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ORIGINAL ARTICLE

Effect of etranacogene dezaparvovec on quality of life for severe and moderately severe haemophilia B participants: Results from the phase III HOPE-B trial 2 years after gene therapy

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Abstract

Introduction: For people with haemophilia B (PwHB), bleeding may occur despite prophylaxis, negatively affecting health-related quality of life (HRQoL). The pivotal phase 3 HOPE-B trial investigating the adeno-associated virus gene transfer product, etranacogene dezaparvovec (EDZ), demonstrated sustained factor IX (FIX) activity and bleed protection in PwHB with baseline FIX levels ≤2%.

Aim: Assess how EDZ affects HRQoL in HOPE-B trial participants.

Methods: HRQoL was evaluated using generic and disease-specific patient reported outcomes (PROs) including the EQ-5D-5L and the Hem-A-QoL questionnaires. Mean domain and total scores were compared 6 months pre- and the first 2 years post-EDZ administration using repeated measures linear mixed models. The percentage of participants with minimal clinically important improvements in HRQoL was also evaluated.

Results: Two years post-EDZ, there were nominally significant increases in the least squares (LS) mean score for the EQ-5D-5L Index Value (.04; $p = .0129$), reflecting better HRQoL. Nominally significant decreases in the LS mean scores, reflecting better HRQoL, were also found for the Hem-A-QoL total score (−6.0; $p < .0001$) and the Treatment (−13.94; $p < .0001$), Feelings (−9.01; $p < .0001$), Future (−6.45; $p = .0004$) and Work/School (−5.21; $p = .0098$) domains. The percentage of participants with ≥15-point improvement ranged from 45.83% (95% CI: 31.37%, 60.83%) for Treatment to 13.89% (95% CI: 4.67%, 29.50%) for Family Planning. Results were similar for Year 1.

Conclusion: In conclusion, gene therapy with EDZ improved HRQoL in the first and second years in several Hem-A-QoL domains, including Treatment, Feelings, Work/School and Future domains, whereas improvement in other aspects of HRQoL were not demonstrated.

KEYWORDS
adeno-associated virus, Gene therapy, haemophilia B, patient-reported outcomes, quality of life

1 | INTRODUCTION

Haemophilia B is a rare, X-linked, congenital bleeding disorder caused by pathogenic mutations in *F9*, the gene coding coagulation factor IX (FIX), affecting approximately 33,000 individuals worldwide in 2020.[1,2] Joint bleeds are a major concern, resulting in chronic pain, long-term joint damage and mobility deficits.[3] Bleeds cause fear and impairment in physical functioning that negatively affects health-related quality of life (HRQoL).[4]

Haemophilia B treatment currently involves FIX replacement with either standard or extended half-life products.[1,5] FIX replacement adherence can be difficult, with 25% of people with haemophilia aged 18–30 years being non-adherent, and some choosing to decrease their dosing frequency to mitigate this burden.[6,7] FIX activity levels fluctuate and people with haemophilia B (PwHB) may experience bleeds.[8] Joint damage can occur despite prophylaxis, resulting from inadequate control of clinical and subclinical bleeding.[3,9,10] The time required for administration of prophylaxis negatively affects HRQoL by interfering with daily activities, relationships, and decisions regarding careers or education.[11,12]

Etranacogene dezaparvovec (EDZ) may help address some of the unmet needs of PwHB utilising FIX replacement prophylaxis. The pivotal phase 3 HOPE-B trial investigating this adeno-associated virus-5 (AAV5) gene transfer product demonstrated sustained FIX activity and bleed protection in haemophilia B participants with FIX levels ≤2%.[13] Stable FIX activity levels were seen two years post-infusion.[14] Annualised bleeding rate (ABR) was significantly reduced by 64% (p = .0002) compared with infusion-based prophylaxis, and 96% ($p < .0001$) of participants discontinued prophylaxis.[14]

This study demonstrates how EDZ affected HRQoL using the various generic and disease-specific patient reported outcomes (PROs) included in the HOPE-B study.

2 | MATERIALS AND METHODS

2.1 | Trial design and study population

The HOPE-B phase 3 study (NCT03569891) is an open-label, single-dose, multi-centre, multi-national trial conducted at 33 sites across the United States ($n = 17$), the European Union ($n = 13$) and the United Kingdom ($n = 3$). The study is conducted in accordance with International Council for Harmonisation Good Clinical Practice guidelines and ethical principles originating in the Declaration of Helsinki. The protocol was approved by appropriate institutional review boards and independent ethics committees at each study site. All the participants provided written informed consent. After a lead-in period (≥6 months) of standard-of-care FIX prophylaxis, one dose of AAV5 vector expressing the padua FIX variant (EDZ; 2×10^{13} genome copies/kg) was infused in 54 men with haemophilia B (mean age 41.5 years; FIX activity ≤2%). Participants with a history of FIX inhibitor development, uncontrolled human immunodeficiency virus infection and advanced liver fibrosis were excluded. Figure 1 depicts the study design with the PRO schedule of assessments. Additional information regarding the clinical trial objectives has been previously published.[14] Here, we analyse the HRQoL data for the full analysis set (FAS) with all 54 participants included. Additionally, the results for the full-dose, treatment-responsive population ($n = 52$) and the two participants excluded from this population are included in the online supplement in Tables S1 and S2. These two participants never discontinued prophylactic FIX infusions and their reported outcomes may represent HRQoL associated with prophylaxis instead of gene therapy. One participant (Subject A) was excluded because he only received a partial dose (~10%) but continued in the study. The other excluded participant (Subject B) had an exceptionally high pre-dose AAV5 neutralising antibody (NAb) titre of 3212 on the day of dosing and did not respond to treatment.

2.2 | Patient reported outcomes (PROs) included in the HOPE-B study

The generic PROs included the EQ-5D-5L,[15] the International Physical Activity Questionnaire (IPAQ),[16] the Brief Pain Inventory (BPI) short form,[17] and the Work Productivity and Activity Impairment (WPAI) Questionnaire.[18] The disease-specific PROs included the Haemophilia Activities List (HAL),[19] and the Haemophilia Quality of Life Questionnaire for Adults (Hem-A-QoL).[20] The effect of treatment on the mean EQ-5D-5L Visual Analogue Scale (VAS) and the IPAQ summary scores in the first 12 months after EDZ were included as secondary endpoints in the trial. All other PRO domains and total scores were included as exploratory endpoints not adjusted for multiplicity.

The EQ-5D-5L includes a descriptive profile (Index Value) as well as a VAS score.[15] The Index Value reflects responses to five questions associated with mobility, self-care, usual activities, pain/discomfort and anxiety/depression. A numerical value is then linked to each combination of responses to reflect how good or bad a health state is according to the preferences of the general population in a given country.[21] The values vary from 0 to 1, with higher scores reflecting better HRQoL.[21] For the VAS, respondents rate their overall health on a 0–100 scale on the day of reporting from 'worst imaginable health state' to 'best imaginable health state'.[15] The IPAQ measures the level of physical activity performed in the last 7 days using metabolic equivalent task (MET) minutes per week.[16] The BPI short form measures pain intensity as well as pain interference with activities in the last 24 h.[17] The WPAI measures absenteeism, presenteeism or the degree to which a health condition interferes with productivity while at work, work productivity loss reflecting both absenteeism and presenteeism, and impairments in unpaid activity because of health problems in the last 7 days.[18] The HAL measures the impact of haemophilia on self-perceived functional abilities in adults across seven domains: lying/sitting/kneeling/standing, function of the legs, function of the arms, use of transportation, self-care, household tasks, and leisure activities/sport in the past month.[19] The Hem-A-QoL measures the impact of haemophilia on HRQoL across ten domains, with lower scores indicating less impairment due to haemophilia in the past

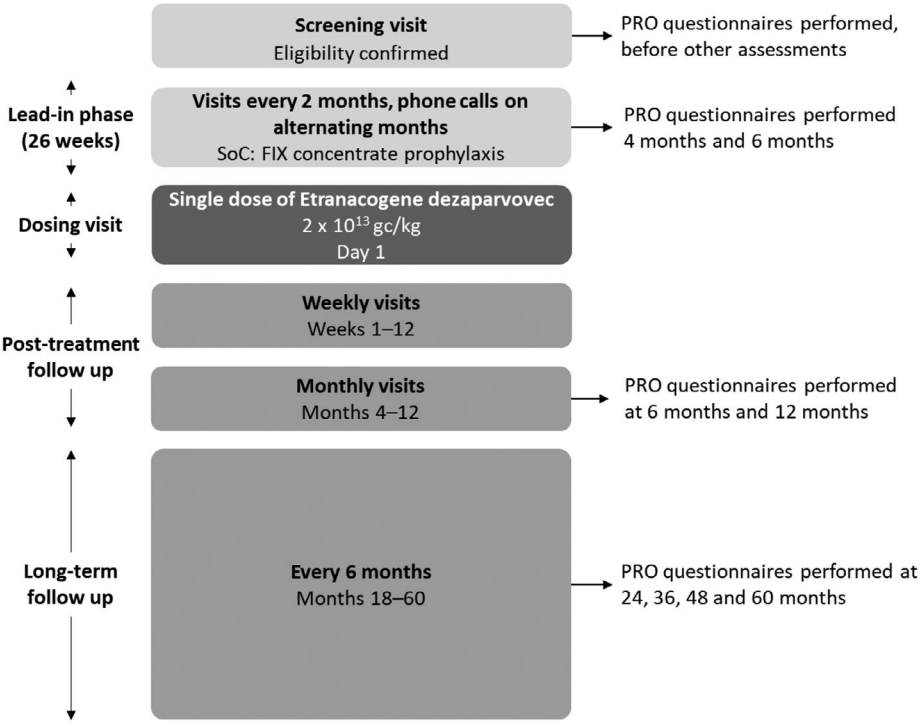

FIGURE 1 Trial design including PRO timepoints. FIX, factor IX; PRO, patient reported outcomes; SoC, standard of care.

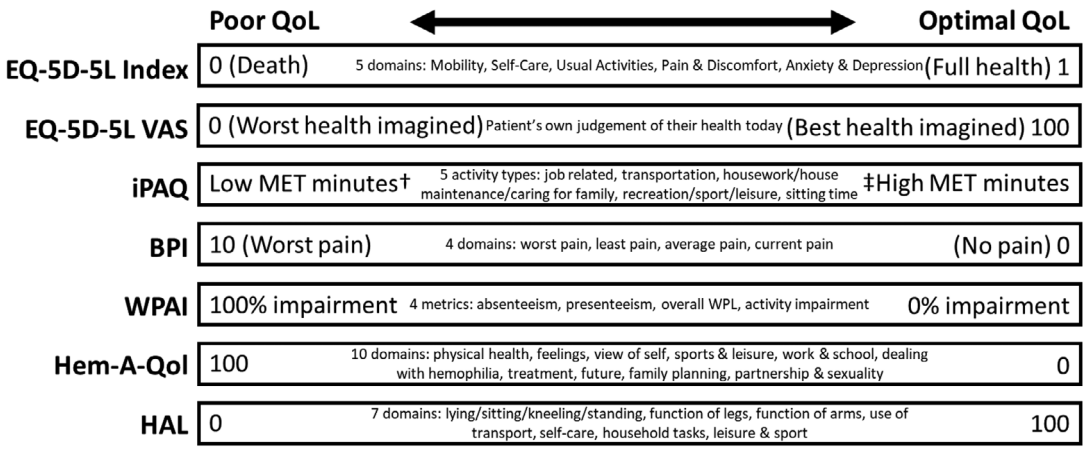

FIGURE 2 Scales Used in the Patient Reported Outcomes (PROs) Included in the HOPE-B Study. †Low MET minutes are considered ≤600 min.[35] ‡High MET minutes are considered ≥3000 min.[35] BPI, Brief Pain Inventory; HAL, Haemophilia Activities List; Hem-A-QoL, Hemophilia Quality of Life Questionnaire for Adults; IPAQ, International Physical Activity Questionnaire; MET, metabolic equivalent task; QoL, quality of life; VAS, Visual Analogue Scale; WPAI, Work Productivity and Activity Impairment; WPL, work productivity loss.

4 weeks.[20,22] Descriptions of the ten domains are provided in the legend for Table 2. The domains and range of scores for all the PROs can be seen in Figure 2.

2.3 | Statistical analysis

Repeated measures linear mixed models (MMRM) were used to evaluate the effect of treatment on mean scores before and after receiving EDZ. Mean total scores were evaluated for the IPAQ, the HAL, and the Hem-A-QoL. Mean domain scores were only evaluated for these PROs if there were nominally significant improvements in the summary scores or no summary scores exist. Since the EQ-5D-5L, the WPAI, and the BPI did not have total summary scores, MMRM was used to evaluate the effect of treatment on each of the domain scores for these PROs. Responder analyses were performed to assess the percentage of participants achieving minimal clinically important improvements, with exact Clopper Pearson 95% confidence intervals (CI) provided. Since there were very few established minimal clinically important thresholds in the published literature for these PROs, a 15% change in the

range of scores was used based on the recent Institute for Quality and Efficiency in Health Care guidance.[23] For the PROs with a 100-point range in scores, the minimal clinically important threshold was 15 points. For those PROs where higher scores reflect better HRQoL, the threshold was based on a ≥15% increase in scores. For those PROs where lower scores reflect better HRQoL, the threshold was based on a ≥15% reduction in scores. Separate analyses were conducted based on the FAS ($n = 54$) and the full-dose, treatment-responsive population ($n = 52$) for the first and second years after EDZ. In addition, Table S3 in the supplement provides the mean, median and either the minimum scores for those PROs where lower scores reflect better HRQoL, or maximum scores for those PROs where higher scores reflect better HRQoL, for the participants who exceeded the 15% threshold and those participants who did not exceed the threshold, in the FAS.

Details regarding the MMRM models are included in the footnotes for the respective tables. The one-sided p-value and two-sided 95% CI are presented. The treatments were compared for superiority. Questionnaires completed within 2 weeks after a bleeding episode were not included in the analysis because bleeds are more likely in the lead-in period. This could result in an overestimation of the difference between lead-in and post-treatment. A comparison of the change in the categorical responses for the EQ-5D-5L descriptive profile was also presented to explain changes in the EQ-5D-5L Index Value.

3 | RESULTS

3.1 | Summary scores for the IPAQ, HAL, and the Hem-A-QoL based on the FAS

The PRO results for the first and second years after EDZ are presented in Tables 1 and 2. The least squares (LS) mean for the average of the lead-in month 4 and final visits may differ somewhat between the first and second year because the statistical model makes adjustment for all the data employed in the respective analyses. There were no nominally significant differences in the mean summary scores before and after EDZ for the IPAQ or the HAL. However, there were nominally significant improvements in the Hem-A-QoL total score. The LS mean difference (standard error [SE]) between the post-treatment period and lead-in period was −5.50 (.97; nominal $p < .0001$) in the first year and −6.0 (1.15; nominal $p < .0001$) in the second year after receiving EDZ. The percentage of participants achieving a minimal clinically important threshold of ≥15 points (as per Institute for Quality and Efficiency in Health Care guidance) was 17.02% (95% CI: 7.65%, 30.81%) and 15.22% (95% CI: 6.34%, 28.87%) in the first and second years after receiving EDZ, respectively.

3.2 | Hem-A-QoL domain scores based on the FAS

Four Hem-A-QoL domains mainly contributed to the improvement in the total score (Table 2). They included Treatment, Feelings, Future and Work/School. In the first year after receiving EDZ, the LS mean differences (SE) between the post-treatment period and the lead-in period were as follows: Treatment −14.88 (1.79; nominal $p < .0001$), Feelings −9.42 (1.94; nominal $p < .0001$), Future −5.02 (1.74; nominal $p = .0023$) and Work/School −4.99 (1.83; nominal $p = .0036$). In the second year after receiving EDZ, the LS mean differences (SE) between the post-treatment period and the lead-in period were as follows: Treatment −13.94 (2.00; nominal $p < .0001$), Feelings −9.01 (1.92; nominal $p < .0001$), Future −6.45 (1.82; nominal $p = .0004$) and Work/School −5.21 (2.17; nominal $p = .0098$). Results were not nominally significant for the six remaining Hem-A-QoL domains in the first or second years after receiving EDZ. Of those four domains with nominally significant improvements, the percentage of participants achieving the minimal clinically important threshold of ≥15-point improvement was 45.83% (95% CI: 31.37%, 60.83%) for Treatment, 28.57% (95% CI: 16.58%, 43.26%) for Feelings, 26.53% (95% CI: 14.95%, 41.08%) for Future and 15.79% (95% CI: 6.02%, 31.25%) for Work/School in Year 2. Similar results were found for Year 1. For those six domains where there were no nominally significant improvements, the percentage of subjects achieving a minimal clinically important threshold of ≥15 point improvement ranged from 32.65% (95% CI: 19.95%, 47.54%) for Sports & Leisure to 13.89% (95% CI: 4.67%, 29.50%) for Family Planning in Year 2. The proportion above and below the threshold for all domain scores are presented in Table S3.

3.3 | Domain-specific scores for the EQ-5D-5L, BPI and the WPAI based on the FAS

There were no nominally significant improvements in pain intensity and pain interference in activities (based on the BPI) or absenteeism, presenteeism, work productivity loss and activity impairment (based on the WPAI) in the first 2 years after receiving EDZ for the FAS. There was also no significant improvement in the EQ-5D-5L VAS score in the first two years after receiving EDZ, and no change in the LS mean (SE) for the EQ-5D-5L Index Value in the first year. However, the EQ-5D-5L Index Value improved by .04 (.02; nominal $p = .0129$) in the second year after EDZ. The LS mean (SE) for the EQ-5D-5L Index Value for year 2 in the lead-in period was .79 (.03) and the LS mean (SE) of the month 12 and 24 visits was .84 (.02) for the year 2 post-treatment period. The improvement in the EQ-5D-5L Index Value in the second year was primarily due to improvements in pain and mobility and, to a lesser extent, usual activities. The proportion of participants reporting no or slight pain increased from 72.8% at the lead-in final visit to 78% at 24 months and the proportion with severe/extreme pain dropped from 11.4% at the lead-in final visit to 0% at 24 months. Similarly, the proportion of participants reporting no or slight problems walking increased from 77.2% at the lead-in final visit to 80% at 24 months. Those unable to walk or with severe problems walking decreased from 9.0% at the lead-in final visit to 0% at 24 months (Figure 3). The percentage of subjects exceeding the minimal clinically important threshold was 12.00% (95% CI: 4.53%, 24.31%) for the EQ-5D-5L Index Value in the second year after EDZ.

TABLE 1 Repeated measures linear mixed model results for year 1 and year 2 based on the full analysis set*.

PRO	Year 1			Year 2		
	LS mean lead-in (SE)†	LS mean post-treatment (SE)	LS mean difference, 95% CI, (SE) *p*-value‡	LS mean lead-in (SE)†	LS mean post-treatment (SE)	LS mean difference, 95% CI, (SE) *p*-value‡
IPAQ physical Activity summary score	4548.1 (512.38)	3826.9 (480.44)	−721.2 (528.61); 95% CI: −1770.6, 328.3; *p* = .9121	4185 (499.46)	3378.2 (471.28)	−806.8 (547.82); 95% CI: −1906.6, 293.0; *p* = .9265
HAL	79.73 (2.73)	80.89 (2.71)	1.16 (1.29); 95% CI: −1.38, 3.71; *p* = .1843	79.6 (2.78)	81.4 (2.61)	1.8 (1.32); 95% CI: −.9, 4.4; *p* = .0905
Hem-A-QoL total score	25.56 (2.07)	20.06 (2.05)	−5.50 (.97); 95% CI: −7.42, −3.58; *p* < .0001	26.3 (2.21)	20.3 (2.03)	−6.0 (1.15); 95% CI: −8.3, −3.7; *p* < .0001
EQ-5D-5L VAS score	80.9 (2.20)	81.0 (2.15)	.1 (1.84); 95% CI: −3.5, 3.8; *p* = .4753	81.1 (2.11)	83.6 (1.67)	2.6 (1.40); 95% CI: −.2, 5.4; *p* = .0363
EQ-5D-5L index value	.79 (.03)	.83 (.03)	.03 (.02); 95% CI: −.01, .07; *p* = .0530	.79 (.03)	.84 (.02)	.04 (.02); 95% CI: .01, .08; *p* = .0129
BPI pain intensity	2.20 (.28)	1.96 (.28)	−.25 (.14); 95% CI: −.53, .04; *p* = .0431	2.2 (.29)	1.9 (.26)	−.3 (.15); 95% CI: −.6, .0; *p* = .9589
BPI pain interference	1.85 (.31)	1.64 (.30)	−.21 (.16) 95% CI: −.52, .11; *p* = .1023	1.9 (.34)	1.6 (.29)	−.3 (.18) 95% CI: −.7, .1; *p* = .9491
WPAI absenteeism	4.58 (1.81)	2.91 (1.83)	−1.67 (1.75); 95% CI: −5.15, 1.81; *p* = .1716	5.1 (1.78)	3.1 (1.76)	−2.1 (2.46); 95% CI: −6.9, 2.8; *p* = .7965
WPAI presenteeism	16.74 (3.66)	13.32 (3.64)	−3.41 (2.75); 95% CI: −8.88, 2.05; *p* = .1088	16.2 (3.87)	10.3 (2.84)	−5.9 (3.25); 95% CI: −12.4, .6; *p* = .9620
WPAI work productivity loss	15.49 (3.63)	14.01 (3.60)	−1.48 (2.27); 95% CI: −6.00, 3.04; *p* = .2582	16.1 (3.80)	11.7 (2.85)	−4.4 (2.85); 95% CI: −10.1, 1.4; *p* = .9337
WPAI activity impairment	21.91 (3.64)	19.47 (3.55)	−2.44 (3.05); 95% CI: −8.48, 3.61; *p* = .2133	21.8 (3.78)	18.6 (3.26)	−3.1 (3.14); 95% CI: −9.4, 3.2; *p* = .8379

BPI, Brief Pain Inventory; CI, confidence interval; HAL, Haemophilia Activities List; Hem-A-QoL, Hemophilia Quality of Life questionnaire for Adults; IPAQ, International Physical Activity Questionnaire; LS, least squares; MMRM, repeated measures linear mixed models; PRO, patient reported outcome; SE, standard error; VAS, Visual Analogue Scale; WPAI, Work Productivity and Activity Impairment.

*For the year 1 comparisons, the MMRM models included phase (lead-in or post-treatment), visit, and phase-by-visit interaction as categorical covariates; subject was modelled as a random effect. For the year 2 comparisons, the MMRM model included visit as the sole categorical covariate. Visits were given equal weight. In year 1, the mean across the visits for the post-treatment period (month 6 and month 12 visits) was compared with the mean across the visits from the lead-in period (month 4 and last visit before infusion [L-Final]) using a contrast. In year 2, the mean across the visits for the post-treatment period (month 12 and month 24 visits) was compared with the mean across the visits from the lead-in period (month 4 and L-Final) using a contrast.

†The LS mean for the average of lead-in month 4 and final visits may differ somewhat between the first-year analysis and the second-year analysis because the statistical model makes adjustment for all the data employed in the respective analysis.

‡A one-sided p-value ≤.025 for the post-treatment, lead-in period was considered statistically significant. All but the IPAQ Physical Activity Summary Score and the EQ-5D-5L VAS scores in the first 12 months after gene therapy were exploratory, and these analyses were not adjusted for multiplicity.

3.4 | Additional sensitivity analyses

3.4.1 | Effect of excluding PRO assessments within two weeks of a bleed

Sensitivity analysis was done to explore the impact of including PRO assessments within two weeks of a bleed for the Hem-A-QoL total score and the four domain scores with a nominal p-value ≤.025; changes in these domains were most likely to influence the results. However, this led to minimal differences in scores. A full description of the sensitivity analysis is included in Figure S1.

3.4.2 | Comparison of PRO results for the full-dose, treatment-responsive population and the two participants excluded from this population

Overall, the study participant with baseline NAb titre ≥3000 had much poorer HRQoL during the lead-in period compared to the participant who received a partial dose. While there were improvements in the full-dose, treatment-responsive population for the LS mean EQ-5D-5L Index Value in Year 2, as well as the Hem-A-QoL Total Score and the Hem-A-QoL Treatment and Future domain scores in Years 1 and 2, no such improvements were observed for the two study participants

TABLE 2 Hem-A-QoL domain scores for year 1 and 2 based on the full analysis set*.

Domain	Year 1			Year 2		
	LS Mean Lead-In Score (SE)†	LS Mean Post-Treatment (SE)	LS Mean Difference, 95% CI, p-value‡	LS Mean Lead-In Score (SE)†	LS Mean Post-Treatment (SE)	LS Mean Difference, 95% CI, p-value‡
Total Score	25.56 (2.07)	20.06 (2.05)	−5.50 (.97); 95% CI: −7.42, −3.58; p < .0001	26.3 (2.21)	20.3 (2.03)	−6.0 (1.15); 95% CI: −8.3, −3.7; p < .0001
[a] Work/School	17.34 (2.56)	12.35 (2.53)	−4.99 (1.83); 95% CI: −8.61, −1.38; p = .0036	17.38 (2.81)	12.17 (2.04)	−5.21 (2.17); 95% CI: −9.56, −.87; p = .0098
[b] Feelings	20.61 (2.84)	11.19 (2.79)	−9.42 (1.94); 95% CI: −13.26, −5.59; p < .0001	20.32 (3.27)	11.30 (2.44)	−9.01 (1.92); 95% CI: −12.86, −5.17; p < .0001
[c] Treatment	25.24 (1.86)	10.36 (1.80)	−14.88 (1.79); 95% CI: −18.42, −11.34; p < .0001	25.91 (1.97)	11.98 (2.02)	−13.94 (2.00); 95% CI: −17.94, −9.93; p < .0001
[d] Future	30.94 (2.75)	25.92 (2.71)	−5.02 (1.74); 95% CI: −8.45, −1.58; p = .0023	31.18 (2.86)	24.73 (2.41)	−6.45 (1.82); 95% CI: −10.10, −2.80; p = .0004
[e] Physical Health	31.16 (3.74)	26.95 (3.70)	−4.21 (2.18); 95% CI: −8.52, .10; p = .0278	30.97 (3.86)	27.47 (3.38)	−3.51 (2.33); 95% CI: −8.17, 1.16; p = .0688
[f] Family Planning	11.12 (3.07)	9.73 (2.97)	−1.39 (3.18); 95% CI: −7.70, 4.93; p = .3316	11.49 (2.68)	10.83 (2.92)	−.66 (2.36); 95% CI: −5.40, 4.08; p = .3910
[g] Dealing with Haemophilia	18.52 (3.42)	22.97 (3.31)	4.45 (3.76); 95% CI: −2.99, 11.88; p = .8806	18.31 (2.65)	25.23 (3.4)	6.91 (3.38); 95% CI: .14, 13.69; p = .9771
[h] Sports and Leisure	41.09 (4.12)	39.27 (4.08)	−1.82 (2.45); 95% CI: −6.67, 3.03; p = .2296	41.38 (3.78)	37.56 (4.12)	−3.82 (2.88); 95% CI: −9.59, 1.96; p = .0952
[i] View of Yourself	33.01 (2.81)	30.71 (2.76)	−2.30 (2.01); 95% CI: −6.27, 1.67; p = .1270	33.19 (2.79)	29.74 (2.62)	−3.45 (1.88); 95% CI: −7.22, .32; p = .0360
[j] Partnership & Sexuality	9.45 (2.29)	8.07 (2.27)	−1.39 (1.23); 95% CI: −3.82, 1.05; p = .1311	9.56 (2.30)	8.54 (2.35)	−1.03 (1.29); 95% CI: −3.61, 1.56; p = .2151

CI, confidence interval; LS, least squares; MMRM, repeated measures linear mixed models; SE, standard error.

*For the year 1 comparisons, the MMRM models included phase (lead-in or post-treatment), visit, and phase-by-visit interaction as categorical covariates; subject was modelled as a random effect. For the year 2 comparisons, the MMRM model included visit as the sole categorical covariate. Visits were given equal weight. In year 1, the mean across the visits for the post-treatment period (month 6 and month 12 visits) was compared with the mean across the visits from the lead-in period (month 4 and last visit before infusion [L-Final]) using a contrast. In year 2, the mean across the visits for the post-treatment period (month 12 and month 24 visits) was compared with the mean across the visits from the lead-in period (month 4 and L-Final) using a contrast.

†The LS mean for the average of lead-in month 4 and final visits may differ somewhat between the first-year analysis and the second-year analysis because the statistical model makes adjustment for all the data employed in the respective analysis.

‡A one-sided p-value ≤.025 for the post-treatment, lead-in period was considered statistically significant. These are nominal p values and the analyses were not adjusted for multiplicity.

[a]Work/school considers how participants think haemophilia interferes with their performance.

[b]Feelings indicates the extent to which PwHB feel burdened, angry, worried or excluded because of haemophilia.

[c]Treatment reflects how burdened participants are by haemophilia.

[d]The future domain reflects concerns about how haemophilia will affect life plans.

[e]Physical health focuses on the effects of swelling, joint pain, and mobility due to haemophilia.

[f]Family planning considers whether PwHB are concerned about having or raising children.

[g]Dealing with haemophilia reflects their ability to recognise and control bleeds.

[h]Sports and leisure reflect the capability to plan and participate in sports and travel.

[i]The view of yourself domain indicates how having haemophilia affects self-esteem.

[j]Partnerships and sexuality indicate the extent to which PwHB are concerned about dating and intimate relationships.

excluded from the full-dose, treatment-responsive population. However, numerically, there did appear to be some improvements in the mean scores for the EQ-5D-5L VAS, the BPI Pain Intensity and BPI Pain Interference scores and the WPAI Work Productivity Loss. For the Hem-A-QoL domains, there also appear to be some numerical improvements in the Work/School, Feelings and View of Yourself domains. These results can be found in the online supplement in Tables S1 and S2.

3.4.3 | Comparison of lead-in scores for study participants with and without minimal clinically important improvements by domain score

As shown in Table S3, HRQoL was better in the lead-in period for those who did not achieve a 15% improvement compared to those who did achieve a 15% improvement. For example, in the group with <15% improvement in Year 1, the median scores in the lead-in period were

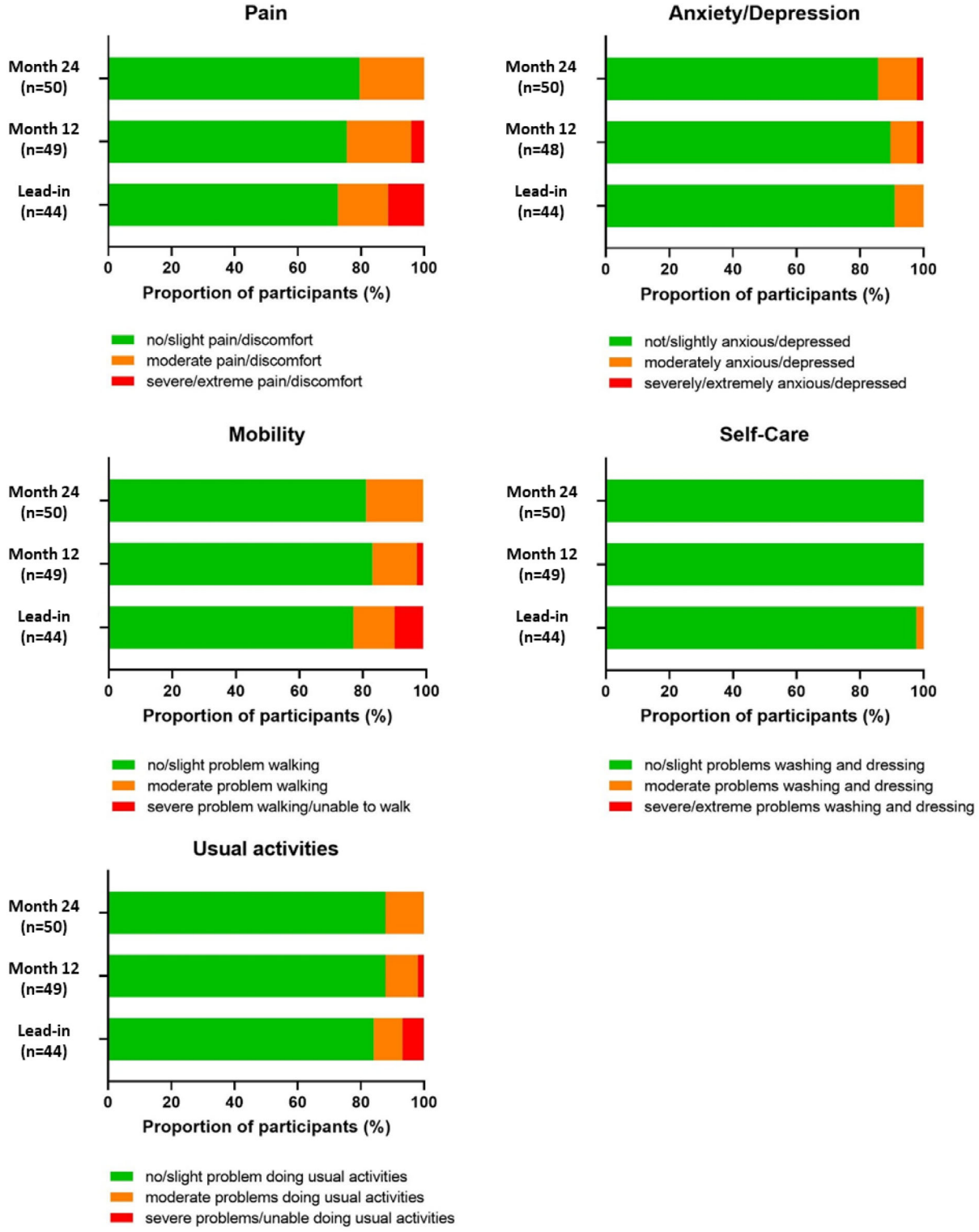

FIGURE 3 EQ-5D-5L index values for each domain, comparing lead-in to year 1 and 2 scores.

85.00 for the EQ-5D-5L VAS and .84 for the EQ-5D-5L Index Value. These scores are, in fact, comparable to the general US population norms without haemophilia B.[24] The other median PRO scores in the group who did not achieve a 15% improvement were 87.93 for the HAL, 1.63 for the BPI Pain Intensity score, .57 for the BPI Pain Interference score, 0 for WPAI Absenteeism, 0 for WPAI Productivity Loss, 0 for WPAI Activity Impairment and 16.88 for the Hem-A-QoL Total Score. By comparison, in the group with ≥15% improvement in Year 1, the median scores were 62.50 for the EQ-5D-5L VAS, .52 for the EQ-5D-5L Index Value, 51.35 for the HAL, 4.88 for the BPI Pain Intensity score,

TABLE 3 Comparison of HOPE-B Mean/Median Lead-in Scores with Observational Studies for the IPAQ, HAL, BPI and WPAI.

PRO	Lead-In Scores for HOPE-B	Scores for Observational Studies	Data Source
Mean IPAQ Summary Score	**4185** MET minutes/week*	1427.4 MET minutes/week	P-FIQ[28]
Median Total HAL Score	86.2 (month 4 visit)	60	B-HERO-S[29]
	85.7 (Final visit)	76.6	P-FIQ[28]
Median BPI Pain Intensity	1.8 (month 4 visit)	3.3	P-FIQ[28]
	1.5 (Final visit)	4.75†	B-HERO-S[29]
Median BPI Pain Interference with Activities	.7 (month 4 visit)	2.7	P-FIQ[28]
	1.4 (Final visit)		
Mean WPAI Scores*			
Absenteeism	**5.1%**	**0**‡	CHESS[27]
Presenteeism	16.2%	25.6%‡	CHESS[27]
Work Productivity Loss	16.1%	16.2%‡	CHESS[27]
Activity Impairment	21.8%	23.1%‡	CHESS[27]

*Values for the HOPE B trial are based on the LS means for the lead-in period.
†Patients with severe haemophilia.
‡The WPAI scores for the CHESS study were limited to the subgroup of haemophilia A patients on primary prophylaxis (N = 55).
P-FIQ is a cross-sectional observational study with Haemophilia A and B patients in pain, regardless of severity, in the US (295 Haemophilia A; 86 Haemophilia B). Median age 34 years. Participants must have joint pain and/or joint bleeding to be included. Severe haemophilia 70.5%; Moderate with joint involvement 13.2%; Mild with joint involvement 16.3%.
B-HERO-S is a prospective observational study with Haemophilia B regardless of severity in the US (N = 299). Mean age 29 years. Moderate haemophilia 63%; mild 25%; severe 11%.
CHESS is a retrospective, cross-sectional observational study with severe Haemophilia A and B in France, Germany, Spain, Italy and the UK (996 Haemophilia A; 289 Haemophilia B). Median age 24 years for primary prophylaxis and 26 years for secondary prophylaxis.

5.57 for the BPI Pain Interference score, 20.00 for WPAI Absenteeism, 85.00 for WPAI Presenteeism, 48.00 for WPAI Work Productivity Loss, 60.00 for WPAI Activity Impairment and 38.99 for the Hem-A-QoL Total Score.

4 | DISCUSSION

In the HOPE-B trial, there were nominally significant improvements in the Hem-A-QoL total score in the first and second years after receiving EDZ. This was driven by improvements in the Treatment, Feelings, Work/School and Future domains. The EQ-5D-5L Index Value was also nominally improved in the second year, with increases mainly due to improved pain and mobility. However, there were no nominally significant improvements in the other Hem-A-QoL domains, nor the mean summary scores for the IPAQ or HAL, domain-specific scores for the BPI and WPAI, the EQ-5D-5L VAS scores or the first year EQ-5D-5L Index Value.

The improvement in the Hem-A-QoL Treatment, Feelings, Work/School and Future domains suggests that infusion time reduction as well as fewer bleeds may have allowed people to feel more focused on their work and school responsibilities, potentially also reducing participants' negative feelings about living with haemophilia B and thus causing them to be more optimistic about the future.

It is not certain why there were no nominally significant improvements observed in physical functioning or pain in the IPAQ, HAL, or BPI. However, elevated factor levels alone would not be expected to improve advanced joint disease or to reverse established osteochondral damage, particularly over a period of one to two years. At screening, more than 80% of HOPE-B participants (45/54 participants) provided medical histories of at least one joint with chronic haemophilic damage (arthritis, arthralgia, or a history of orthopaedic surgery related to haemophilia B); ten participants reported a total of 22 active target joints at screening. Nevertheless, the improvement in the LS mean EQ-5D-5L Index Value in the second year suggests that there is a subset of patients who do experience improvements in pain and mobility.

A "disability paradox" has been documented in some chronic disease states,[25] including haemophilia,[26] wherein people report higher HRQoL than healthy individuals with the same level of impairment. For several of the instruments used in the trial, the HRQoL status reported at baseline is favourable (e.g., IPAQ, BPI, HAL; see Table 3). It is difficult to ascertain whether a disability paradox contributes to this baseline reporting, but it is possible this presents a relative ceiling effect for the opportunity to demonstrate improved status after gene therapy.

The mean and median scores for the IPAQ, the HAL, the BPI and the WPAI in the HOPE-B lead-in period reflected less impairment compared with what was reported in previous observational studies (Table 3).[27–29] Clearly, there are differences in the populations of PwHB included in the HOPE-B trial compared with the earlier observational studies; these include differences in geographic location, severity and type of haemophilia, and treatment practice patterns. However, the HOPE-B trial participants had FIX levels ≤2% and one would expect them to report more impairment. Their HRQoL scores may

have been better because they were required to be on standard or extended half-life therapies for at least six months in the lead-in period before receiving EDZ and were closely monitored in a clinical trial setting compared with the real-world observational studies. The CHESS study, found that the use of long-term prophylaxis and high therapy adherence was associated with reduced activity impairment and work productivity loss.[30]

Given that PwHB may benefit from EDZ in different ways, focusing on the group-level change in LS mean scores may mask the improvements in HRQoL for individuals enrolled in HOPE-B. It is important to examine the percentage of trial participants who meet or exceed established thresholds for minimal clinically important improvements. Our results showed that, after receiving EDZ for two years, nearly half of the HOPE-B participants had ≥15-point improvement in the Hem-A-QoL treatment domain and approximately thirty percent of the participants had ≥15-point improvements in how they feel about their haemophilia and the future, reflecting a more positive attitude toward living with this chronic condition.

While a change of 15-points or more on a 100-point scale is considered by the Institute for Quality and Efficiency in Health Care to be a plausible threshold for a minimal clinically important improvement, there is currently no widespread consensus.[23] Taking this approach allows us to apply the same threshold for minimal clinically important difference across all of the PRO instruments assessed in the HOPE-B study (Table S3). It is worthwhile to note that this is a conservative threshold relative to minimal clinically important thresholds proposed for Hem-A-QoL outcomes in other publications.[22,31,32] However, validated thresholds for the Hem-A-QoL do not exist for most of the domains and we wanted to assess the magnitude of the minimal clinically important improvements for each domain in our analysis. A recent report from a Phase 1/2 gene therapy trial in haemophilia B patients considered a 7-point change from baseline as a validated clinically meaningful difference for the Total Score for the Hem-A-QoL questionnaire.[32] In addition to demonstrating improvement from baseline in the mean Total Score, results from this smaller trial (n = 14 participants) demonstrated improvement in the Treatment, Feelings and Future domains among others, consistent with the HOPE-B study results.[32] A larger study in haemophilia A patients receiving gene therapy considered a 5.5-point change from baseline to be clinically meaningful for the Haemo-QOL-A Total Score.[33] This is a different questionnaire than the PRO used in the HOPE-B study.

All individuals enrolled in the HOPE-B study had been treated with prophylactic FIX prior to study screening and as indicated previously, were then treated and observed prospectively with prophylaxis for at least 6 months in the lead-in period. This standard of care may explain why the scores in the lead-in period for this study are better than the scores reported in other observational studies. As a result, the PROs provide less margin for possible improvement after gene therapy. Also, it is important to note that the PRO instruments included in the HOPE-B study were initially designed to evaluate the effect of clotting factor concentrates on HRQoL, infused on-demand or prophylactically. Rasul E et al. suggested these conventional PRO instruments may be less sensitive to detecting changes in HRQoL in the context of gene therapy.[34]

While the current analysis provides important insights into treatment benefits, future studies will be needed to obtain responder thresholds based on other commonly used anchor and distribution-based methods. The median lead-in PRO scores for those who did not achieve a minimal clinically important difference of 15% were much better than the median lead-in scores for those who did achieve 15%. As a result, there was less opportunity for the group not achieving the threshold to improve after gene therapy.

One limitation of the study is that the clinical trial setting may not reflect real-world practice. An assessment of HRQoL in PwHB who receive EDZ in a real-world setting is planned. Also, it is important to note that the results of the PROs, particularly the EQ-5D-5L VAS score which measures global health not specific to haemophilia, could have been influenced by the coronavirus pandemic. All the participants had their lead-in visits prior to the declaration of the global pandemic in March 2020. All but one participant had their month 12 PRO data collected just after the pandemic began when people were required to isolate but before vaccines were available. By the time the month 24 PRO data were collected, the COVID vaccines were on the market and available for use. This likely influenced how participants viewed their general health and may explain the difference in the results between Year 1 and Year 2. Another limitation is that the LS means for the lead-in period differs between year 1 and 2 due to differences in the overall set of data employed and the covariates included in the MMRM models. Nevertheless, the LS mean difference of the average of the post-treatment month 6 and month 12 minus the average of the lead-in month 4 and month 6 visits is very similar regardless of the MMRM model used. This illustrates the consistency of the two analyses for treatment comparisons. Finally, we acknowledge the exclusion of the PRO assessments within two weeks of a bleed as another possible limitation. For this reason, a separate analysis which included these PRO assessments was performed, which did not change the results.

5 | CONCLUSION

In conclusion, gene therapy with EDZ improved HRQoL in the first and second years in several Hem-A-QoL domains, including Treatment, Feelings, Work/School and Future domains, whereas improvement in other aspects of HRQoL were not demonstrated.

AUTHOR CONTRIBUTIONS

R.I., T.W.B., F.W.G.L., J.M., M.R., P.E.M. and S.W.P. were involved in the design of the study and the analysis of the data. All authors were involved in the drafting of the paper and all authors approved the final draft for publications.

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CONFLICT OF INTEREST STATEMENT

D. Drelich and P. E. Monahan are currently employees of CSL Behring. R. Itzler was an employee of CSL Behring at the time this manuscript was drafted. T. W. Buckner has worked as a paid consultant to BioMarin and Tremeau Pharmaceuticals. He has served as an advisory board member and received honoraria from CSL Behring, Genzyme, and Octapharma. F WG Leebeek has received research support from CSL Behring, Sobi, Takeda, and uniQure and is a consultant for Biomarin, CSL Behring, Takeda and uniQure, of which the fees go to the institution. He was a data safety monitoring board member for a study by Roche. J Miller is an employee of Everest Clinical Research, which does contract work for CSL Behring. M Recht has received research support from Bayer, BioMarin, CSL Behring, Genentech, Grifols, Hema Biologics, LFB, Novo Nordisk, Octapharma, Sanofi, Spark, Takeda, uniQure; consultancy fees from Catalyst Biosciences, CSL Behring, Genentech, Hema Biologics, Kedrion, Novo Nordisk, Pfizer, Sanofi, Takeda, uniQure; and sits on the Board of Directors for Foundation for Women and Girls with Blood Disorders, and Partners in Bleeding Disorders. S W Pipe has received consultancy fees from Apcintex, ASC Therapeutics, Bayer, BioMarin, CSL Behring, GeneVentiv, HEMA Biologics, Freeline, LFB, Novo Nordisk, Pfizer, Regeneron/Intellia, Roche/Genentech, Sanofi, Takeda, Spark Therapeutics and uniQure, and research funding from Siemens and holds a membership on a scientific advisory committee for GeneVentiv.

DATA AVAILABILITY STATEMENT

C.S.L. will only consider requests to share Individual Patient Data (IPD) that are received from systematic review groups or bona-fide researchers. C.S.L. will not process or act on IPD requests until 12 months after article publication on a public website. An IPD request will not be considered by CSL unless the proposed research question seeks to answer a significant and unknown medical science or patient care question. Applicable country specific privacy and other laws and regulations will be considered and may prevent sharing of IPD. Requests for use of the IPD will be reviewed by an internal CSL review committee. If the request is approved, and the researcher agrees to the applicable terms and conditions in a data sharing agreement, IPD that has been appropriately anonymized will be made available. Supporting documents including study protocol and Statistical Analysis Plan will also be provided. For information on the process and requirements for submitting a voluntary data sharing request for IPD, please contact CSL at clinicaltrials@cslbehring.com.

ETHICS STATEMENT

The study is conducted in accordance with International Council for Harmonisation Good Clinical Practice guidelines and ethical principles originating in the Declaration of Helsinki. The protocol was approved by appropriate institutional review boards and independent ethics committees at each study site. All the participants provided written informed consent.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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