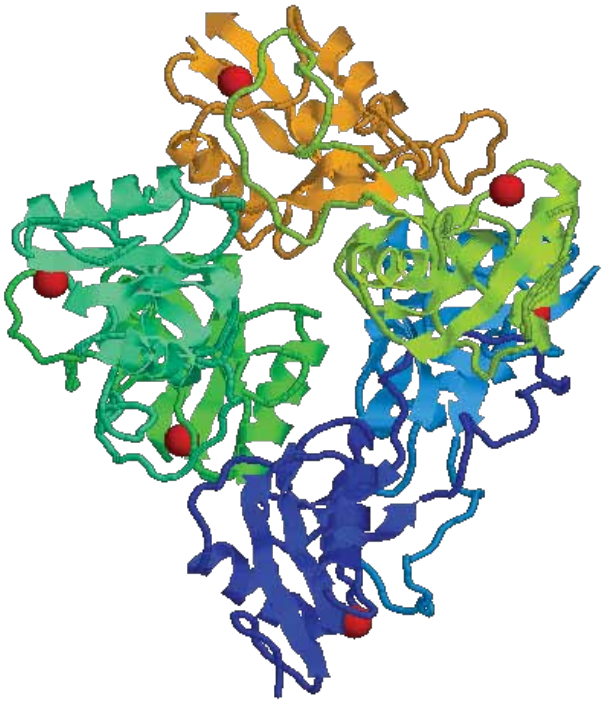
MediciNova, who acquired Avigen, has apparently put on hold further development of Avigen's AV513, a heparin-like molecule that promotes clotting activity.

Novo Nordisk is also working on a TFPI inhibitor, NN7415, which is in Phase 1 clinical studies. They were originally interested in this because TFPI inhibits the factor VII-tissue factor step in the coagulation cascade and thus decreases the effectiveness of NovoSeven used to treat inhibitors.

PAION is in Phase 1 clinical studies with Solulin, a modified thrombomodulin product. Thrombomodulin stabilizes clots and thus is thought to be able to reduce the amount of factor VIII or factor IX needed to prevent bleeding. It may be able to reduce the frequency of prophylactic injections.

Pfizer is also working on a recombinant factor Xa as a general hemostatic agent.

Thrombotargets is developing TT-173, a topical drug for treating external bleeding in patients with many types of bleeding disorders, including hemophilia. Although external bleeding is not a major issue in hemophilia treatment, TT-173 may be useful in some cases.



PTC Therapeutics is collaborating with Genzyme to develop Ataluren, an oral drug that gives cells the ability to translate genes containing certain nonsense mutations that produce a premature stop signal. This could restore the ability of hemophilia patients who have this type of gene mutation to produce functional factor VIII or IX. Ataluren had shown promising results in early clinical studies in patients with certain types of muscular dystrophy and cystic fibrosis caused by similar mutations. However, a later Phase 2b study on muscular dystrophy with a larger number of patients produced disappointing results. They had also started a Phase 2b study with hemophilia A and B, which has been suspended while they go back to the drawing board to figure out what went wrong.

Hemophilia Health Services

...for the human factor®

BEYOND PHARMACY SERVICES.

We believe pharmacy services reach beyond our ability to accurately fill prescriptions. That's why we provide dedicated care teams to help you manage your therapy from the time medication arrives on your doorstep. Our registered nurses can walk you through the infusion process, including how to self-infuse, so you can become empowered in your care. A personal touch from people who know hemophilia—that's just one example of something we like to call the human factor.

1 800 800-6606

accredo®

Learn.
Explore.
Connect With Our Hemophilia Community on **Facebook**.

Our Hemophilia Community

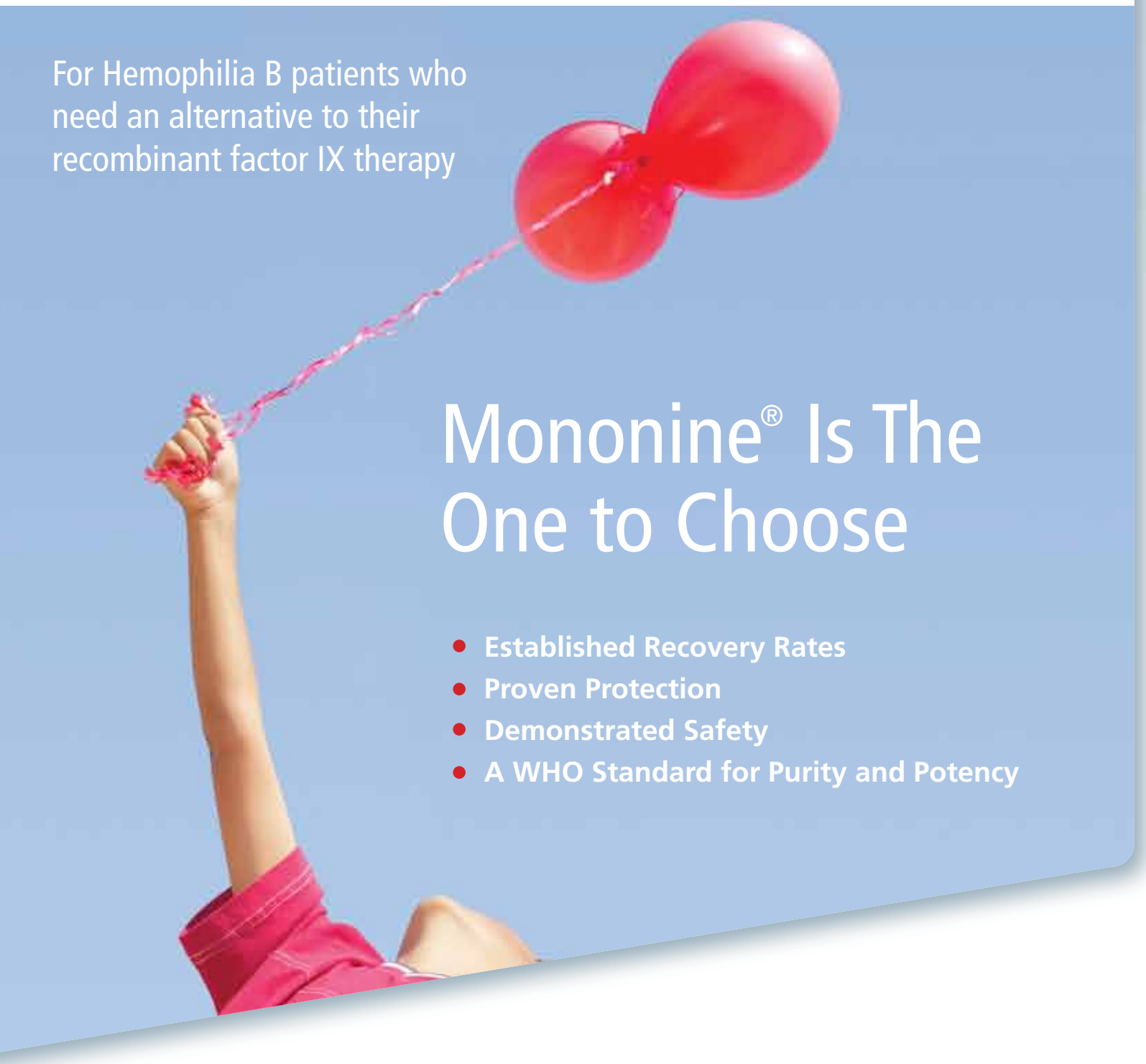
Find us on **Facebook.com/OurHemophiliaCommunity**

Printed in USA/March 2011

Pfizer

Biotherapies for Life™ **CSL Behring**

For Hemophilia B patients who need an alternative to their recombinant factor IX therapy



Mononine® Is The One to Choose

- **Established Recovery Rates**
- **Proven Protection**
- **Demonstrated Safety**
- **A WHO Standard for Purity and Potency**

Important Safety Information

Mononine® is contraindicated in patients with known hypersensitivity to mouse protein.

The following adverse reactions may be observed after administration: headache, fever, chills, flushing, nausea, vomiting, tingling, lethargy, hives, stinging or burning at the infusion site, or other manifestations of allergic reactions, including anaphylaxis.

Mononine® is derived from human plasma. As with all plasma-derived products, the risk of transmission of infectious agents, including viruses and, theoretically, the Creutzfeldt-Jakob disease (CJD) agent, cannot be completely eliminated.

Please see brief summary of prescribing information on adjacent page.

Mononine®
MONOCLONAL ANTIBODY PURIFIED
Coagulation Factor IX (Human)

Promising Results in Gene Therapy Trial for Hemophilia B

By Dr. David Clark

Results from the ongoing clinical trial of gene therapy for hemophilia B were simultaneously presented at the American Society of Hematology meeting in San Diego and published in the New England Journal of Medicine the weekend of December 10. The results, representing the work of researchers from across the U.S. and United Kingdom, potentially represent a real breakthrough in the continuing quest to overcome the genetic mutations causing hemophilia B.

Six severe (less than 1% of normal) hemophilia B patients were treated by intravenously infusing low, medium or high doses of a modified adeno-associated virus (AAV) containing the gene for normal human factor IX. The patients are male with ages ranging from 27 to 64. Two patients had a complete lack of factor IX protein and four had some factor IX, but less than 1% prior to the treatment.

The patient's factor IX levels increased to 2 - 11% of normal and have remained steady at those levels for at least six months, one for more than 15 months. Four of the patients have been able to discontinue prophylaxis without bleeding, and the other two have been able to increase the length of time between prophylactic infusions. The two patients still on partial prophylaxis both have severe pre-existing joint disease, which may require higher factor IX levels for treatment.

The therapy was generally well tolerated, although both high-dose patients had temporary evidence of liver injury, which was treated with short courses of steroids. None of the patients had evidence of inhibitor formation after treatment.

One of the problems in earlier studies of factor IX gene therapy was that many people already have antibodies to the type 2 AAV (AAV2) that was used. This resulted in an immune response against the AAV2-factor IX treatment and apparently prevented long-term expression of factor IX. This study used a different type of AAV, AAV8, to which fewer humans have been

exposed and already have antibodies. In addition, only patients who had no existing antibodies to AAV8 were used in the study. Another innovation in this study was to use a factor IX gene that had been optimized to provide a higher level of production of factor IX protein.

Although promising, there is still a long way to go. One mystery that has to be solved is the varying response from patient to patient. Also, until a larger number of patients has been treated and observed for longer periods of time, the true safety and effectiveness will not be known. The treatment is estimated to be about $30,000 per patient.

The article is online at http://www.nejm.org/doi/full/10.1056/NEJMoa1108046 along with an editorial "Merry Christmas for Patients with Hemophilia B" at http://www.nejm.org/doi/full/10.1056/NEJMe1111138.

Novo Nordisk is helping people with inhibitors realize their dreams.

changing possibilities in hemophilia™

Novo Nordisk offers financial, educational, and community support programs to people with hemophilia A or B with inhibitors so they can live more normal lives.

Find out more about how you can change your possibilities by calling **1-877-668-6777** today!

For more information, please visit **ChangingPossibilities-US.com**.

Novo Nordisk Inc., 100 College Road West, Princeton, New Jersey 08540 U.S.A.
 136847A December 2008

novo nordisk®

CVS CAREMARK Specialty Pharmacy

Trust the Experience

At CVS Caremark, we've been helping families like yours for over 30 years. Our caring patient support helps ensure safety, convenient access and satisfaction.

Jane Faghan, BS, M.Ed
Client Relations Executive
1-508-638-8162
jane.faghan@caremark.com

CVS Caremark Specialty Pharmacy
Milford, MA
1-800-950-2688

www.cvscaremarkspecialtyrx.com

Save the Date!

Hemophilia Federation of America Annual Symposium

March 29-31, 2012 Santa Clara, California

The Coalition for Hemophilia B Family Meeting

Please visit the Coalition for Hemophilia B Booth
for information regarding the Factor Nine Family Meeting.

In conjunction with the HFA Annual Symposium
Santa Clara, California

We look forward to seeing you!

COMING SOON!

The Coalition for Hemophilia B will soon be on FACEBOOK!

William N. Drohan Scholarship

The William N. Drohan Scholarship application form for 2012 is now available on our website under scholarships: www.coalitionforhemophiliab.org.
The deadline for submissions is March 1, 2012.

Reminder

The Factor Nine Group moderated by Jill Lathrop is now located on Facebook search Hemophilia B Group

For back issues of **Factor Nine Newsletter** or for more information on research, please call or write to:
Kim Phelan; 825 Third Avenue, Suite 226; New York, New York 10022; Telephone (212) 520-8272
Telefax (212)520-8501; E-mail: hemob@ix.netcom.com Website: www.coalitionforhemophiliab.org