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Gene Therapy: Changing the Landscape of Hemophilia B Care

ReachMD Announcer:
Welcome to ReachMD.

This medical industry feature, titled “Gene Therapy: Changing the Landscape of Hemophilia B Care,” is sponsored by CSL Behring.

Here’s your host, Dr. Jennifer Caudle.

Dr. Caudle:
This is ReachMD, and I’m your host Dr. Jennifer Caudle. And joining me today to discuss HEMGENIX for the treatment of hemophilia B, including its supporting efficacy and safety data, is Dr. Tammuella Singleton. Dr. Singleton is a board-certified pediatric hematologist at Ochsner Clinic Foundation in New Orleans, Louisiana.

Dr. Singleton, thank you so much for being here today.

Dr. Singleton:
Thanks so much for having me.

Dr. Caudle:
And before we dive in, let’s take a moment to hear the Indication for HEMGENIX, etranacogene dezaparvovec-drlb.

ReachMD Announcer:
INDICATION
HEMGENIX®, etranacogene dezaparvovec-drlb, is an adeno-associated virus vector-based gene therapy indicated for the treatment of adults with Hemophilia B (congenital Factor IX deficiency) who:

- Currently use Factor IX prophylaxis therapy, or
- Have current or historical life-threatening hemorrhage, or
- Have repeated, serious spontaneous bleeding episodes.

HEMGENIX is for single use intravenous infusion only.

Dr. Caudle:
And now that we’ve reviewed the Indication, let’s begin our discussion of hemophilia B and HEMGENIX.

To begin, Dr. Singleton, can you provide an overview of the challenges faced by patients with hemophilia B with standard-of-care treatments?

Dr. Singleton:
Absolutely. Thanks for that question. So, hemophilia B is a tough condition to manage and really, despite advances in treatment, many patients still deal with spontaneous bleeds, joint pain, joint damage and excessive bleeding during surgeries.[1,2]

Even on treatment, many patients struggle to maintain the necessary Factor IX levels to prevent bleeds completely. So ideally, prophylactic treatment should keep Factor IX trough levels between three to five percent. But for many patients, their levels are often only one to three percent, which isn't enough to fully prevent bleeding episodes. Now, these ongoing issues really highlight the significant burden on patients, including poor quality of life, frequent injections, and social isolation.[3–5]

So these findings really underscore the need for new treatment options that can not only reduce bleeds more effectively, but can ultimately lessen the overall burden on patients' lives with fewer infusions and a durable treatment response.

This is really why HEMGENIX is really exciting. And unlike traditional treatments that need frequent injections and monitoring, HEMGENIX is a one-time infusion.

And it offers the opportunity for elevated and sustained Factor IX levels. And this is potentially eliminating the need for routine prophylaxis therapy, which can greatly improve the quality of life for patients.

Dr. Caudle:
As HEMGENIX may offer a new hope for hemophilia B patients, let's take a closer look at how it works. Can you explain what HEMGENIX is and why it's particularly suitable for patients with hemophilia B?

Dr. Singleton:
Of course. So, HEMGENIX is a major advancement in treating hemophilia B. And hemophilia B is well-suited for this treatment because it stems from mutations in the relatively simple F9 gene.[6] The treatment uses a non-pathogenic viral vector to introduce a functional F9 gene into liver cells, which ultimately enables hemophilia B patients to produce their own Factor IX.[6–10] Now, HEMGENIX uses the adeno-associated viral vector AAV5, which is proven technology for delivering gene transfer therapy.[6,11]

HEMGENIX has been studied since 2018 and was approved by the FDA in 2022 as the first gene therapy for hemophilia B. It involves a single intravenous infusion to deliver the F9 gene using the AAV5 vector. And as mentioned in the Indication, this treatment is for adults with hemophilia B who are on Factor IX prophylaxis, have a history of life-threatening hemorrhage, or those who experienced repeated serious spontaneous bleeding episodes.

Dr. Caudle:
Dr. Singleton, could you walk us through the clinical evidence behind HEMGENIX that led to its FDA approval, starting with the study design?

Dr. Singleton:
Sure. So, the key evidence comes from the HOPE-B study, which was a multinational, open-label, single-dose, single-arm phase 3 trial. The trial had a six-month lead-in period during which patients with hemophilia B received routine Factor IX prophylaxis. They kept symptom diaries and recorded any additional Factor IX doses for breakthrough bleeds. This allowed patients to serve as their own control for comparing conditions before and after the gene therapy. And in the study, no prophylactic immunosuppression was required.[12]

Now, in the HOPE-B study, 54 patients with moderately severe or severe hemophilia B received HEMGENIX. The primary endpoint of the study compared the annual bleeding rate from seven to 18 months after HEMGENIX treatment to the six-month lead-in period when patients were on routine Factor IX prophylaxis. 53 patients completed at least two years of follow-up, and they'll be monitored for up to five years in HOPE-B, with an extension study planned for up to 15 years of follow-up.[12]

Now, the key inclusion criteria in HOPE-B were for males of at least 18 years of age who had severe or moderately severe hemophilia B, defined as a Factor IX activity level at or below two percent of normal. It also included patients who had over 150 previous exposure days to Factor IX and had been on continuous prophylaxis for at least two months prior to screening.[12]

Now, the key exclusion criteria included a positive Factor IX inhibitor test, a positive HIV test, with a viral load that was not controlled with antivirals, active infection with the hepatitis B or C, advanced liver disease, and any of the following laboratory values that were over twice the upper limit of normal. So this includes ALT, AST, bilirubin, alkaline phosphatase, or creatinine.[12]

Now, the baseline characteristics of the full analysis set showed that the mean age was 41.5 years, the majority of patients– at 81.5 percent –had severe hemophilia at diagnosis, and neutralizing antibodies to AAV5 were detected in 38.9 percent of the study patients.[13]

Dr. Caudle:
And before we continue, let's take this moment to hear some more Important Safety Information on HEMGENIX.

ReachMD Announcer:
IMPORTANT SAFETY INFORMATION
Warning and Precautions

Infusion Reactions

Infusion reactions, including hypersensitivity reactions and anaphylaxis, may occur. Monitor during administration and for at least 3 hours after end of infusion. If symptoms occur, slow or interrupt administration. Re-start administration at a slower infusion once resolved.

Hepatotoxicity/Hepatocellular Carcinoma
Post-dose, monitor for elevated transaminase levels. Consider corticosteroid treatment should elevations occur. The integration of liver-targeting AAV vector DNA into the genome may carry the theoretical risk of hepatocellular carcinoma development. For patients with preexisting risk factors for hepatocellular carcinogenicity, perform regular (eg, annual) abdominal ultrasound and alpha-fetoprotein testing following administration.

Immune-mediated neutralization of the AAV5 vector capsid
Preexisting neutralizing anti-AAV antibodies may impede transgene expression at desired levels.

Monitoring Laboratory Tests
In addition to monitoring liver function, monitor for Factor IX activity and Factor IX inhibitors after administration.

Please see full prescribing information for HEMGENIX.

Dr. Caudle:
For those of you who are just tuning in, you're listening to ReachMD.

I'm Dr. Jennifer Caudle, and today I'm speaking with Dr. Tammuella Singleton about HEMGENIX, the first ever FDA-approved gene therapy for hemophilia B.

As we return from that Important Safety Information, let's now review the results. Dr. Singleton, what can you tell us about the efficacy data supporting HEMGENIX?

Dr. Singleton:
Currently, we have HOPE-B data through three years after HEMGENIX administration showing a mean sustained Factor IX activity of 38.6 percent.[12,14]

A significant reduction in the annualized bleed rate was seen with HEMGENIX versus routine Factor IX prophylaxis. So, through year three, more than half of patients had no bleeds.[12,14]

So, HEMGENIX three-year follow-up data support long-term bleed protection with a one-time infusion for hemophilia B.[12,14]

Looking further into the data, 94 percent of patients were able to discontinue prophylaxis entirely, with 51 out of 54 study patients remaining free of regular infusions after three years.[14]

And over 90 percent of patients achieved a Factor IX levels in the mild to normal range.[14]

In total, these results underscore a significant benefit of HEMGENIX over standard-of-care therapy.[14]

I'd like to point out that in the HOPE-B study, all patients were tested for preexisting anti-AAV5 neutralizing antibodies, but they weren't excluded from the trial. Of the study's 54 participants, 21 had detectable neutralizing antibodies at baseline.[12,13]

When looking at the results by anti-AAV5 neutralizing antibody status, patients both with neutralizing antibodies below 700 and without these neutralizing antibodies had bleed protection after infusion with HEMGENIX. And an increase of Factor IX activity was seen at 18 months regardless of AAV5 neutralizing antibody status.[14]

Dr. Caudle:
And with that in mind, let's turn now to the safety and tolerability results. Dr. Singleton, can you review these results for our audience?

Dr. Singleton
Yes, HEMGENIX demonstrated a favorable safety and tolerability profile consistent with prior observations. Around 70 percent of patients experienced at least one treatment-related adverse event, with the most common being an increased ALT at 16.7 percent, headache at 14.8 percent, and a flu-like illness with 13 percent, and increased AST in 9.3 percent. But no treatment-related serious adverse events were reported.[12]

Also, no Factor IX inhibitors or thrombotic events were reported. There was one patient death and one case of hepatocellular carcinoma, but both cases were deemed to be unrelated to the treatment.[14]

Infusion-related reactions occurred in about 13 percent of patients, including hypersensitivity reactions and anaphylaxis, but the majority of these were mild and resolved within a day with a pause or slowing of the infusion and/or supportive medications, such as antihistamines or corticosteroids.[12]

Liver transaminase elevations, particularly ALT, were mostly mild and asymptomatic, usually appearing within the first four months. And although most returned to baseline, some persisted at lower levels, so it's recommended to obtain weekly transaminase levels for the first three months post-infusion to quickly identify and manage any hepatotoxicity risk early with corticosteroids.[12,14]

Dr. Caudle:
And now that we've discussed the clinical trial results, why should providers discuss HEMGENIX with all of their adult hemophilia B patients?

Dr. Singleton:
To me, this is compelling data for a new and innovative treatment option for our patients. While most providers discuss treatments during annual visits, the impressive results may warrant earlier conversations, so it's worth proactively introducing this option to eligible patients. And ultimately, through the process of shared decision-making, our patients will tell us their level of interest, so it's important that we do our due diligence to provide all of the information. If it's a good fit, the next step is a clinical evaluation.

So this includes that the patient must be an adult with hemophilia B who meets at least one of these criteria: currently using Factor IX prophylaxis, or having a history of life-threatening hemorrhage, or experiencing repeated serious spontaneous bleeding episodes.[12]

If your patients fit into any of these baseline criteria, then you can go through the additional steps for the screening process, which includes factor IX inhibitor testing, and liver health assessments, including enzyme testing, hepatic ultrasound, and elastography. Assessing AAV5 neutralizing antibodies is also a part of the process that was done in the HOPE-B trial but wasn't exclusionary.

Now, there may be situations where a patient is just not an ideal candidate at this time. For example, if there's concern for the commitment that's needed post-vector infusion for follow-up. Or, certainly, if there are any concerns with active or ongoing infections or other comorbidities. This would also include patients with a current life situation that prohibits them from really committing to the post monitoring assessment.[12]

There are some who believe that patients who can't adhere to prophylaxis therapy may not be good candidates for gene therapy, but I see it differently. It's important to understand why a patient struggles with adherence. For instance, life circumstances or poor IV access may make it difficult for them to follow a regular prophylaxis regimen, but that doesn't mean they wouldn't be committed to the required follow-up for gene therapy. By understanding these barriers, we can avoid excluding patients from a potentially life-changing therapy.

But the most important thing is that there's a shared decision-making process with the patient.

This is really essential to healthy discussions—managing expectations, talking about goals within the context of those expectations, and overall the benefits versus the risks.

It's also important to bring up the commitment that's required for HEMGENIX after the infusion, to monitor for safety and that the therapy is also as effective as possible.

Dr. Caudle:
So as we come to the end of our program, Dr. Singleton, what key takeaways would you like to leave with our audience today?

Dr. Singleton:
Given the data we now have supporting safety and efficacy of HEMGENIX three years out from the initiation of our clinical trial program,[14] and experience with this treatment option since its 2022 FDA approval, I'd encourage all healthcare providers treating hemophilia B to start the discussion with their adult patients.

It's important to spread awareness about this treatment option, so let's familiarize ourselves with the HOPE-B results and prepare our practices to offer this one-time gene therapy.

HEMGENIX has shown long-term benefits with sustained Factor IX activity, reducing annual bleeding rates and potentially eliminating the need for prophylaxis. Its safety profile includes manageable side effects with no serious treatment-related events. HEMGENIX has the potential to greatly improve patients' quality of life by reducing bleeds and eliminating the need for ongoing prophylaxis.[14]

So, I encourage healthcare providers to really become familiar and comfortable with the data and learn more about HEMGENIX as a therapeutic option for our patients—so we can together significantly improve the lives of our patients living with hemophilia B.

Dr. Caudle:
Well those are great final insights as we come to a close today.

And I'd like to thank my guest, Dr. Tammuella Singleton, for helping us better understand the role of HEMGENIX as a gene therapy for hemophilia B treatment.

Dr. Singleton, it was great speaking with you today.

Dr. Singleton:
It was fantastic being here. Thanks again for having me.

Dr. Caudle:
And to review the latest follow-up data from the HOPE-B trial, please visit HEMGENIX.com/HCP.

For ReachMD, I'm Dr. Jennifer Caudle.

Please stay tuned to hear some Important Safety Information.

ReachMD Announcer:
Adverse Reactions
The most common adverse reactions (incidence ≥5%) were elevated ALT, headache, blood creatine kinase elevations, flu-like symptoms, infusion-related reactions, fatigue, nausea, malaise, and elevated AST.

Contraindications: None.

Please see full prescribing information for HEMGENIX.

To report SUSPECTED ADVERSE REACTIONS, contact the CSL Behring Pharmacovigilance Department at 1-866-915-6958 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

This medical industry feature was sponsored by CSL Behring. If you missed any part of this discussion, visit Industry Features on ReachMD.com, where you can Be Part of the Knowledge.

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