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CSL Behring – Global Program Call for Grants

Therapeutic Area: Hematology

Disease State: Gene Therapy

Call for Grants Application Details:

- Your title must begin with ID Information "**GT_2025**"
- Refer to Grant Submission Instructions for further information on submitting your formal grant application at www.CSL.com/grants under Independent Medical Education.
- Additional communication on the process will be conducted exclusively through Educational.Grants@cslbehring.com or the portal grant record.

Submission Deadline:	January 2nd, 2026
Proposal:	US continuing medical education programs. Multi-support encouraged.
Program Format:	Interactive US live/web programs with an enduring component seeking HCP gene therapy subject matter experts' presentations and panel discussion.
Program Cost:	up to $250,000.

CSL Behring is seeking to offer grant support to an established Continuing Medical Education (CME) provider to conduct a live educational program for healthcare providers (HCPs) coinciding with an impactful hematology conference. The non-promotional opportunity would allow HCPs to learn more about the history and success of AAV gene therapy research with a focus on the clinical differentiation between hemophilia A and B gene therapy options.

Needs Assessment: Evolution and Impact of AAV Gene Therapy with a Focus on Differentiation of Gene Therapy Treatment Options for Hemophilia A/B.

The Adeno-associated virus (AAV) is a leading modality in gene therapy due to its minimal pathogenicity and ability to establish long-term gene expression, however there is increasing need to communicate AAV's clinical data following several pharmaceutical companies withdrawing their investment in AAV gene therapy programs.[1,2,3] HEMGENIX® (etranacogene derzaparvovce-drlb) became the first gene therapy approved for the treatment of hemophilia B in November 2022.[4] This milestone was followed by the approval of ROCTAVIAN® (valoctogene roxaparvovec) for hemophilia A in June 2023, and BEQVEZ® (fidanacogene elaparvovec-dzkt) for hemophilia B in April 2024.[5,6] However, both ROCTAVIAN and BEQVEZ were subsequently withdrawn from the market due to limited uptake and commercial challenges.[2,3] With pharmaceutical companies divesting their AAV gene therapy programs, it is vital that HCPs understand the legacy of AAV gene therapy and heterogeneity of clinical data as it relates to distinct clinical outcomes between Hemophilia A/B to inform their decision-making.

AAV Gene Therapy History and Success:
A variety of viral vectors have been investigated for in vivo gene delivery, including adenovirus, retrovirus, lentivirus, and herpes simplex virus (HSV). Among these, adeno-associated virus (AAV) vectors have emerged as the leading platform in both clinical trials and approved therapies. First discovered in the mid-1960s, AAV has become a cornerstone of gene therapy research. Advances in AAV biology led to the successful cloning and sequencing of its

genome, which enabled the identification of multiple AAV serotypes with distinct tissue tropisms paving the way for targeted gene delivery strategies. To date, 26 viral gene therapies have received regulatory approval. The first of these, Luxturna, was approved by the FDA in 2017 as a gene replacement therapy for Leber congenital amaurosis type 2 (LCA2).[1]

Nathwani et al reported the first clinical trial of scAAV-mediated gene transfer in hemophilia B in 2011. All patients demonstrated stable FIX expression over the long term, with average FIX levels ~5% of normal in the high-dose cohort.[7] These participants have maintained stable and therapeutic expression of FIX extending >13 years (as of December 31, 2023) with no late toxicity observed.[8]

Etranacogene dezaparvovec evolved from research in another recombinant viral vector, AMT-060. The only difference is the switch of transgene associated with the AAV5 viral vector from wild-type FIX to the Padua variant FIX. Etranacogene dezaparvovec and its predecessor (AMT-060) have demonstrated stable expression of FIX up to 5 and 8 years, respectively with no emergent safety signals.[9]

Outcomes in Hemophilia with Differentiation of Hemophilia A and B:

Eligibility: Valoctocogene roxaparvovec's phase III clinical trial (GENEr8-1) included adults with severe hemophilia A (FVIII <1 IU/dL) without FVIII inhibitors or pre-existing neutralizing antibodies (NAbs) to AAV5.[10] Etranacogene dezaparvovec's phase III clinical trail (HOPE-B) included adults with moderate or moderately severe hemophilia B (FIX ≤2 IU/dL) without FIX inhibitors. A key difference is that pre-existing NAbs to AAV5 was not an exclusion criteria for the HOPE-B trial.[11] Further when analyzing NAb-positive v. NAb-negative subject responses to etranacogene dezaparvovec, no clinically meaningful or statistically significant correlation between an individual's baseline AAV5 NAb titer and FIX activity levels was identified, up to an AAV5 NAb titer of <1:700.[12]

Factor Expression: Both valoctocogene roxaparvovec and etranacogene dezaparvovec have phase III published data for 5 years-post dosing, with a key difference in the durability of factor expression. Valoctocogene roxaparvovec showed a mean FVIII expression of 42.8 IU/dL at year one that continued to decline to 23.0 IU/dL at year 2, 18.4 IU/dL at year 3, and 24.0 IU/dL at year 5. At year 5, 18.7% (25/134) of trial participates returned to continuous prophylaxis.[13,14] Etranacogene dezaparvovec FIX expression has remained consistent and >36% with a mean of 41.5 IU/dL at year one, 36.7 IU/dL at year 2, 38.6 at year 3, 37.4 at year 4, and 36.1% at year 5. Over 5 years post-gene therapy, only 1 (1.9%) responding participant eventually resumed continuous FIX prophylaxis.[15,16]

Safety: The safety profiles of valoctocogene roxaparvovec and etranacogene dezaparvovec are also distinct specifically when examining transaminitis. Transaminitis is important because it may be associated with partial loss of transgene expression. In the phase III trial, within the first year of valoctocogene roxaparvovec administration, 115 (85.8%) of participants reported ALT elevation, of which 106 (79.1%) received glucocorticoids for a median duration of 230 days.[10] Throughout year 2 and 3, there continued to be ALT elevation in participants with 39 (29.1%) and 34 (25.4%) participants respectively.[13] In the first year of the etranacogene dezaparvovec phase III trial, ALT increase was seen in 9 (16.7%) participants, all of whom received corticosteroids for a mean of 80 days. Throughout year 5, there was no long-term hepatotoxicity.[11,16]

Monitoring: The substantial differences in the factor expression durability and safety between valoctocogene roxaparvovec and etranacogene dezaparvovec translated to differences in the required monitoring. The prescribing information for of valoctocogene roxaparvovec requires a stringent monitoring of ALT and FVIII post-administration. ALT and FVIII must be monitored weekly for the first 26 weekly, every 1 to 2 weeks from weeks 26-52, every 3 months from year 1-2, and every 6 months after year 2.[18] The prescribing information for etranacogene dezaparvovec requires weekly monitoring of ALT and AST for 3 months post-administration,

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with additional guidance to “regularly” monitor FIX and ALT/AST.[19]

As the same healthcare providers care for both patients with hemophilia A and B, there is a need for continuing medical education for those HCPs to maintain, develop, or increase their knowledge in this key area of distinction. Additionally, as pharmaceutical companies are divesting from their AAV gene therapy programs it is equally important for providers to understand the full spectrum of clinical data available to inform their decision-making.

References:

1. Wang, JH., Gessler, D.J., Zhan, W. *et al.* Adeno-associated virus as a delivery vector for gene therapy of human diseases. *Sig Transduct Target Ther*. 2024: 9,78.
2. Santhosh, C. (2025, February 21). Pfizer stops commercialization of hemophilia gene therapy Beqvez [Article]. https://www.reuters.com/business/healthcare-pharmaceuticals/pfizer-says-it-will-end-global-development-gene-therapy-beqvez-nikkei-reports-2025-02-20/
3. Fidler, B. (2025, October 27). BioMarin, following sluggish sales, to offload hemophilia gene therapy [Article]. https://www.biopharmadive.com/news/biomarin-divest-roctavian-hemophilia-gene-therapy/803931
4. U.S. Food and Drug Administration. (2022, November 22). FDA Approves First Gene Therapy to Treat Adults with Hemophilia B [Press release]. https://www.fda.gov/news-events/press-announcements/fda-approves-first-gene-therapy-treat-adults-hemophilia-b
5. U.S. Food and Drug Administration. (2023, June 29). FDA Approves First Gene Therapy for Adults with Severe Hemophilia A [Press release]. https://www.fda.gov/news-events/press-announcements/fda-approves-first-gene-therapy-adults-severe-hemophilia
6. Pfizer Inc. (2024, April 26). U.S. FDA Approves Pfizer’s BEQVEZ™ (fidanacogene elaparvovec-dzkt), a One-Time Gene Therapy for Adults with Hemophilia B [Press release]. https://www.pfizer.com/news/press-release/press-release-detail/us-fda-approves-pfizers-beqveztm-fidanacogene-elaparvovec
7. Nathwani AC, Tuddenham EG, Rangarajan S, et al. Adenovirus-associated virus vector-mediated gene transfer in hemophilia B. *N Engl J Med*. 2011;365(25):2357-2365.
8. Reiss UM, Davidoff AM, Tuddenham EGD, et al. Sustained Clinical Benefit of AAV Gene Therapy in Severe Hemophilia B. *N Engl J Med*. 2025;392(22):2226-2234.
9. von Drygalski A, et al. AMT-060 and etranacogene dezaparvovec in hemophilia B: duration of freedom from bleeding and prophylaxis. ISTH 2025.
10. Ozelo MC, Mahlangu J, Pasi KJ, et al. Valoctocogene roxaparvovec gene therapy for hemophilia A. N Engl J Med. 2022;386(11):1013-1025.
11. Pipe SW, Leebeek FWG, Recht M, et al. Gene therapy with etranacogene dezaparvovec for hemophilia B. N Engl J Med. 2023;388(8):706-718.
12. Pipe SW, Leebeek FWG, Recht M, et al. Durability of bleeding protection and factor IX activity in those with and without AA5 neutralising antibodies in the Phase 3 HOPE-B clinical trial of etranacogene dezaparvovec hemophilia B. Poster presented at: 16th Annual Congress of the European Association for Haemophilia and Allied Disorders (EAHAD); February 7-10, 2023; Manchester, England.
13. Mahlangu J, von Drygalski A, Shapiro A, et al. Bleeding, FVIII activity, and safety 3 years after gene transfer with valoctocogene roxaparvovec: Results from GENEr8. Poster presented at: International Society on Thrombosis and Haemostasis (ISTH); June 24-28, 2023; Montreal, Canada.
14. Leavitt A, et al. Efficacy safety and quality of life 5 years after valoctocogene roxaparvovec gene transfer. ISH 2025.

15. Pipe S. Long-Term Bleeding Protection, Sustained FIX Activity, Reduction of FIX Consumption and Safety of Hemophilia B Gene Therapy: Results from the HOPE-B Trial 3 Years after Administration of a Single Dose of Etranacogene Dezaparvovec in Adult Patients with Severe or Moderately Severe Hemophilia B. Presented at: 65th Annual American Society of Hematology (ASH) Meeting; December 7-10, 2023; San Diego, California.
16. Pipe S, et al. End-of-Study Analysis of the HOPE-B Trial Confirms the Durable Efficacy and Safety of Etranacogene Dezaparvovec Hemophilia B Gene Therapy Over 5 Years. ASH 2025.
17. ROCTAVIAN[prescribing information]. Novato, CA: BioMarin Pharmaceutical Inc.
18. HEMGENIX [prescribing information]. Kankakee, IL: CSL Behring LLC.

Program Requirements:

The Program must be accredited and fully compliant with the ACCME standards for commercial support.

CSL Behring's grant in support of the Program is not subject to any condition or restriction regarding the content or execution of the Program or the selection of Program presenters or faculty members. The grant recipient will be solely responsible for the selection of the Program venue, faculty and/or educational methods, and for the quality and scientific integrity of the Program. CSL Behring will not influence the grant recipient's exercise of these responsibilities, even if asked by the recipient to do so.

The grant recipient must ensure that: (i) the Program is free of commercial bias; (ii) the Program presents objective information about any product(s) based on scientific methods generally accepted in the medical community; (iii) if CSL Behring products, or other productsused to treat or being investigated to treat the same indications, are featured in the Program, featured data is objectively selected and presented, with both favorable and unfavorable information in respect of the products fairly represented, and that there is a balanced presentation and, if applicable, interactive discussion of the prevailing body of scientific information in respect of the products and alternative treatment options; (iv) there is meaningful disclosure during the Program of any limitations on information presented in the Program; and (v) if the Program addresses unapproved (unlabeled) uses of any product, or an investigational use not yet approved for any purpose, the Program includes disclosure that the product is not approved in the United States for the use under discussion or, as may be applicable, that the product is still under investigation in respect of such unapproved use.

The grant recipient also must ensure meaningful disclosure in Program announcements and materials, and to the audience during the Program, that (i) CSL Behring is funding the Program, and (ii) a relationship exists between the grant recipient and CSL Behring and, if applicable, between the Program presenters or faculty and CSL Behring.

Additional requirements will be included in the Grant Agreement between CSL Behring and the grant recipient to be executed following award of the grant.