NHF News Briefs

January 5 – January 11, 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.

January 5, 2018
Fiercepharma.com

Roche Makes Headway in Hemophilia as U.K. Grants Early Access to Hemlibra

By Arlene Weintraub

The race to develop better treatments for the clotting disorder hemophilia A is getting more heated by the day, with the list of companies vying for a market-leading position including such big names as Roche, Spark, Shire and Alnylam. Roche picked up FDA approval in November for its drug Hemlibra (emicizumab)—and now it has taken a big step forward in Europe, where the product is under regulatory review.

The Medicines and Healthcare Regulatory Agency in the U.K. granted a positive opinion under its early-access program for Hemlibra to prevent bleeding episodes in patients with hemophilia A. The early-access opinions are meant to provide guidance to physicians in the U.K. who might want to prescribe drugs before they obtain regulatory approval there.

The agency's opinion was based on data from the company's phase 3 program, Haven, according to a public report (PDF) it issued. It also cited the high unmet need for more effective treatments for hemophilia A in the U.K. The disease is often treated with drugs that replace coagulation factor VIII (FVIII), but these treatments fail in up to 40% of patients, according to the agency. Patients who develop FVIII inhibitors can be treated with so-called bypassing agents, but they have to be administered frequently and are often ineffective.

Expectations for Hemlibra have been high ever since the FDA gave Roche breakthrough therapy designation for the drug in 2015, but the path to approval has been anything but easy. Data from the pivotal trial showed an 87% reduction in bleeding episodes. But there were some non-responders, and some patients suffered thromboembolic side effects. Although the FDA approved the drug a full three months earlier than expected, it required Roche to include a boxed warning on the label explaining that Hemlibra can cause dangerous blood clots when used with bypassing agents, specifically Shire's Feiba.

Roche had cited repeated dosing of bypassing agents like Feiba as the cause of the adverse events seen in its phase 3 program, raising the hackles of Shire, which obtained a preliminary injunction last year meant to stop Roche from making "inaccurate and misleading" statements. Shire is looking to protect its own hemophilia franchise, which includes treatments it picked up in 2016 in a $32 billion acquisition of Baxalta. In September, the Court of Hamburg reviewed evidence from both companies and concluded Roche had not acted inappropriately. Shire withdrew its complaint.

But Shire is far from the only competitor Roche will need to contend with as it moves forward in hemophilia. RNAi specialist Alnylam restarted its trials of fitusiran to treat hemophilia A in December after the FDA lifted a clinical hold so the company could develop a strategy to improve safety monitoring. Spark Therapeutics—which recently gained acclaim for winning FDA approval of its gene therapy to treat a rare form of blindness—is in phase 2 trials of a gene therapy treatment for hemophilia A. And California-based BioMarin Pharmaceutical announced in December that it has enrolled the first patient in a phase 3 trial of its gene therapy to treat the disease.

Still, investors' hopes remain high for Roche’s Hemlibra. Analysts on average expect the product to eventually be pulling in $2 billion in sales per year. Analysts at Jefferies have been even more optimistic, projecting an ambitious $5 billion a year for the product.

January 5, 2018
Hemophilianewstoday.com

Software to Help Personalize ADVATE Treatment of Hemophilia A Receives FDA Clearance

By Jose Marques Lopes, PhD

A web-based software to help personalize dosing regimens for some hemophilia A patients has received marketing clearance from the U.S. Food and Drug Administration (FDA).

The 510(k) marketing clearance was granted to Shire, the developer, following its submission of a "premarket notification," which is necessary if a new device is intended for commercial distribution, or if an already existing device will be significantly modified so that its safety or effectiveness could be affected.

The software, called myPKFiT, will assess prophylactic (preventive) dosing regimens for hemophilia A patients treated with ADVATE, a recombinant factor VIII (FVIII) product. Shire plans availability of myPKFIT for this spring.

myPKFIT is the first and only FDA-cleared software helping healthcare professionals estimate key pharmacological data of ADVATE-treated hemophilia A patients age 16 and older and weighing at least 45 kilograms.

The new tool enables estimation of a patient's individual pharmacokinetic (PK) profile (drug response in the body) with as few as two measurable blood samples; that is compared with the current nine to 11 as recommended by the International Society on Thrombosis and Haemostasis (ISTH).

Using PK data and additional patient information (age, body weight, and FVIII clotting activity measurements), healthcare professionals will be able to evaluate various prophylaxis regimens to create a personalized ADVATE treatment dose and schedule to maintain appropriate FVIII activity levels.

"The FDA clearance of myPKFiT for ADVATE marks an important milestone in the personalization of hemophilia care, building on Shire's strong commitment to continued innovation in hematology," Howard B. Mayer, MD, ad-interim global head of research and development at Shire, said in a press release.

"We know patients have complex needs and treatment goals that cannot be met with a one-size-fits-all approach," said Michael Denne, head of U.S. Hematology Medical Affairs at Shire. "myPKFiT for ADVATE offers a personalized approach to hemophilia care that allows healthcare professionals to consider their patients' individual needs and to educate them on their personal PK profiles."

Hemophilia primarily affects males, with an incidence of one in 5,000 male births in the U.S. Hemophilia A is the most common type of the condition. Lower amounts of VIII in the blood are associated with aggravated disease severity. Of note, more than half of hemophilia A patients have the severe form of the disease.

ADVATE is currently used for the control and prevention of bleeding episodes, and for preoperative management of children and adults with hemophilia A. The treatment is currently approved in 69 countries worldwide, including the U.S., Canada, and 28 countries in the European Union.

January 9, 2018
9news.com

Man with Severe Hemophilia Climbs the Seven Summits

By Allison Sylte

Climbing the Seven Summits is already a huge accomplishment, but Coloradan Chris Bombardier did it with severe hemophilia – something no one else can say.

The Seven Summits are the tallest peaks on each continent: Denali in North America, Mount Elbrus in Europe, Mount Aconcagua in Argentina, Mount Everest in Asia, Carstesz Pyramid in Oceania/Australia and finally Mt. Vinson in Antarctica.

By standing at the top of Mt. Vinson over the weekend, Bombardier finished his quest to notch the Seven Summits.

"No longer can anyone say that a person with hemophilia is limited – that they can't achieve the impossible without property treatment, training and medical care," Bombardier wrote on Facebook.

Bombardier says he wanted to climb the Seven Summits to bring awareness to the fact that only 25 percent of the people in the world who live with hemophilia have access to proper treatment.

This means "to dream without limitations is dependent on which country you are born into," Bombardier wrote on Facebook.

If you want to follow Bombardier's journey in his future, then check out his website.

To help Chris in helping others with hemophilia visit http://www.saveonelife.net/everest-2017.php or http://cohemo.org.

January 10, 2018
Medicalnewstoday.com

HIV Could Be Treated with A Once-A-Week Pill

By Honor Whiteman

HIV therapy involves a combination of drugs that must be taken once or twice daily, making treatment adherence challenging for many people. But researchers may have found a solution to this problem, in the form of a pill that only needs to be taken once per week.

Researchers from the Massachusetts Institute of Technology (MIT) and Brigham and Women's Hospital — both located in Boston, MA — have developed an ingestible capsule that can slowly release 1 weeks' worth of antiretroviral drugs.

The team's novel creation has the potential to transform HIV therapy, as it means that people may only need to take a single pill once every week, rather than multiple medications every day.

Co-lead study author Robert Langer, the David H. Koch Institute Professor at MIT, and his colleagues believe that their "pillbox in a capsule" could combat the current problem of adherence to antiretroviral therapy; research has indicated that up to 30 percent of people with HIV fail to stick to their treatment regimen.

Langer and his colleagues recently reported the details of their new creation in the journal *Nature Communications*.

HIV and antiretroviral therapy

HIV is a virus that attacks and destroys immune cells that are important for staving off infection and disease. If left untreated, HIV can progress to AIDS, wherein a person's immune system is so severely damaged that they become vulnerable to serious illnesses.

In 2016, there were around 36.7 million people across the globe living with HIV or AIDS. Of these individuals, around 1.8 million were newly infected.

Just 30 years ago, HIV was considered by many as a death sentence. Today, the virus can be successfully managed with antiretroviral drugs, which work by reducing the level of HIV in the body.

A combination of different antiretroviral drugs must be taken every day in order for treatment to be successful, but patients can find it hard to stick to such a regimen.

"One of the main barriers to treating and preventing HIV is adherence," notes the study's co-author Giovanni Traverso, of the MIT's Koch Institute for Integrative Cancer Research. "The ability to make doses less frequent stands to improve adherence and make a significant impact at the patient level."

"These slow-release dosage systems perform equal or better than the current daily doses for HIV treatment in preclinical models," he adds.

Building the 'pillbox in a capsule'

With this in mind, the researchers decided to build on an idea that first emerged in 2016, which was an ingestible capsule that could remain in the stomach for 2 weeks and deliver drugs.

In a previous study, Langer and his colleagues demonstrated how the capsule could help to treat malaria by slowly releasing controlled doses of the malaria drug ivermectin.

For their latest study, the team looked at whether the capsule could be effective for the treatment of HIV, but some design changes were required.

The original capsule consisted of six arms made of a single, strong polymer. Each arm was loaded with drugs and folded in. After ingestion, the arms folded out and released the drugs.

For the treatment of HIV, however, the capsule would need to be able to release different drugs at different rates — something that the original design did not allow.

As such, the team adapted the design. The main structure of the new capsule is still built from a single, strong polymer, but each of the six arms can hold a different medication, thanks to the addition of "release polymers."

"In a way, it's like putting a pillbox in a capsule. Now you have chambers for every day of the week on a single capsule," says Traverso.

Pill effective in pigs

To test whether the newly designed capsule could be effective against HIV, the researchers loaded it with three different antiretroviral drugs — dolutegravir, rilpivirine, and cabotegravir — that are currently used to both prevent and treat HIV.

On testing the drug-loaded capsule on pigs, the researchers found that the capsule successfully settled in the animals' stomachs, and they gradually released each of the three drugs over a 1-week period.

Once all of the drugs are released, the capsule disintegrates, allowing it to be passed through the gastrointestinal tract.

Of course, the capsule needs to be tested in humans before it can be used for the prevention and treatment of HIV, but the researchers believe that their study results show promise.

The researchers calculated the potential impact of this once-a-week capsule at population level, and they suggest that the pill could boost preventive treatment efficacy for HIV by 20 percent. Also, approximately 200,000–800,000 new HIV infections could be prevented in South Africa over the next 20 years.

Commenting on the findings, Anthony Fauci — director of the National Institute of Allergy and Infectious Disease, which helped to fund the study — says, "A longer-acting, less invasive oral formulation could be one important part of our future arsenal to stop the HIV/AIDS pandemic."

January 11, 2018
Raredr.com

UniQure CEO Speaks AMT-061 at J.P. Morgan

By Mathew Shanley

At the 36th Annual J.P. Morgan Healthcare Conference, uniQure announced that in 2018, the company intends to advance its gene therapy AMT-061 into a pivotal study for hemophilia B.

Patients with the rare genetic disorder hemophilia B have reduced factor IX activity, which significantly reduces the blood's ability to properly clot. As a result, people with the condition risk excessive, recurrent, and potentially life-threatening bleeding episodes from even the most minor injuries.

The company has plans to initiate a global, pivotal program for the drug during the third quarter of 2018, and top-line data from the enrolled patients are expected to be announced before the end of the year. uniQure has achieved alignment with the U.S. Food and Drug Administration (FDA) and European Medicines Agency (EMA) on expedited and clinical regulatory pathway for AMT-061, a potential best-in-class gene therapy that combines Factor IX (FIX)-Padua gene with adeno-associated virus 5 (AAV5).

At the 59th American Society of Hematology (ASH) Meeting and Exposition in Atlanta last month, uniQure presented data exhibiting the drug's ability to increase FIX activity in non-human primates with AMT-061 6-to-7 times as effectively as AMT-060, a previous version of the same compound. With these results, the drug was granted Breakthrough and PRIME designations from the FDA and EMA, respectively.

Rare Disease Report (RDR) sat down with Matthew Kapusta, uniQure's CEO, to discuss AMT-061, the excitement surrounding it, and what he expects to see from the drug in 2018.

RDR: What's the background of AMT-061? How long has it been in development?

Kapusta: We've been developing, for a number of years, a gene therapy targeting hemophilia B, and we have one that is an AAV5-delivering Padua-FIX construct. It is administered through a simple IV infusion that is typically infused over 30 minutes, and ultimately, I think the vision is that, commercially, this will be a fairly simple outpatient procedure. We did a Phase 1/2 study on the first generation of the product that was using the wild-type gene cassette, and at the most recent ASH meeting in December, we presented 2-year follow-up data that showed a dramatic clinical effect on the patients. What we decided to do last year, though, was to make a slight modification to the trans gene that increases the potency of the Factor IX protein that is actually produced and we demonstrated that this slight modification will increase the clotting activity of each protein molecule by about 6-8 times.

RDR: What were the driving forces behind the update to the compound?

Kapusta: One of the things that we were hearing from the key opinion leaders was that they wanted to see higher levels of Factor IX activity, and curative levels of Factor IX are generally considered to be above 40-50%. With this new potency change, we think we can get patients into the 30-50% range of normal Factor IX activity level, so near curative levels. At those levels, the expectation is that patients

will no longer require Factor IX replacement therapy, and that there will be a near cessation of bleeding. The potential that the long-term prognosis of their joint health will be significantly benefitted. It's really, really exciting stuff. The data that we presented at ASH in December showed remarkably durable levels of Factor IX activity up to 2 years post-treatment. The patients, really, were not bleeding, and if you look at the presentation, you'll see actual images of the patients who were in the study. We've met these patients and their lives have been remarkably transformed. We're taking this construct into a pivotal study. We expect to initiate this study in the third quarter of this year. The pivotal study will include approximately 40 patients who will serve as their own control. We will be administering the gene therapy to these patients and then following them up for about 52 weeks. We think that this single registration study will provide sufficient enough evidence for us to submit a BLA (Biologics License Application).

RDR: How have people within the hemophilia community been reacting to the potential of AMT-061?

Kapusta: The reception has been really very exciting. There's been a lot of media coverage, and the hemophilia community, not unlike a lot of these other rare and orphan disease communities, are very tight-knit. There's been a growing level of excitement about gene therapy. I think, initially, there might have been some pretty reasonable anxiety about what to expect as it pertained to safety and how long the treatment would last, but the first gene therapy clinical studies were done more than 8 years ago. All of the clinical work that has been done in hemophilia – and there have been multiple studies conducted – have shown well-tolerated, highly safe gene therapy with the ability to have a dramatic impact on the lives of patients.

I think there's a growing level of excitement. This is a patient population that has become increasingly cautious over the years, and they have gotten used to taking replacement therapy. If you think about what is happening to these patients, some hemophiliacs are taking 3+ infusions per week, and if you multiply that out, you're talking about 150-200 infusions per year for the rest of their lives. The mere thought of being able to take a 30-minute IV infusion that eliminates the need to do that, and not only eliminate the need to do it, but that it might completely eliminate the propensity for bleeding, it's pretty remarkable. Even the payers are getting greater appreciation and excitement for it. Not only is it 150-200 infusions per year, but the cost of this could be $300-500 per patient per year for the rest of their lives. It's really millions of dollars per patient, and the potential to have a one-time curative therapy is very exciting even to the payers. We're very pleased to be in the middle of this, and in a position to begin a registrational study. We're excited to potentially be first-to-market with a transformative therapy.

RDR: What kinds of milestones is uniQure hoping to hit in 2018?

Kapusta: We have a number of important milestones. I would say that the key ones are we expect to file our IND (investigational new drug) application with the FDA this quarter. We expect to initiate the treatment of patients in our program in the third quarter of this year. We expect to release data from those initial patients before the end of the year. Those are the key milestones on the hemophilia B program.

RDR: There are a lot of other players in the gene therapy space. What makes uniQure stand out?

Kapusta: One of the most critical things about bringing the gene therapies to market successfully is going to be the ability to manufacture these products. One of the differentiator points for UniQure is that we've been in the field of gene therapy for more than 20 years, and we've spent more than 10

years refining and optimizing our manufacturing capabilities. There aren't many other players in the gene therapy space that can boast like that.