BioMarin Pharmaceutical Inc. Response to 18-month Follow-up for Evidence Regarding "Gene Therapy for Hemophilia B and An Update on Gene Therapy for Hemophilia A: Effectiveness and Value" Report

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BioMarin Pharmaceutical Inc. appreciates the opportunity to submit new evidence regarding valoctocogene roxaparvovec (ROCTAVIAN™) since the publication of the report, "Gene Therapy for Hemophilia B and An Update on Gene Therapy for Hemophilia A: Effectiveness and Value" published on December 22, 2022 to be included as an addendum to the existing report. Several publications and congress presentations have continued to add evidence regarding clinical, economic, and health-related quality of life (HRQOL) data for ROCTAVIAN, the first adeno-associated virus vector-based gene therapy indicated for the treatment of adults with severe hemophilia A (HA).

- **Longer-term safety and outcomes:** Four-year outcomes on the efficacy and safety of valoctocogene roxaparvovec in GENEr8-1 showed continued long-term FVIII expression, bleed control, and improvements in HRQOL,[1] consistent with earlier time points, including three-year outcomes.[2] No new safety signals emerged. Updated outcomes have also been reported for five- to seven-years.[3,4] The safety and efficacy remained consistent with previous reports, demonstrating haemostatic control for most participants. Pharmacokinetic modeling has also simulated that FVIII activity levels remain in the mild hemophilia range for ≥5 years post-gene transfer for most patients treated.[5]
- **Comparative analyses:** Comparative effectiveness of valoctocogene roxaparvovec versus FVIII prophylaxis was evaluated using propensity scoring.[6] Participants receiving valoctocogene roxaparvovec experienced lower annualized bleed rate, and a higher proportion had zero bleeds compared to participants receiving prophylactic FVIII. In a matching-adjusted indirect comparison of bleeding outcomes, valoctocogene roxaparvovec provided lower bleeding rates and higher probability of no bleeds than emicizumab.[7]
- **Economic impact:** A model was developed to estimate the change in burden after the introduction of valoctocogene roxaparvovec over a 10-year horizon.[8] Assuming 10% of the cohort receive valoctocogene roxaparvovec, the cumulative 10-year reduction in national economic burden was $564 million, with cost savings demonstrated after 4 years.
- **HRQOL:** HRQOL was analyzed in adult men with severe HA without inhibitors after valoctocogene roxaparvovec gene transfer in the phase 3 trial GENEr8-1.[9] Valoctocogene roxaparvovec was shown to provide clinically meaningful HRQOL improvement at 12 weeks and maintained through at least 2 years post gene transfer.

Literature for Review

1. “Safety and efficacy of valoctocogene roxaparvovec gene transfer for severe hemophilia A: an update from 4 years after treatment.” Thsna.org, 2024, thsna.org/online-admin/mobile/show_presentation.php?abstractno=345. Accessed 05 July 2024.

2. Madan, Bella, et al. "Three-year outcomes of valoctocogene roxaparvovec gene therapy for hemophilia A." Journal of Thrombosis and Haemostasis (2024).

3. Symington, Emily, et al. "Long-term safety and efficacy outcomes of valoctocogene roxaparvovec gene transfer up to 6 years post-treatment." Haemophilia 30.2 (2024): 320-330.

4. Symington, Emily, et al. "Valoctocogene roxaparvovec gene therapy provides durable haemostatic control for up to 7 years for haemophilia A." Haemophilia (2024).

5. Loureiro, L., et al. "QUANTITATIVE PHARMACOKINETIC MODEL TO CHARACTERIZE AND EXTRAPOLATE LONG-TERM FVIII ACTIVITY LEVELS IN PATIENTS WITH SEVERE HEMOPHILIA A TREATED WITH VALACTOCOGENE ROXAPARVOVEC." Hematology, Transfusion and Cell Therapy 45 (2023): S451.

6. Oldenburg, Johannes, et al. "Comparative Effectiveness of Valoctocogene Roxaparvovec and Prophylactic Factor VIII Replacement in Severe Hemophilia A." Advances in Therapy (2024): 1-15.

7. Astermark, Jan, et al. "Matching-adjusted indirect comparison of bleeding outcomes in severe haemophilia A: Comparing valoctocogene roxaparvovec gene therapy, emicizumab prophylaxis, and FVIII replacement prophylaxis." Haemophilia 29.4 (2023): 1087-1094.

8. Wang, T., et al. "EE706 Impact of Valoctocogene Roxaparvovec on the Economic Burden of Adults with Severe Hemophilia A Managed with Prophylaxis in the United States." Value in Health 26.12 (2023): S190.

9. O’Mahony, Brian, et al. "Health-related quality of life following valoctocogene roxaparvovec gene therapy for severe hemophilia A in the phase 3 trial GENEr8-1." Journal of Thrombosis and Haemostasis 21.12 (2023): 3450-3462.

Update in Hemophilia A, B Gene Therapy (Dr. Margaret V. Ragni, MD, MPH)
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In 2024 there have been a few updates in hemophilia gene therapy, pertaining to durability, joint health, inhibitor resolution, HIV infection, minimum data collection, and liver health monitoring.

1) Durability of FVIII, FIX expression after gene therapy

- Long-term follow-up by the first open-label phase 1,2 dose escalation hemophilia A trial[1] seven years after valoctocogene roxaparvovec, reported (at the June 2024 ISTH meeting) durable FVIII expression (n=13) with a median FVIII activity 10.3 IU/dL in the $6x10^{13}$ vg/kg cohort and 7.2 IU/dL in the $4x10^{13}$ vg/kg cohorts, mean 96% and 88% decrease in ABR, and 95% and 93% decrease in factor use, respectively, with no safety issues.

- Long-term follow-up by the phase 3 GENEr8-1 intention to treat trial[2] four years after valocotcogene roxaparvovec, reported (at the June 2024 ISTH meeting) durable FVIII expression (n=112) after $6x10^{13}$ vg/kg, a median FVIII 16.1 IU/dL (chromogenic) and 27.1 IU/dL (one-stage). During year 4, no immunosuppressants for ALT elevation were initiated, with no safety issues.

- Long-term follow-up by the phase 2b AMT-060 hemophilia B trial[3] five years after etranacagene dezaparvovec, reported (at the June 2024 ISTH meeting) durable FIX expression in 3 participants, with FIX 46.8%, 39.0%, and 51.2%, and one bleed, with no safety issues.

- Long-term follow-up of a phase 1,2 SPARK-8011 hemophilia A trial[4] four years after dirloctocogene samoparvovec and novel (non-steroid) toxilizumab or mycophenolate mofetil immunosuppression, reported (at the June 2024 ISTH meeting) durable FVIII expression (N=25) after $5x10^{11}$, $1x10^{12}$, $1.5x10^{12}$, or $2x10^{12}$ vg/kg, with vector-related and immunomodulation-related AEs). Non-steroid immune prophylaxis does not eliminate steroid use.

2) Long-term improvement in joint health after gene therapy

- Joint health among (N=24) participants of the phase 1,2 dirloctocogene samoparvovec trial (SPK-8-11),[5] reported at the April 2024 World Federation of Hemophilia Congress, indicates resolution of all target joints and improved JHJS scores and activity at median 191 weeks.

3) Early data reporting eradication of inhibitors using HA gene therapy

- Preliminary results from the GENEr8-INH phase 1,2 trial,[6] (same product, dose as GENEr8-3 trial) reported at the April 2024 EAHAD Congress, suggest the potential the tolerization potential of gene therapy. One participant with a past non-tolerized inhibitor, peak 72 BU, 2.2 BU at study baseline, following anamnestic inhibitor response to 20 BU at week 9 requiring transient steroids, experienced an increase in FVIII Ag at week 12

and FVIII at 13 IU/dL at 32 weeks and inhibitor decline to 0 BU by week 32. These findings mirror previously reported findings in hemophilia dogs[7] and in vitro studies.[8]

4) ISTH SC WG recommended Minimum Data set for monitoring gene therapy

- The WFH Gene Therapy Registry for all gene therapy recipients recommends demographic, diagnostic, AAV antibody, HIV/HCV/HBV status, safety, LFT, immunosuppression, inhibitor development, efficacy (factor activity, factor use, bleeds), and mortality data.[9]

5) Liver Health Monitoring before and after HA gene therapy

- While current liver-based AAV-based gene therapy depends on healthy hepatocyte function, those with hemophilia may have past or current hepatitis C virus and/or metabolic dysfunction-associated steatohepatitis. This paper provides practical guidance to assess and monitor potential liver health before and after gene therapy.

References:

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