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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 "**GT2024L**"
- 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:	April 26th, 2024
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 $350,000.

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 gene therapy options for hemophilia with a focus on outcome differences between hemophilia A/B, and clinical differentiation between hemophilia B gene therapy options.

Needs Assessment: Differentiation of Gene Therapy Treatment Options for Hemophilia A/B and between Hemophilia B Gene Therapy Treatment Options.

HEMGENIX® (etranacogene derzaparvovce-drlb), the first gene therapy product approved for the treatment of hemophilia B, was approved in November of 2022, shortly followed by the approval of ROCTAVIAN® (valoctogene roxaparvovec), a gene therapy product for the treatment of hemophilia A, in June 2023.[1,2] While both current FDA-approved gene therapy treatment options for hemophilia utilize a recombinant adeno-associated viral (AAV) vector for delivery of the transgene to the liver, there is a distinction in the clinical outcomes associated with each therapeutic option.[3,4] Furthermore, with other gene therapies on the horizon, including one with an anticipated approval in 2024 for hemophilia B, it is vital that HCPs understand all clinical data available to inform their decision-making.

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.[3] 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.[4] 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.[5]

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Factor Expression: Both valoctocogene roxaparvovec and etranacogene dezaparvovec have phase III published data for 3 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 and 18.4 IU/dL at year 3. At year 3, 24.2% of trial participants had a FVIII level <3 IU/dL and 17/134 (12.6%) returned to continuous prophylaxis.[6] Via a linear mixed-effects approach, FVIII transgene expression was extrapolated for up to 5 years with valoctogene roxaparvovec.[3] Etranacogene dezaparvovec FIX expression has remained consistent with a mean of 41.5 IU/dL at year one, 36.7 IU/dL at year 2, and 38.6 at year 3. At year 3, one participant had a FIX level <5% and 3/54 (5.6%) of etranacogene dezaparvovec participants returned to continuous prophylaxis.[7] Through a linear mixed models approach estimated FIX levels were extrapolated to 25 years with etranacogene dezaparvovec.[8]

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.[3] Throughout year 2 and 3, there continued to be ALT elevation in participants with 39 (29.1%) and 34 (25.4%) participants respectively.[6] 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 years 2 and 3, there was no additional ALT elevation observed.[4,7]

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.[9] The prescribing information for etranacogene dezaparvovec requires weekly monitoring of ALT and AST for 3 months post-administration, with additional guidance to "regularly" monitor FIX and ALT/AST.[10]

The gene therapy options for hemophilia A and B have clinically distinct outcomes. 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, with new gene therapy options emerging within hemophilia B it is equally important for providers to understand the full spectrum of clinical data available to inform their decision-making.

References:

1. 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
2. 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
3. Ozelo MC, Mahlangu J, Pasi KJ, et al. Valoctocogene roxaparvovec gene therapy for hemophilia A. N Engl J Med. 2022;386(11):1013-1025.
4. 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.
5. 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.
6. 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.
7. 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.
8. Shah J, Kim H, Sivamurthy K, Monahan PE, Fries M. Comprehensive analysis and prediction of long-term durability of factor IX activity following etranacogene dezaparvovec gene therapy in the treatment of hemophilia B. Current Medical Research and Opinion. 2023;39(2):227-237.
9. ROCTAVIAN[prescribing information]. Novato, CA: BioMarin Pharmaceutical Inc.
10. 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.