haematologica
Journal of the Ferrata Storti Foundation

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Received: November 10, 2026.
Accepted: November 16, 2026.

Citation: Manuel Rodríguez López and Michael Calviño Suárez. Analytical harmonization and clinical comparability of gene therapies for hemophilia B. Comment on: "Adeno-associated virus gene therapy for hemophilia B: a comparative appraisal of the licensed products".
Haematologica. 2026 Nov 26. doi: 10.3324/haematol.2026.302342 [Epub ahead of print]

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Analytical harmonization and clinical comparability of gene therapies for hemophilia B. Comment on: "Adeno-associated virus gene therapy for hemophilia B: a comparative appraisal of the licensed products"

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Running head

Assay harmonization and clinical comparability

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Contributions

MRL: Conceptualization (lead), investigation, writing – original draft (lead), writing – review and editing.

MCS: Conceptualization (supporting), investigation, writing – review and editing.

Both authors contributed to the scientific discussion and interpretation of the literature, critically revised the manuscript, and approved the final version.

Data-sharing statement

Data sharing is not applicable to this article. No new data were generated or analysed. All figures discussed are taken from the published sources cited in the reference list.

Disclosures

Dr. Rodriguez Lopez has participated as speakers, in advisory boards and sponsored symposia with Novo Nordisk, Takeda, Roche, Pfizer, Octapharma, Amgen, Novartis, CSL Behring and Sobi. Dr Calviño Suarez has participated as speaker and advisory boards and sponsored symposia of Sobi, Amgen, Novonordisk, Roche and Rovi.

Artificial Intelligence

The authors used Google Flash, Gemini for translation of the manuscript from Spanish into English and for language editing of the authors' own draft. All references were identified, retrieved and verified by the authors. The authors take full responsibility for the content of the manuscript, including its accuracy and integrity.

We have read with interest the review by Miesbach and Pierce comparing the three FIX-Padua gene therapies approved for hemophilia B.[1] Expressing factor IX (FIX) activity on a single one-stage scale, based on the HemosIL SynthASil reagent, is a useful step. It reduces a source of variability that has made the reading across trials difficult. The authors recognize that populations, doses, manufacturing and follow-up differ. From this caution we want to raise two questions: what does a common activity scale allow us to compare? and what differences remain once it is harmonized?

The abstract states that standardization permits a “like-for-like” comparison. The mean of 55.1 IU/dL of dalnacogene ponparvovec (DP) in phase 3 is presented as “directly comparable” because it was obtained with the same reagent.[1] We understand that both expressions refer to analytical activity. In this sense they are correct. Sharing the reagent allows the measured means to be ordered numerically. It does not, by itself, convert this order into a hierarchy of clinical benefit. The authors themselves point this out in the text. They remind us that no method for determining FIX activity has been validated against bleeding outcomes after gene therapy. In addition, differences between trials should moderate any classification based on activity.[1]

It would be convenient to keep a second distinction visible. FIX-Padua activity depends on the reagent employed.[2] Table 3 combines values measured with SynthASil and estimates obtained by multiplying Actin FSL results by 1.3. This factor comes from paired samples. The relation between reagents varies with the level of activity.[1,3] In the phase 3 trial of DP, the SynthASil/Actin FSL ratio was 1.35, with a standard deviation of 0.54.[4] The authors present these values only as orientation. However, in the same column an estimated value of about 77 IU/dL in six participants appears next to a

measured value of 55.1 IU/dL in 26. A reader could interpret them as equivalent. Presenting converted values separately, or with some indication of their uncertainty, would help to avoid it.

Bleeding results show that the time window is part of the result. In Table 2, the proportion of participants without bleeds is expressed in three ways: at least 67% in each semestral period between months 7 and 24 for etranacogene dezaparvovec, 64% between week 12 and month 15 for fidanacogene elaparvovec and 81% between day 1 and week 52 after infusion for DP.[1,4-7]

These figures do not describe the same magnitude. A proportion that is maintained in each semestral interval does not indicate how many participants remained without bleeds during the whole period of months 7 to 24. Participants without bleeds in one semester may not be the same as in the next. In Figure 2B, the value of HOPE-B, the pivotal trial of etranacogene dezaparvovec, appears labeled as months 7 to 24, together with proportions calculated over other windows. This representation could suggest an equivalence that the summary data do not establish. Annualized bleeding rates raise a similar question. They were calculated between months 7 and 60, between week 12 and month 15, and between day 1 and week 52. The authors of the DP trial themselves note that their evaluation started on day 1, in contrast with the delayed windows of the other two trials.[4] Only two of the trials had a prospective intrapatient prior period. The DP trial compared its result with an assumed reference rate of 5.0.[1,4] In HOPE-B the annual rate decreased progressively to 0.40 in years 4 and 5,[5] so the chosen window conditions the reported value. None of this takes value away

from the individual trials. It means that the bars of Figure 2 answer somewhat different questions.

Means could also hide different distributions. In the adolescent cohort of DP, mean activity was 41.8 IU/dL with a standard deviation of 30.1.[1] When distributions are reported, thresholds and timepoints of evaluation do not coincide. HOPE-B uses a threshold of at least 12 IU/dL at five years. In the phase 3 trial of DP, the threshold was more than 5 IU/dL at week 52.[4,5] Immunosuppression is another difference that analytical harmonization does not solve. Two trials used corticosteroids in a reactive way and one in a prophylactic way. The proportions of corticosteroid use in Table 2 reflect the design of the trial as much as the clinical need.[1] Describing exposure according to strategy, duration and cumulative dose would allow assessment of the therapeutic burden that accompanies the observed expression.

We propose a way to present future comparisons, without creating a new composite index. At common moments of follow-up, for example at 12, 24 and 60 months, FIX activity could be reported as a mean together with its distribution, indicating whether each value was measured or converted. The proportion of participants without bleeds during the whole interval could also be reported, separated from the proportion without bleeds in each subinterval. It would be convenient as well to communicate the restart of prophylaxis, the episodic use of FIX, which a part of patients could require in case of surgery or trauma,[8] and the exposure to corticosteroids.

Each reported proportion would need an explicit denominator. This should indicate if it includes nonresponders and those who restarted prophylaxis. We would keep these

outcomes separate. Combining them in a single score could hide differences that are relevant for each patient. Within the same figure it could be helpful to separate increases of least squares means from absolute means, as the legend of Figure 1 already explains for HOPE-B.[1] The common scale proposed by Miesbach and Pierce makes this type of presentation more feasible. Making its clinical scope as explicit as its analytical basis would help these data to serve in the shared decision with each patient.

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