

**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Biologics Evaluation and Research  
Division of Pharmacovigilance**

**Pharmacovigilance Original BLA Memorandum**

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**Subject:** Review of Pharmacovigilance Plan

**Applicant:** CSL Behring, LLC

**Product:** Hemgenix [etranacogene dezaparvovec]

**Application Number:** BLA 125772/0

**Proposed Indication:** 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

**Submission Date:** Mar 24, 2022

**Action Due Date:** Nov 22, 2022

## 1. OBJECTIVES

This memorandum is in response to a request from the Office of Tissues and Advanced Therapies (OTAT) to the Division of Pharmacovigilance (DPV) to review the original BLA 125772/0. The purpose of this review is to assess the adequacy of the pharmacovigilance plan based on the safety profile of Hemgenix (etranacogene dezaparvovec).

## 2. PRODUCT INFORMATION

### 2.1. Product description

Hemgenix is a gene therapy product that uses the non-replicating, recombinant adeno-associated virus 5 (rAAV5) vector containing a codon-optimized DNA sequence of the Padua-variant (R338L) of the human factor IX (hFIXco-Padua) controlled by a liver specific promoter (LP1). The proposed indication is 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.

### 2.2. Proposed dosing regimen and formulation

Hemgenix is administered as a single intravenous infusion of  $2 \times 10^{13}$  gc/kg body weight (2mL/kg bw) after dilution with 0.9% sodium chloride.

## 3. PERTINENT REGULATORY HISTORY

- Hemgenix was granted Orphan Drug Designation for treatment of adults with hemophilia B on April 17, 2019.
- Hemgenix was granted a Priority Review as analyses from study AMT-061 indicated that treatment with Hemgenix was superior to standard of care routine FIX prophylaxis for all bleeding episodes and FIX-treated bleeding episodes.
- Hemgenix is currently not marketed in any country.

## 4. MATERIALS REVIEWED

Source	Subtype	Document Reviewed
CSL Behring	125772/0.9	Pharmacovigilance (PV) Plan, version 1.0
CSL Behring	125772/0.9	EU Risk Management Plan, version 1.0
CSL Behring	125772/0	Summary of Clinical Safety, Feb. 22, 2022
CSL Behring	125772/0	Study CT-AMT-061-02 Study Report including select individual narratives and safety data tables

Source	Subtype	Document Reviewed
CSL Behring	125772/0.10	Response to FDA Information Request sent on May 17, 2022
CSL Behring	125772/0	Annotated Prescribing Information
CSL Behring	125772/0.20	Summary of Clinical Efficacy, June 29, 2022
CSL Behring	125772/0.20	Summary of Clinical Safety with 4-month safety update, June 28, 2022
CSL Behring	125772/0.52	Response to FDA Information Request sent on Oct. 20, 2022
CSL Behring	125772/0.54	Response to FDA Information Request sent on Oct. 24, 2022
CSL Behring	125772/0.56	Response to FDA Clinical Information Request sent on Oct 24, 2022
CSL Behring	125772/0.59	Pharmacovigilance Plan, version 2.0, and Clinical Study Protocol for Observational Phase 4 Study (CSL222_4001), dated Nov. 2, 2022
CSL Behring	125772/0.63	Response to FDA Information Request sent on Nov. 4, 2022
CSL Behring	125772/0.67	Response to FDA Information Request sent on Nov. 10, 2022
CSL Behring	125772/0.73	Response to FDA Information Request sent on Nov. 16, 2022
CSL Behring	125772/0.76	Additional response to FDA Information Request sent on Nov. 16, 2022

## 5. NON-CLINICAL SAFETY DATABASE

The Pharmacology/Toxicology team will review and interpret the non-clinical studies fully. A brief summary of the sponsor's conclusions is included here to provide context for the clinical study results.

The initial preclinical studies were conducted with the AAV5-hFIX precursor product that was later changed by (b) (4) to form the FIX Padua variant (AAV5-hFIXco-

Padua, Hemgenix). Studies in mice and (b) (4) showed a comparable safety profile for the original AAV5-hFIX and the final AAV5-hFIXco-Padua variant. Vector DNA integration into the host genome was studied in liver samples of animals and was not found to indicate a carcinogenic risk. Both episomal and a small amount of integrated AAV5-hFIX DNA were retrieved, but non-integrated episomal forms were almost exclusively present.

There were microthrombi found in the lungs of mice who had received the highest tested dose and had supraphysiologic levels at approximately 2000% of the Padua FIX or 500% of the non-Padua FIX. Microthrombi were not seen at lower doses or in a second study with high doses administered.

A paternal germline transmission and reproduction study in mice using the AAV5-hFIX product showed no paternal germline transmission at a dose of 10 times the proposed dose. The fertility of the mice was not affected. There was vector DNA in the semen, but there was no vector transmission to reproductive tissues or to the fetuses of untreated female mice mated with the treated males.

A study in (b) (4) monkeys showed a transient mild increase in liver enzymes during the first week after single dose treatment. A transaminitis may indicate an immune-mediated liver injury that could decrease transgene maintenance and FIX-Padua expression.

All animals treated with either AAV5-hFIX or AAV5-hFIXco-Padua developed high titer antibodies to the AAV5 capsid proteins following treatment.

## **6. CLINICAL SAFETY DATABASE**

The clinical program for Hemgenix consisted of 4 clinical trials, two of which were with the precursor AAV5-hFIX form and two of which were the final Hemgenix product (AAV5-hFIXco-Padua). The two trials with the earlier form, AAV5-hFIX, were phase 1/2 trials. CT-AMT-060-01 was an open-label, uncontrolled, single-dose, dose-ascending trial with AAV5-hFIX in adults, and CT-AMT-060-04 was an extension study for long-term safety and efficacy of AAV5-hFIX used in subjects from the first trial. The two studies using the final Hemgenix product, AAV5-hFIXco-Padua, are listed in Table 1 and described in the text below.

**Table 1: Clinical Trials for Hemgenix**

Study	No. of subjects	Description	Age range/Sex
CT-AMT-061-01 Phase 2b	3	Open-label, single-dose, single-arm trial of FIX activity level of AAV5-hFIXco-Padua	43-50 years old All male
CT-AMT-061-02 Phase 3 Pivotal Study	54	Open-label, single-dose trial of AAV5-hFIXco-Padua	19-75 years old All male
Total receiving Hemgenix	57 subjects received AAV5-hFIXco-Padua (Hemgenix)		19-75 years old All male

### **6.1. Study CT-AMT-061-01**

Study CT-AMT-061-01 is a 5-year, phase 2b, open-label, single-dose, single-arm, multicenter study to determine FIX activity resulting from Hemgenix administered to adult subjects with severe or moderately severe hemophilia B. The study's 2.5-year Clinical Study Report has been submitted to the FDA, and the study is currently ongoing. The safety endpoints included adverse events, anti-AAV5 antibodies (total IgM and IgG, neutralizing antibodies), AAV5 capsid-specific T-cell response, anti-FIX inhibitors, presence of vector DNA in blood and semen, inflammatory markers, hematology and serum chemistry results, alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels, use of corticosteroids to preserve FIX activity with ALT/AST elevations, vital signs, abdominal ultrasound, and alpha-fetoprotein (AFP). There were weekly visits for the first 12 weeks and then every second week until Week 26. Visits were then once a month until 1 year post treatment. Follow-up visits were twice a year for the next 4 years.

Three patients were enrolled in this study. With the 4-month safety update, safety data to 3 years is available.

### **6.2. Study CT-AMT-061-02**

Study CT-AMT-061-02 is the pivotal, phase 3, open-label, single-dose, single-arm, multinational study to investigate Hemgenix administered to adult subjects with severe or moderately severe hemophilia B. The primary objective is to demonstrate noninferiority of Hemgenix in the year following treatment compared to a  $\geq 6$ -month lead-in period with standard of care FIX prophylaxis. The safety endpoints were the same as in study CT-AMT-061-01. Weekly visits were conducted for the first 12 weeks. There were once-a-month visits from 4-11 months post treatment. Then, there were twice-a-year visits for the following 4 years.

There were 67 patients enrolled in the study and 53 subjects received a full dose of Hemgenix. One patient received a partial dose of Hemgenix due to a hypersensitivity reaction during infusion. The study is ongoing, and safety data is available for the 24 months following treatment.

### **6.3. Summary of Clinical Safety including 4-Month Safety Update**

There were 57 subjects treated with Hemgenix in the two clinical trials. The subjects ranged in age from 19-75 years old. There were no children or adolescents in the trials. Of the subjects with racial data available, 41 were White and 11 were Non-White. Four were Hispanic. Exclusion criteria included a history of or current positive for FIX inhibitors, elevated liver function tests, elevated creatinine, uncontrolled HIV, active hepatitis B or C, a history of hepatitis B or C exposure currently controlled by antiviral therapy, thrombocytopenia, a coagulation disorder other than hemophilia B, planned surgery in the initial 6 months, previous thrombotic event, active severe infection or other uncontrolled medical condition, and a history of allergic reaction to FIX products.

Before Hemgenix treatment, all subjects tested negative for FIX inhibitors. Of the 57 subjects, 1 (1.8%) was positive for anti-FIX antibodies (non-inhibiting), 3 (5.3%) were positive for IgM to AAV-5, and 13 (22.8%) were positive for IgG to AAV-5. There were 24 (42.1%) subjects positive for anti-AAV5 neutralizing antibodies (NABs). One subject had an anti-AAV5 NAB titer of >1:700.

There were 42 (62.7%) of 67 enrolled subjects who experienced a total of 103 adverse events (AEs) during the ≥6-month lead-in period of Study CT-AMT-061-02. The most common AEs were nasopharyngitis and arthralgia.

All 57 subjects who received Hemgenix had at least 1 treatment-emergent adverse event (TEAE), resulting in a total of 613 TEAEs being reported. The most common TEAEs were arthralgia (36.8%), headache (31.6%), nasopharyngitis (26.3%), fatigue (24.6%), and ALT increased (21.1%).

There were 6 (10.5%) subjects who experienced 11 TEAEs in the Neoplasms Benign, Malignant and Unspecified (including cysts and polyps) System, Organ, Class (SOC). The events were adenoma benign in a patient with diverticulosis, basal cell carcinoma, prostate cancer, hepatocellular carcinoma and colon adenoma in a single subject, benign breast neoplasm and wart-like skin papilloma in a single subject, and, lastly, gastrointestinal neoplasm, gastrointestinal lymphoma, pancreatic neuroendocrine tumor and intracranial meningioma in a single subject. All of these neoplastic events were assessed by the investigators as unlikely or not treatment related. The events of basal cell carcinoma, prostate cancer, and hepatocellular carcinoma were Adverse Events Qualifying for Special Notification (AEQSN) per the study protocols and are further described below.

The subject with basal cell carcinoma was a 53-year-old male with a 4-year history of skin abnormalities with itching and crusting prior to the diagnosis of basal cell carcinoma. The prostate cancer occurred in a 61-year-old male who was diagnosed by biopsy on study day 350. Both of these cases were considered by the investigator to be unlikely related to treatment.

The one case of hepatocellular carcinoma was investigated further because Hemgenix uses a liver-specific promoter and hepatocellular carcinoma would be the neoplasm of most concern with this gene therapy. The case of hepatocellular carcinoma occurred in a 68-year-old man with a history of hepatitis B since 1983, hepatitis C since 2003 (eradicated in 2016), alcohol use, and fatty liver disease. On study day 365, an ultrasound per the study protocol showed a subcapsular lesion which was determined to be hepatocellular carcinoma. Surgery was performed on study day 443 and results of an integration site analysis showed that <0.03% of the hepatocellular carcinoma and adjacent tissues had AAV integration. Per CBER Chemistry, Manufacturing, and Controls (CMC) experts, the carcinoma was investigated thoroughly and the relationship to AAV was not proven. There was not enough material to do thorough analysis of integrations sites, however, so AAV could not be completely ruled out. A dominant integration site was not identified. Whole genome sequencing also did not identify a dominant integration site. The whole genome sequencing did show alteration on 3 chromosomes that indicated a pattern of gene expression in the carcinoma adjacent tissue characteristic of a premalignant state. The conclusion was that a minor degree of vector integration had occurred but was unlikely to be casually related to the development of the hepatocellular carcinoma.

There were 39 (68.4%) subjects who had at least 1 TEAE for a total of 95 adverse events that were considered by the investigators to be treatment related. The most common treatment-related TEAEs were headache (9, 15.8%), ALT increased (9, 15.8%), influenza-like illness (7, 12.3%), and AST increased (5, 8.8%). Of the 39 subjects with events, the majority had mild events (27, 47.4%). There was 1 subject who had events that were considered severe (ALT and AST increased).

There were 15 (26.3%) subjects who had a total of 18 serious TEAEs, and none of these was considered by investigators to be treatment related. Each reported event PT only had a single case, except for blood loss anemia, which had 2 cases. There was no pattern of serious TEAEs in anti-AAV5 neutralizing antibody positive subjects versus negative subjects.

There was one death, and it was not considered by investigators to be treatment related. The patient was a 75-year-old White male with a history of atrial enlargement, atrial fibrillation, and atrial hypertension who died of cardiogenic shock following a urinary tract infection. The death occurred on study day 464.

One subject discontinued the study because of a TEAE. The event was a hypersensitivity reaction after about 10% of the dose had been infused. A second subject withdrew consent at 24-months post treatment.

Per the sponsor's determination, there were 12 subjects who had a total of 14 TEAEs of ALT increased and 8 subjects who had a total of 9 TEAEs of AST increased. There was significant overlap between the two groups as 8 of the 9 events of elevated AST also had an elevated ALT. All of the TEAEs of elevated transaminases were non-serious, but 1 subject had a transaminase increase that was rated as severe. The OTAT clinical team reviewed the data and used a more inclusive definition of ALT and AST elevations. Thus, OTAT concluded that there were 24 subjects who experienced increased ALT levels and 23 subjects who experienced increased AST levels after receiving Hemgenix. Nine (16.7%) of the subjects received steroids for elevated transaminases. The mean time of steroid treatment duration was 80 days, with a range of 51-130 days. There were no SAEs as a result of prolonged steroid use. All of the transaminase elevations resolved, either with or without steroid treatment.

There were 24 (42.1%) subjects between the two studies who were positive for anti-AAV5 neutralizing antibodies (NAb) prior to treatment, using a clinical trial assay that was not validated\*. After treatment, all subjects were positive for AAV5 neutralizing antibodies. There were overall no clear differences in safety data between subjects positive versus negative for anti-AAV5 neutralizing antibodies prior to treatment. However, there was a single patient with a very high anti-AAV5 neutralizing antibody pre-treatment titer (1:3212), and that patient had increased bleeding following Hemgenix. The subject was a 34-year-old male diagnosed with severe hemophilia B at 1 year of age. In the 1 year prior to the study screening, he had 0 spontaneous, 4 unknown, and 0 traumatic bleeds while on Rixubis for prophylactic FIX replacement. He was a non-responder to Hemgenix treatment and restarted prophylactic FIX replacement therapy. Post Hemgenix, he had 7 bleeding episodes, including 5 spontaneous bleeds, during the 18-month follow-up despite routine FIX prophylaxis. One bleed was a serious adverse event of severe upper GI hemorrhage with a duodenal ulcer and anemia that was treated with emergency esophagogastroduodenoscopy with hemostasis during study month 8.

*\*Reviewer comments:* Note that the clinical trial assay, used for these measurements, (b) (4). Thus, the available data do not allow adequate assessment of an association between pre-treatment anti-AAV5 NAb titers and bleeding episodes. Please see further discussion in section 9 of memo.

There was a trend toward worse efficacy outcomes in pre-treatment positive anti-AAV5 NAb positive subjects among the 9 subjects who had increased annualized bleeding rates (ABRs) following Hemgenix treatment in the clinical trials. With only 4 positive subjects in this group, however, there was no definitive conclusion of an association.



There were 13 infusion-related reactions in 7 (12.3%) subjects in the clinical trials. Infusion-related reactions included the following preferred terms: infusion related reaction (2), dizziness (2), abdominal pain upper, chest discomfort, eye pruritus, flushing, headache, hypersensitivity, infusion site reaction, pyrexia, and urticaria. All of the events were non-serious, and 11 of the 13 events resolved on the same day. The occurrence of infusion reactions was higher in patients with pre-treatment anti-AAV5 neutralizing antibodies (5/57, 8.8%) compared to pre-treatment anti-AAV5 negative patients (2/57, 3.5%).

There was AAV vector DNA present in both semen and blood. The 4-month safety update reported that at month 24 post-treatment, 59.4% of subjects in the CT-AMT-061-02 study had cleared the vector DNA from semen (3 negative tests). The median time to clearance for subjects in the study was 47.3 weeks. On the most recent single test available before the data lock date, 51 (96.2%) of 54 subjects had a negative test for the semen. For AAV vector biodistribution in blood, 55.6% of subjects had clearance by 24 months post-treatment (3 negative tests). The median time to clearance in the blood was 52.3 weeks. On the most recent single test, 53 (98.1%) of 54 subjects had negative results for the blood. The sponsor noted that it was difficult to have subject compliance for repeat samples after the subject had 1 or 2 negative tests. Thus, the percentage reaching 3 negative samples remained lower than expected.

There was one subject who was positive for anti-factor IX antibodies (non-inhibitory) at baseline through 1-year post-treatment. He was then negative at 2 years post treatment. There was one other subject who was positive for anti-factor IX antibodies (non-inhibitory) before dosing and then periodically post-treatment up to month 6.

All 57 Hemgenix subjects were negative for factor IX inhibitors at baseline and remained negative through the data lock date of month 24 post-treatment.

The Hemgenix clinical trials required the use of contraception, but there were 2 pregnancies in partners of male subjects in the phase 1 study of the Hemgenix predecessor, AAV5-hFIX wild type. Both of these pregnancies resulted in healthy, live births.

## **7. SUMMARY OF PRIOR MARKETED EXPERIENCE**

The product has not been previously approved or used outside of the clinical trials so there is no prior marketed experience. It is a first-in-class product.

## **8. APPLICANT'S PHARMACOVIGILANCE PLAN**

The applicant submitted an initial Pharmacovigilance Plan (PVP), version 1, as well as an EU Risk Management Plan, version 1. Following an information request from DPV asking for several important identified and potential risks to be added to the US PVP, the sponsor submitted the PVP, version 2. This PVP, version 2, now includes the

expanded safety specifications and is in closer alignment with the EU Risk Management Plan, version 1. The PVP, version 2, will be the focus of this review. The safety specifications are outlined in Tables 2 and 3 below.

**Table 2: Important Identified and Potential Risks**

Type of Concern	Safety Concern	Planned pharmacovigilance activity
Identified	Hepatotoxicity	<ul style="list-style-type: none"> <li>• Routine pharmacovigilance</li> <li>• Questionnaire on liver toxicity</li> <li>• Phase 4 observational study</li> </ul>
Identified	Infusion reactions (including hypersensitivity)	<ul style="list-style-type: none"> <li>• Routine pharmacovigilance</li> <li>• Phase 4 observational study</li> </ul>
Potential	Risk of malignancy in relation to vector integration in the DNA of body cells	<ul style="list-style-type: none"> <li>• Routine pharmacovigilance</li> <li>• Questionnaire on Hemgenix liver malignancy</li> <li>• Phase 4 observational study</li> </ul>
Potential	Bleeding as a result of lack of efficacy due to immune-mediated neutralization of the AAV5 vector capsid*	<ul style="list-style-type: none"> <li>• Routine pharmacovigilance</li> <li>• Phase 4 observational study</li> </ul>
Potential	Thromboembolic events	<ul style="list-style-type: none"> <li>• Routine pharmacovigilance</li> <li>• Questionnaire on thromboembolic events</li> <li>• Phase 4 observational study</li> </ul>
Potential	Germline transmission	<ul style="list-style-type: none"> <li>• Routine pharmacovigilance</li> <li>• Phase 4 observational study</li> </ul>
Potential	Transmission to third parties (horizontal transmission)	<ul style="list-style-type: none"> <li>• Routine pharmacovigilance</li> <li>• Phase 4 observational study</li> </ul>
Potential	Development of FIX inhibitors	<ul style="list-style-type: none"> <li>• Routine pharmacovigilance</li> <li>• Phase 4 observational study</li> </ul>

\*Note that in addition to the routine pharmacovigilance, and the voluntary sponsor observational study for long term follow up, the sponsor will be required to do a clinical study, using a validated assay, to assess the association of pre-treatment anti-AAV5 NAb with bleeding episodes.

**Table 3: Applicant's Pharmacovigilance Plan for Areas of Missing Information**

<b>Area of Missing Information</b>	<b>Planned pharmacovigilance activity</b>
Use in patients with advanced hepatic impairment	<ul style="list-style-type: none"><li>• Routine pharmacovigilance</li><li>• Questionnaire on liver toxicity</li><li>• Phase 4 observational study</li></ul>
Long-term efficacy	<ul style="list-style-type: none"><li>• Routine pharmacovigilance</li><li>• Phase 4 observational study</li></ul>
Long-term safety	<ul style="list-style-type: none"><li>• Routine pharmacovigilance</li><li>• Phase 4 observational study</li></ul>

### **Phase 4 Observational Study**

In addition to routine pharmacovigilance, the applicant is proposing an observational, multinational phase 4 study (Study CSL222\_4001) that would consist of patients with hemophilia B treated with Hemgenix. The patients would be enrolled in the American Thrombosis and Hemostasis Network (ATHN) registry or directly enrolled by the sponsor. The study would follow patients for up to 15 years after Hemgenix treatment and would focus on long-term safety and effectiveness of Hemgenix. There is also an exploratory objective that would compare Hemgenix recipients with a control population on routine FIX prophylaxis. The sponsor is planning to enroll 250 patients globally over 5 years. The protocol was submitted on Nov. 8, 2022, with the plan to start data collection in March 2023. Progress reports would be submitted annually, and interim reports would be submitted every 3 years. Data collection would end in 2043 and the final study report would be submitted in 2044.

### **Clinical Extension Study**

The sponsor is also continuing an interventional long term follow-up extension study titled: An Extension Study Assessing the Long-term Safety and Efficacy of Etranacogene Dezaparvovec Previously Administered to Adult Male Subjects with Hemophilia B During Studies CSL222\_2001 (CT-AMT-061-01) and CSL222\_3001 (CT-AMT-061-02). Subjects will be followed for a total of 15 years with the clinical extension study.

## **9. ANALYSIS OF APPLICANT'S PHARMACOVIGILANCE PLAN**

The applicant has outlined the important identified and potential risks as well as the areas of missing information in the safety specifications of Hemgenix's submitted PVP, version 2. The applicant has proposed labeling which provides information on the risks and instructions on post-administration monitoring. Additionally, the applicant has proposed the actions outlined in section 8 and discussed below.

## **Safety Issues identified in the Pharmacovigilance Plan**

- Important Identified Risk: Hepatotoxicity

There was a total of 12 subjects with 14 events of ALT elevation reported as TEAEs in the two Hemgenix clinical trials. There were 9 AST elevations in 8 subjects reported as TEAEs in the two Hemgenix clinical trials. Eight of the 9 AST elevation events also had ALT elevations. Nine subjects were treated with steroids, and all recovered. All of the transaminase elevations resolved, either with or without steroid treatment.

Liver function abnormalities have been seen in other clinical trials for AAV vectors that target the liver. A potential mechanism is that the vector capsid sequences displayed on the hepatocytes trigger an immune reaction with the cytotoxic T cells. This could lead to selective death of the transduced hepatocytes and decrease in transgene expression. Transaminitis with AAV-vector gene therapy appears to be dose dependent so using the Padua variant of FIX with its enhanced function could allow for lower doses of gene therapy to be effective.<sup>1</sup>

Risk factors include advanced age, concomitant drug interactions, and alcohol abuse with cirrhotic changes. The sponsor advises that the transaminases be monitored regularly (e.g., once per week for 3 months) after Hemgenix receipt. A corticosteroid taper should be considered if ALT becomes elevated. Proper monitoring and use of corticosteroids as described in the product label are expected to be adequate to manage this identified risk. The sponsor will follow-up relevant cases with a questionnaire on liver toxicity.

- Important Identified Risk: Infusion reactions (including hypersensitivity)

There were infusion reactions and hypersensitivity reactions seen during the clinical trials. One reaction resulted in the patient only receiving 10% of the Hemgenix dose. This event led to a protocol amendment that provided guidance on managing infusion reactions. Mitigation of the immune response may include slowing or pausing the infusion and using antihistamines, antipyretics, or glucocorticoids. These further instructions avoided any additional partial treatment cases during the trials, even when some infusion reactions were seen. Patients should also be monitored for at least 3 hours after the infusion to watch for any reactions. It is possible that patients with pre-treatment anti-AAV5 neutralizing antibodies may have an increased risk of infusion reactions, but small numbers in the study make it difficult to draw a conclusion. Since patients develop anti-AAV

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<sup>1</sup> Nathwani AC. Gene Therapy for Hemophilia. Hematology Am Soc Hematol Educ Program. 2019 Dec 6;2019(1):1-8.

antibodies following exposure to Hemgenix, a partially treated patient may be ineligible to receive the full treatment at a later time. Optimizing the administration of the treatment is especially important. Instructions and a warning regarding infusion reactions and hypersensitivity reactions are provided in the package insert, but further characterization of this risk would improve treatment administration.

- Important Potential Risk: Risk of malignancy in relation to vector integration in the DNA of body cells

Vectors that have chromosomal integration can be a risk for tumor formation by causing insertional mutagenesis and an alteration of host cell regulation. Recombinant AAV vectors, including Hemgenix's rAAV5, remain primarily in episomal form in the nucleus of the transduced cells. Recombinant AAV vectors do not have site-specific integration, but there can be a low level of chromosomal integration at random sites.<sup>2,3,4</sup> The AAV5 vector is non-replicating.

There was one case of hepatocellular carcinoma in the Hemgenix trials. It occurred in a 68-year-old man who had a history of hepatitis B and C virus, alcohol use, and a family history of cancer. In addition to the multiple risk factors for liver cancer in this patient, molecular tumor characterization and vector integration in this case showed that there was no clonal expansion. Therefore, the tumor was determined unlikely to be related to the Hemgenix treatment.

The sponsor recommends that patients with preexisting risk factors for hepatocellular carcinoma receive abdominal ultrasound screenings and alpha fetoprotein (AFP) monitoring for 5 years following Hemgenix administration. The sponsor will follow up reports with a questionnaire on liver malignancy.

The 2020 FDA Guidance for Industry: Long Term Follow-Up After Administration of Human Gene Therapy Products (available at <https://www.fda.gov/media/113768/download>) recommends up to 5 years of long term follow up for AAV vectors. As per this Guidance document, gene therapy products that are based on vectors such as AAV, that do not have a propensity to integrate or reactivate following latency, generally present a lower risk of delayed adverse events.

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<sup>2</sup> Smith RH. Adeno-associated virus integration: virus versus vector. *Gene Ther.* 2008 Jun;15(11):817-22.

<sup>3</sup> Li H, Malani N, Hamilton SR, et al. Assessing the potential for AAV vector genotoxicity in a murine model. *Blood.* 2011 Mar 24;117(12):3311-9.

<sup>4</sup> Gil-Farina I, Fronza R, Kaeppel C, et al. Recombinant AAV integration is not associated with hepatic genotoxicity in nonhuman primates and patients. *Mol Ther* 2016 Jun;24(6),1100-05.

- Important Potential Risk: Bleeding as a result of lack of efficacy due to immune-mediated neutralization of the AAV5 vector capsid

There were 24 (45.6%) of 57 subjects who were positive for anti-AAV5 neutralizing antibodies (NAb) at baseline. One of the subjects had a titer over 1:700 (actual titer was 1:3212) and that subject did not express FIX following Hemgenix treatment. The remaining treated subjects (including one with a titer of 1:678) all had FIX expression following Hemgenix. Of note, (b) (4) the anti-AAV5 NAb assay used in the clinical trials (b) (4), which precludes interpretation of the above data.

As anti-AAV5 neutralizing antibodies may decrease or prevent expression of the FIX transduced gene product,<sup>5,6</sup> the sponsor initially proposed that Hemgenix only be administered to hemophilia B patients with (b) (4)

If the product has decreased effectiveness in patients with high anti-AAV5 titers, these patients could have increased bleeding episodes. The assay to be used for determination of the titer (b) (4)

. The sponsor is planning to submit data on a new (b) (4) assay in Feb. 2023.

After review of the efficacy and safety data, OTAT is planning to approve Hemgenix for use in patients (b) (4)

There was no consistent, clear association between anti-AAV5 NAb and ABR or safety, however, there is uncertainty regarding potential risk of increased bleeding due to high anti-AAV5 NAb titers based on observations from a single subject. The sponsor will be required to conduct a clinical study to assess the association of pre-treatment AAV5 NAb, measured with a validated AAV5 NAb assay, and bleeding episodes. Please see the section below discussing the postmarket requirement.

All patients who received Hemgenix developed anti-AAV5 NAb. As a result, a patient could not receive Hemgenix (or any AAV5 gene therapy) more than once. Since antibody development takes several weeks, the vector DNA is already in

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<sup>5</sup> Colella P, Ronzitti G, Mingozi F. Emerging Issues in AAV-Mediated *In Vivo* Gene Therapy. *Mol Ther Methods Clin Dev.* 2017 Dec 1;8:87-104.

<sup>6</sup> Gorovitz B, Marshall JC, Smith J, et al. Bioanalysis of adeno-associated virus gene therapy therapeutics: regulatory expectations. *Bioanalysis.* 2019 Nov;11(21):2011-24.

the nucleus of the transduced cells. Thus, while pre-treatment anti-AAV5 NABs are a concern, new antibody formation is not a problem for gene expression.

- Important Potential Risk: Thromboembolic events

It is possible that supraphysiologic level of FIX could cause thromboembolic events. There were 4 TEEs in 3 subjects during the clinical studies. The events were angina pectoris (2), peripheral arterial occlusive disease, and transient ischemic attack. They all occurred in elderly subjects with pre-existing cardiac and cerebrovascular disease, and the events were categorized by the investigator to be unrelated to treatment. Of note, the highest FIX activity seen in the clinical trials was 124%, which is within normal limits. The package insert includes information on monitoring FIX activity and there is a follow-up questionnaire for patients who experience thromboembolic events.

- Important Potential Risk: Germline transmission

As described in the clinical trial section, there was vector DNA identified in the semen for months following Hemgenix treatment in some subjects. This vector DNA is unlikely to be transduction competent as the development of anti-AAV5 neutralizing antibodies occurs within 2-3 weeks of Hemgenix treatment. Additionally, the vector DNA is not in the cellular component of the sperm, and nonclinical studies did not show vector DNA in the female reproductive track of mice mated with precursor AAV5-hFIX-treated males. This risk has a low likelihood to occur but is still considered a potential event.

- Important Potential Risk: Transmission to third parties (horizontal transmission)

There was vector DNA detectable in some subject's blood for months following Hemgenix. As described in the germline transmission section, these (b) (4) results do not necessarily indicate the presence of transduction-competent product. The development of anti-AAV5 NAB following treatment would mitigate the presence of any transmissible gene therapy product. The Hemgenix package insert instructs recipients not to donate blood, organs, tissues, or cells.

- Important Potential Risk: FIX inhibitors

There were no cases of FIX inhibitors seen in the Hemgenix clinical trials. The sponsor is only seeking Hemgenix approval for use in adults. Therefore, the risk of inhibitor formation is decreased by not treating children, as patients have higher rates of inhibitor formation when they have a history of fewer FIX exposure days. Additionally, prospective patients are to be tested prior to Hemgenix treatment to ensure they are negative for FIX inhibitors. While these methods decrease the

risk of inhibitor formation, it remains an important potential risk for Hemgenix treatment. Additionally, use of the Padua-variant could increase the risk of FIX inhibitor development, although a study in a canine model was reassuring as the study had no inhibitors develop in the 3 treated dogs.<sup>7</sup> Unlike FIX replacement infusions, once Hemgenix is administered, future exposure for FIX cannot be removed. Thus, FIX inhibitor formation following Hemgenix treatment could pose a serious health risk. There are instructions in the package insert to test patients for FIX inhibitors prior to Hemgenix treatment and to monitor patients for FIX inhibitors following treatment.

### **Areas of Missing Information**

The areas of missing information include use in patients with advanced hepatic impairment, long-term efficacy, and long-term safety. Patients with advanced hepatic impairment were excluded from the clinical trials as transaminitis is a risk with this therapy, as discussed in important identified risks above. All of these areas will be further explored with the phase 4 observational study using the ATHN registry. Patients with advanced hepatic impairment will also have a questionnaire on liver toxicity. Long-term efficacy and long-term safety will have additional information from the two ongoing clinical studies that will be continued until 5 years post-infusion for each patient. The sponsor is also planning to enroll Hemgenix patients from phase 2b and 3 studies into a clinical extension study with a total follow-up of 15 years.

### **Assessment of Pharmacovigilance Activities**

As outlined in Tables 2 and 3 above, the sponsor is proposing routine pharmacovigilance along with follow-up questionnaires for the important risks of hepatotoxicity, malignancy, and thromboembolic events as well as missing information on treatment of patients with underlying advanced hepatic impairment. The applicant is also planning a phase 4 observational registry study to provide additional safety information. The patient safety registry will provide data on long-term safety up to 15 years on patients enrolled in the ATHN registry or directly enrolled by the sponsor. Since AAV5 is a non-replicating and primarily non-integrating vector, five-year follow-up is considered acceptable for this class of vectors, per the FDA Long Term Follow-up After Administration of Human Gene Therapy Products: Guidance for Industry (Jan 2020). The registry study will be conducted by the sponsor on a voluntary basis. The sponsor plans to collect data including pre-treatment anti-AAV5 NAb titers, but this information would only be available if the tests were done as part of standard clinical

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<sup>7</sup> Finn JC, Nichols TC, Svoronos N, et al. The efficacy and the risk of immunogenicity of FIX Padua (R338L) in hemophilia B dogs treated by AAV muscle gene therapy. *Blood*. 2012 Nov 29;120(23):4521-23.



care. Since the current indication for Hemgenix does not include required testing for anti-AAV5 NAb status and a validated assay is not currently available, anti-AAV5 NAb titers are unlikely to be available for patients in this observational study. Separately, the extension study of the clinical trials will provide additional long-term safety information on Hemgenix. The review team determined that this product does not require a Risk Evaluation and Mitigation Strategy (REMS).

### **Postmarketing Requirement Study**

A bleeding episode in hemophilia patients is primarily a lack of efficacy outcome for treatment, but increased bleeding/lack of effect may also be considered a safety outcome under the definition of an adverse event in 21CFR600.80 which includes “any failure of expected pharmacological actions.”<sup>8</sup> The Food and Drug Administration Amendments Act (FDAAA) Section 505(o)(3)(A) states that postmarketing studies and clinical trials may be required for any or all of three purposes listed in section 505(o)(3)(B):

- To assess a known serious risk related to the use of the drug
- To assess signals of serious risk related to the use of the drug
- To identify an unexpected serious risk when available data indicates the potential for a serious risk

The important potential serious risk of increased bleeding with anti-AAV5 neutralizing antibodies would fall under the third purpose above, i.e., to identify an unexpected serious risk when available data indicates the potential for a serious risk.<sup>9</sup>

As required under Section 901 of FDAAA and as described in CBER SOPP 8415: Procedures for Developing Post-marketing Requirements and Commitments, a Sentinel Sufficiency assessment was conducted to determine the sufficiency (i.e., capability) of the CBER Sentinel program to characterize the serious risk of increased bleeding following Hemgenix treatment in patients with high pre-treatment anti-AAV5 neutralizing antibody titers, in lieu of a postmarket requirement (PMR) study under FDAAA. As outlined in the Sentinel Sufficiency memorandum, the CBER Sentinel Team has

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<sup>8</sup> <https://www.fda.gov/files/vaccines%2C%20blood%20%26%20biologics/published/Draft-Guidance-for-Industry--Postmarketing-Safety-Reporting-for-Human-Drug-and-Biological-Products-Including-Vaccines.pdf> The definition of adverse experience includes any failure of expected pharmacological action that is synonymous with lack of effect (see definition of adverse experience in Appendix A of this guidance and at 310.305(b), 314.80(a) and 600.80(a)).

<sup>9</sup> Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act, added by section 901 of the Food and Drug Administration Amendments Act of 2007 (FDAAA)

determined that CBER Sentinel is NOT sufficient to characterize this serious risk. The study involves monitoring of reported bleeding in a lead-in period, then an 18-month follow-up period, and correlating bleeding with pre-treatment anti-AAV5 NAb titers, based on a validated anti-AAV5 NAb assay that is currently not available. CBER Sentinel data sources are unable to identify outcomes which require patient-level serology testing and development of a validated assay. The follow-up period needed for this type of study is also too long to assure that the patient will stay with the same insurance company to have his/her data captured in the CBER Sentinel databases. Sentinel insufficiency serves as a justification for requiring a safety-related postmarketing study under Section 901, Title IX of FDAAA.

Therefore, the PMR was presented at the CBER Safety Working Group (SWG) meeting on Nov. 3, 2022, and Nov. 10, 2022. The SWG supported requiring a PMR to characterize the serious risk of increased bleeding related to the presence of pre-existing anti-AAV5 neutralizing antibodies against the AAV5 capsid of Hemgenix leading to reduced effectiveness of Hemgenix in patients with hemophilia B. To address this concern, two PMRs were established:

1. To validate a sensitive and accurate assay for the detection of anti AAV5 neutralizing antibodies, specifically to detect anti-AAV5 NAb titers up to 1:1400 or higher.
2. A post-marketing study to assess the association between the serious risk of bleeding related to the failure of expected pharmacological action of Hemgenix and pre-existing anti-AAV5 NAb to the AAV5 capsid of Hemgenix with a validated assay (required in PMR 1). The study will evaluate at least 35 Hemophilia B patients treated with Hemgenix, to include at least 10 patients with high (1:1400 or higher) pre-treatment anti-AAV5 Nab titers. The assessment will compare pre- and post-treatment annualized bleeding rates (ABRs), with a lead-in period to establish the patients' baseline ABR on routine treatment and 18-month follow up following Hemgenix administration.

The sponsor was notified of the PMRs on Nov. 16, 2022.

For the assay validation, the sponsor will use a (b) (4) assay that will be (b) (4) and will achieve reportable titers up to 1:1100. An assay to achieve reportable titers  $\geq 1100$  (and above 1:1400) will be submitted to the FDA by May 31, 2023. Of note, the new (b) (4) assay has titer results that are different from the results of the unvalidated assay used in the clinical trials. The clinical trial titer of 1:700 is roughly similar to the new (b) (4) assay titer of 1:1400. For the PMR, titer results will be stated using the new assay ranges, with 1:1400 representing high titer patients. Note that OBPV defers to OTAT and CDRH for review activities related to PMR#1.

For the clinical study PMR#2, the sponsor has proposed an open-label, single-dose, multinational study in adults with severe or moderately severe hemophilia B with detectable pre-treatment anti-AAV5 NAb using a validated NAb assay. The primary objective would be to assess an association of pre-treatment anti-AAV5 NAb titers on safety and efficacy during the 52 weeks following establishment of stable FIX expression (months 6 to 18 after Hemgenix treatment) compared to standard of care continuous routine FIX prophylaxis during the 6-month Lead-in Period, as measured by ABR. There would be 35 subjects and the sponsor will do the utmost to ensure at least 10 of these patients have high titers (1:1400 or higher with the new (b) (4) assay). The study milestone dates are:

Final Protocol Submission: Feb. 10, 2023

Study Completion: Dec. 31, 2028

Final Study Report Submission: May 31, 2029

To encourage enrollment in the PMR#2 study, OBPV has recommended that the US package insert include the following language to refer to the study in the Warnings and Precautions section on immune-mediated neutralization of the AAV5 vector capsid:

*Anti-AAV antibody study: Patients who intend to receive treatment with Hemgenix are encouraged to enroll in a study to measure pre-existing anti-AAV antibodies by calling [CSLB].*

OBPV defers to OTAT on the final labeling language. Please see the approved USPI for the final approved upon language.

The sponsor is also planning a Dear Healthcare Provider letter to provide information on the PMR#2 study and maximize enrollment.

This PMR#2 study will be limited by several different factors. A validated anti-AAV5 NAb assay is currently not available, and it will become available only at lower titers first. An assay for higher titers is expected to be available later in 2023. This is especially significant as the concern for increased bleeding arises with titers >1:700 with the clinical trial assay (approximately >1:1400 with the proposed new (b) (4) assay). The sponsor plans to store pretreatment samples for later assessment when an anti-AAV5 NAb assay is available. There would still be a delay in obtaining any safety data on high titer patients. Additionally, it may be difficult to reach a significant number of patients with high titers as there was only 1 in 57 in the trial, and data on the prevalence of this titer range in the hemophilia B population is not available. As noted above, PMR#2 specifically requires enrollment of a minimum of 10 high titer patients, but the actual prevalence of anti-AAV5 high titer patients in the Hemophilia B patient population is unknown at this time. If the study enrolls mostly low titer patients, it would not yield

useful information to assess the serious risk of bleeding with high pre-treatment anti-AAV5 NAb titers.

## **10. DPV CONCLUSIONS**

Based on review of available data, there is a safety signal from the clinical trials for Hemgenix which warrants two FDAAA Title IX postmarketing requirement (PMR) studies to assess the serious risk of increased bleeding related to the presence of pre-existing anti-AAV5 neutralizing antibodies against the AAV5 capsid of Hemgenix leading to reduced effectiveness of Hemgenix in patients with hemophilia B. This study will be limited in its ability to provide useful data primarily due to current inability to test anti-AAV5 NAb titers and expected low enrollment of high titer patients when testing is available, as described in Section 9 above. There will also be a delay before any additional information is available related to the effect of pre-treatment anti-AAV5 NAb titers. In the meantime, passive surveillance with routine safety monitoring will not be able to correlate adverse events related to bleeding with anti-AAV5N Ab status, and providers will be unable to assess the patient's anti-AAV5 NAb status prior to treatment. OBPV has recommended including language in the USPI to increase awareness that testing of pre-treatment anti-AAV5 NAb may be done by enrollment of patients in an anti-AAV5 antibody study (i.e., PMR#2).

In addition to the PMR studies, the sponsor will conduct routine and enhanced pharmacovigilance activities as outlined in the Pharmacovigilance Plan, version 2. The sponsor is also planning a voluntary, 15-year observational study and a long-term clinical extension study. The review team determined that a Risk Evaluation and Mitigation Strategy (REMS) is not required for this product.

## **11. RECOMMENDED PHARMACOVIGILANCE ACTIONS**

OBPV/DPV recommends the following for the postmarketing safety monitoring of Hemgenix:

- 1) Routine pharmacovigilance activities proposed by the applicant in the Pharmacovigilance Plan, version 2, with adverse event reporting as required under 21CFR600.80.
- 2) Safety-related postmarketing requirement (PMR) studies under 505 (o) of the FDCA (amended by FDAAA, Title IX, Section 901): Two FDAAA Title IX PMR studies have been established to assess the unexpected serious risk of bleeding due to failure of expected pharmacological action of Hemgenix in the presence of pre-existing anti-AAV5 neutralizing antibodies.
  - a. PMR#1: The first PMR will validate a sensitive and accurate assay for the detection of anti-AAV5 neutralizing antibodies, specifically to detect anti-AAV5 NAb titers up to 1:1400 or higher. OBPV defers to OTAT and CDRH for review of PMR#1.
  - b. PMR#2: A second PMR will use the assay, that was validated in PMR#1, to evaluate hemophilia B patients with pre-existing anti-AAV5 neutralizing antibodies who are treated with Hemgenix. This is a postmarketing study

to assess the association between the serious risk of bleeding related to the failure of expected pharmacological action of Hemgenix and pre-existing anti-AAV5 NAb to the AAV5 capsid of Hemgenix with a validated assay (required in PMR 1). The study will evaluate at least 35 Hemophilia B patients treated with Hemgenix, to include at least 10 patients with high (1:1400 or higher) pre-treatment anti-AAV5 NAb titers. The assessment will compare pre- and post-treatment annualized bleeding rates (ABRs), with a lead-in period to establish the patients' baseline ABR on routine treatment and 18-month follow up following Hemgenix administration. The milestone dates are:

- Protocol Submission: Feb. 10, 2023
- Study Completion Date: Dec. 31, 2028
- Clinical Study Report Submission: May 31, 2029

DPV will review the final study protocol for PMR#2 when available.

- 3) Voluntary sponsor study (Study CSL222\_4001): The sponsor plans to conduct a prospective, observational postmarketing study in 250 Hemophilia B patients treated with Hemgenix; the enrolled patients will be followed for 15 years after product administration.
- 4) The reviewed safety data do not substantiate a need for a Risk Evaluation and Mitigation Strategy (REMS).