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ORIGINAL RESEARCH

Analysis of long-term clinical and cost impact of etranacogene dezaparvovec for the treatment of hemophilia B population in the United States

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ABSTRACT

Introduction: Etranacogene dezaparvovec (EDZ), Hemgenix, is a gene therapy recently approved for people with hemophilia B (PwHB).

Objective: To estimate long-term clinical impact and cost of EDZ in the United States (US).

Methods: A decision-analytic model was developed to evaluate the long-term impact of introducing EDZ for PwHB over a 20-year time horizon. Factor IX (FIX) prophylaxis comparator was a weighted average of different FIX prophylaxis regimens based on US market share data. We compared a scenario in which EDZ is introduced in the US versus a scenario without EDZ. Clinical inputs (annualized FIX-treated bleed rate; adverse event rates) were obtained from HOPE-B phase 3 trial. EDZ durability input was sourced from an analysis predicting long-term FIX activity with EDZ. EDZ one-time price was assumed at $3.5 million. Other medical costs, including FIX prophylaxis, disease monitoring, bleed management, and adverse events were from literature. The model estimated annual and cumulative costs, treated bleeds, and joint procedures over 20 years from EDZ introduction.

Results: Approximately 596 PwHB were eligible for EDZ. EDZ uptake was estimated to avert 11,282 bleeds and 64 joint procedures over 20 years. Although adopting EDZ resulted in an annual excess cost over years 1-5 (mean: $53 million annually, total $265 million), annual cost savings were achieved beginning in year 6 (mean: $172 million annually; total $2.58 billion in years 6-20). The total cumulative 20-year cost savings was $2.32 billion, with cumulative cost savings beginning in year 8.

Conclusion: Introducing EDZ to treat PwHB is expected to result in cost savings and patient benefit over 20 years. Initiating PwHB on EDZ sooner can produce greater and earlier savings and additional bleeds avoided. These results may be a conservative estimate of the full value of EDZ, as PwHB would continue to accrue savings beyond 20 years.

PLAIN LANGUAGE SUMMARY

This analysis assessed the long-term clinical and financial impact of introducing EDZ in the United States of America for people with severe or moderately severe hemophilia B. A decision-analytic model was developed comparing a scenario with EDZ and one without EDZ over 20 years. Introducing EDZ would avert 11,292 bleeds and 64 joint procedures over 20 years and would achieve cumulative cost savings in year 8, with a total cumulative 20-year cost saving of $2.32 billion.

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Introduction

Hemophilia B is a rare bleeding disorder characterized by a lack of blood clotting Factor IX (FIX). The condition is present in less than 1 of 20,000 males born in the United States (US)[1]. Hemophilia B results in costly bleeding events, and joint bleeds caused by hemophilia B can lead to disabling arthropathy[2].

Persons with hemophilia B (PwHB) can be classified as having severe, moderate or mild disease. Current standard of care for those with severe hemophilia B and some with moderate disease who have a severe bleeding phenotype and musculoskeletal complications is regular prophylactic administration of FIX replacement to increase FIX levels and reduce bleed risk. FIX prophylaxis treatment is effective but costly, ranging from $500,000-$900,000 per year[3]. The product costs for FIX therapy represents over 90% of hemophilia B management costs[3]. Additionally, frequent administration of FIX therapy presents a substantial burden for PwHB[4]. An effective treatment that eliminates the need for FIX prophylaxis could provide an opportunity for cost savings and improvement in quality of life for individuals with severe or moderately severe hemophilia B (FIX <2 IU/dL).

Etranacogene dezaparvovec (EDZ) is a novel gene therapy recently approved in the US for the treatment of PwHB[5]. In the "Health Outcomes with Padua Gene; Evaluation in Hemophilia B (HOPE-B)" phase 3 clinical trial, EDZ treatment

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increased and sustained FIX activity and reduced bleed events over a 2-year period for individuals with severe (plasma FIX activity of <1 IU/dL) or moderately severe (plasma FIX activity of 1 to 2 IU/dL) hemophilia B[6]. PwHB in the trial treated with EDZ were generally able to discontinue regular FIX prophylaxis administration over the trial period. A statistical modeling analysis of the patient-level FIX data suggests that the increase in FIX activity provided by EDZ is anticipated to be durable, with over 80% of PwHB expected to maintain FIX activity levels above 2 IU/dL at 25 years after EDZ administration[7]. The 2 IU/dL threshold was chosen as "FIX activity levels below 2 IU/dL were assumed to be correlated with a severe bleeding phenotype needing regular prophylactic treatment with FIX replacement products"[7] and aligns with the HOPE-B clinical trial inclusion criteria[6].

The objective of this study is to assess the long-term clinical and cost impact of introducing EDZ for the treatment of PwHB in the US population.

Methods

We developed a decision-analytic model to examine the impact of EDZ for the treatment of PwHB in the US. The model was developed to be consistent with International Society for Pharmacoeconomics and Outcomes Research (ISPOR) guidelines for decision-analytic modeling methodology. We first estimated the eligible treatment population. These PwHB were then distributed by treatment, either with EDZ or with FIX prophylaxis. We then estimated the expected costs (drug acquisition and administration, bleed treatment, monitoring and disease management, and joint procedure) and outcomes (bleed events, joint procedures) associated with each treatment regimen. Finally, based on the distribution of PwHB by treatment, we estimated total population level costs and outcomes. We considered two scenarios: one without EDZ (100% of PwHB receiving FIX prophylaxis) and one with EDZ with projected product uptake increasing over time. For each scenario, we considered a 20-year time horizon and a third-party payer perspective. The 20-year time horizon was chosen as a balance between the long-term uncertainty of input parameter estimates and allowing a time horizon long enough to sufficiently capture the potential benefits of EDZ.

The model considered the entire PwHB population in the US. We assumed the PwHB population characteristics to be consistent with subjects treated in the HOPE-B study. Subjects in the HOPE-B trial were male PwHB ≥18 years of age diagnosed with severe or moderately severe hemophilia B who had previously received routine FIX prophylaxis.

For FIX prophylaxis, we estimated annual FIX therapy utilization and costs based on a market mix of products including Alprolix, BeneFix, Idelvion, Ixinity, Rebinyn, and Rixubis. For EDZ, PwHB received a one-time treatment with EDZ and no further prophylaxis until they required a return to FIX prophylaxis. For the purposes of this analysis, we have assumed PwHB would return to FIX prophylaxis if their FIX activity dropped below 2 IU/dL. The 2 IU/dL level was chosen as a proxy for return to FIX prophylaxis as it has been assumed to correlate with a severe bleeding phenotype needing regular prophylactic treatment with factor IX replacement products and aligns with the inclusion criteria for the HOPE-B trial[6]. Following a return to FIX prophylaxis, PwHB were assumed to incur the same annual costs and outcomes as those treated with FIX prophylaxis.

Population

The PwHB population eligible for EDZ in the US was estimated to be 596 individuals (Table 1). Annual population growth was assumed to align with the growth of the US population[8] and as such the eligible population increased to 611 by year 20. Population characteristics were assumed to be the same as the patient population in the HOPE-B trial[6]. Specifically, we assume these PwHB had an average age of 41.5 years, were 100% male, and had a mean weight of 85.1 kg.

Market share

To estimate the results for each scenario, a gradual market uptake of EDZ for each year was assumed based on internal market projections (Table S1 of the Appendix). All those not treated with EDZ were assumed to receive FIX prophylaxis. FIX prophylaxis was assumed to be a weighted average of currently available FIX products and dosing schedules based on market share data (Table S2).

Clinical inputs

The key clinical parameters considered in the model were annualized bleed rate (ABR) for EDZ and FIX prophylaxis, and durability of efficacy for EDZ. Only bleed events treated with FIX were considered. Data for ABR (Table 1) for each treatment were obtained from the HOPE-B trial: 0.99 for EDZ based on the 7-24 month data (after stable FIX Padua expression at month 6 post-EDZ infusion)[9] and 3.65 for FIX prophylaxis based on the 6-month lead-in period[6]. The FIX activity

Table 1. Population characteristics and clinical inputs.

Parameter	Estimate	Population	Source
General population size	N/A	334,121,426	8
Percentage male	49.5%	165,390,106	8
Percentage ≥18 years of age	77.8%	128,673,502	8
Prevalence of PwHB	1.60 per 100,000	2,064.7	18
PwHB with FIX ≤2%	45.4%	937.4	18
PwHB on FIX prophylaxis	69.6%	652.7	12
Not excluded for other reasons*	91.2%	595.6	19–27
PwHB eligible		**595.6**	
Annual population growth	1.78 per million	N/A	8
Average age (years)	41.5	N/A	6
Average weight (kg)	85.1	N/A	6
Annualized bleed rates			
EDZ	0.99	N/A	9
FIX prophylaxis	3.65	N/A	6

EDZ = etranacogene dezaparvovec; FIX = factor IX; kg = kilogram; PwHB = persons with hemophilia B; US = United States.
*Exclusion criteria include presence of hepatitis B or C (0.75%); other coagulation disorder (1%); or preexisting neutralizing antibody titre >1:700 (7%). Other criteria were conservatively assumed 0% exclusion: ALT/AST elevation; elevated bilirubin, creatinine, or alkaline phosphate; HIV uncontrolled; thrombocytopenia; history of or presence of FIX inhibitors; etc.

level over time for EDZ was derived using the methods from a published analysis projecting subject-level FIX activity over time[7], based on HOPE-B 3-year data[10]. The proportion of PwHB treated with EDZ and maintaining FIX activity greater than 2 IU/dL (and assumed in the model to be prophylaxis free) each year can be seen in Table S3 of the Appendix.

For FIX prophylaxis, we conservatively assumed no adverse events. For EDZ, we included costs associated with alanine aminotransferase (ALT) elevation. Specifically, per the EDZ US prescribing information[5], we assumed 15.8% (9 of 57) of PwHB treated with EDZ experienced ALT elevation and incurred costs of prednisone treatment. We conservatively assumed that no PwHB receiving EDZ or FIX prophylaxis would develop inhibitors. We also assumed no differences in mortality risk between treatments.

Cost inputs

Costs included in the model were drug acquisition and administration costs, disease management costs, bleed event related costs, joint procedure costs, and adverse event costs (Table 2). All costs were presented in 2022 US dollars (USD), with costs inflated where necessary using medical consumer price indices[11].

We assumed the acquisition price of EDZ of $3,500,000 as a one-time payment. The annual consumption of FIX prophylaxis was estimated assuming a distribution of FIX products (Alprolix, Benefix, Idelvion, Ixinity, Rebinyn, and Rixubis) with a distribution of each products' dose schedule and intensity (Table S2) as obtained from market data[12]. We assumed the same weighted average market mix of FIX therapies throughout the model time horizon: 39.79% Alprolix, 7.98% Benefix, 44.30% Idelvion, 2.58% Ixinity, 2.77% Rebinyn, and 2.58% Rixubis. Annual costs of prophylaxis were then estimated based on unit prices of the FIX products obtained from Micromedex[13] assuming 100% adherence.

Costs of administration, follow-up, disease monitoring and management, bleed event, and joint procedures were estimated from the published literature (Table 2). Adverse event costs were limited to treatment of ALT elevation. We assumed that PwHB experiencing ALT elevation incurred 81.4 days of prednisone treatment. The dosing of prednisone

Table 2. Cost inputs.

One-time EDZ costs	Unit Cost	Resource Use	One-Time Cost	Source
EDZ acquisition	$3.5 million	1	$3.5 million	One-time cost
EDZ administration costs	N/A	N/A	$251.40	Sum of costs below
Initial screening cost (FibroScan)	$31.49	1	$31.49	CPT 91200[28]
Blood tests	$47.85	2	$95.70	CPT codes 80076, 85025, 85250, and 85335[29]. Assumed 2 tests
Abdominal ultrasound	$122.16	1	$122.16	CPT 76700[28]
Steroids and/or diphenhydramine	$2.05	1	$2.05	Prednisone used as proxy for steroids[13]
FIX acquisition costs	**Unit Cost**	**Annual Units**	**Annual Cost**	**Source**
FIX acquisition			$739,082.59	Weighted average of individual FIX regimens
Alprolix	$3.45	2,644.37	$776,375.15	[13,30]
Benefix	$1.49	4,174.29	$529,295.25	[13,31]
Idelvion	$4.98	1,711.54	$725,346.42	[13,32]
Ixinity	$1.98	5,739.64	$967,118.34	[13,33]
Rebinyn	$4.51	2,087.14	$801,047.52	[13,34]
Rixubis	$1.70	5,217.86	$754,867.39	[13,35]
Monitoring and management costs	**Unit Cost**	**Annual Use**	**Annual Cost**	**Source**
EDZ monitoring, year 1				
Physician visit	$92.05	9	$828.47	CPT 99213[28]; Resource use:[36]
Nurse visit	$23.53	20	$470.64	CPT 99211[28]; Resource use:[36]
Liver function test	$8.17	24	$196.08	CPT 80076[29]; Resource use:[36]
Abdominal ultrasound	$122.16	1	$122.16	CPT 76700[28]; Resource use:[36]
EDZ monitoring, years 2+				
Physician visit	$92.05	0	$0.00	CPT 99213[28]; Resource use:[36]
Nurse visit	$23.53	2	$47.06	CPT 99211[28]; Resource use:[36]
Liver function test	$8.17	0	$0.00	CPT 80076[29]; Resource use:[36]
Abdominal ultrasound	$122.16	1	$122.16	CPT 76700[28]; Resource use:[36]
Disease management (EDZ and FIX prophylaxis)				
Joint scans	$223.90	4.29	$960.54	CPT 76700[28]; Resource use:[37]
Hematologist visits	$121.47	2.1	$255.08	CPT 99243[28]; Resource use:[38].
Orthopedist visit	$121.47	2.4	$291.52	CPT 99243[28]; Resource use:[38]
Psychologist/psychiatrist visit	$150.88	0.6	$90.53	CPT 90837[28]; Resource use:[38]
Physiotherapist	$31.03	1	$31.03	CPT 97110[28]; Resource use:[36]
Abdominal ultrasound	$122.16	1	$122.16	CPT 76700[28]; Resource use:[36]
Dental check-up	$137.50	2	$275	Humana[39]; Resource use:[36]
Nurse visit	$23.53	1	$23.53	CPT 99211[28]; Resource use:[36]
Viral screening (HIV, hepatitis B & C)	$8.89	2	$17.78	CPT 86701[29]; Resource use:[36]
Bleed-related care	**Unit Cost**	**Per Bleed Use**	**Cost per Bleed**	**Source**
FIX	$14,593.13	1	N/A	Assumed one dose of FIX per bleed
Hematologist visits	$121.47	0.621	$75.40	CPT 99243[28]; Resource use[15]
Orthopedist visits	$121.47	0.291	$35.43	CPT 99243[28]; Resource use:[40]
ED visits	$617.73	0.279	$172.45	Unit cost[41]. Resource use:[40]
Hospitalizations	$13,636.65	0.279	$3,806.90	Unit cost[42]. Resource use:[40]

AHRQ = Agency for Healthcare Research and Quality; CMS = Centers for Medicare & Medicaid Services; CPT = Current Procedural Code; ED = emergency department; EDZ = etranacogene dezaparvovec; FIX = factor IX; HCUP = Healthcare Cost and Utilization Project; HIV = human immunodeficiency virus.

was 60 mg/day for week 1, 40 mg/day for week 2, 30 mg/day for weeks 3-4, 20 mg/day for week 5, 15 mg/day for week 6, 10 mg/day for week 7, and 5 mg/day for the remaining days until 81.4 days[5]. The cost per patient experiencing ALT elevation was thus estimated to be $18.44[13]. The cost of treatment for infusion reactions in the trial was negligible and as such these costs were excluded.

Distribution among types of health plans

Healthcare costs differ by type of insurance provider. As such, we included a cost adjustment for those PwHB on Medicaid, Medicare, commercial health plan, and other health plans. We assumed the costs for PwHB in Medicaid and other insurance plans to be 82.9% of those for commercial health plans and Medicare. Based on market data, we assumed that 52.9% of PwHB are on private insurance, 10.8% on Medicare, 25.0% on Medicaid, and 11.3% on other insurance.

Analyses

The model estimates the total annual costs and outcomes for the entire US population (aggregating across all insurance types and payers) over 20 years for each scenario. Results were estimated annually and cumulatively. In addition to the base case results, scenario analyses were performed on the following parameters: 1, 2) assuming PwHB FIX levels of <3 IU/dL and <5 IU/dL as proxies for return to FIX prophylaxis, 3) an "accelerated uptake" scenario with a 50%, 70%, and 90% market uptake of EDZ in years 1, 2, and 3-20, respectively, 4) setting annual FIX prophylaxis costs to $546,000[14], 5) accounting for only product costs, and 6) assuming the average weight for males ages 40–49 years in the US (93.9 kg).

Results

Base-case analysis

Base case estimates of the annual and cumulative outcomes over time can be seen in Figure 1. Base case cost estimates can be seen in Figure 2a. Annual and cumulative cost impact results can be seen in Figure 2b.

The introduction of EDZ was found to improve health outcomes, as the model estimated a reduction of 11,282 bleed events and 64 joint procedures in the US over the 20-year horizon. The base case results illustrate that EDZ is expected to save $2.32 billion in total medical costs within the PwHB population over a 20-year horizon. Due to the up-front cost of gene therapy, excess costs were expected for the first 5 years following EDZ introduction, with the highest excess annual cost ($84.95 million) occurring in year 3. Annual excess cost over years 1-5 averaged $53 million annually, totaling $265 million over 5 years. The introduction of EDZ was estimated to become cost saving annually beginning in year 6 and to achieve cumulative cost savings by year 8. Annual cost savings averaged $172 million annually (total savings of $2.58 billion) in years 6–20.

Scenario analysis

The scenario analysis results for outcomes and costs can be seen in Table 3. Changing the FIX level at which we assumed

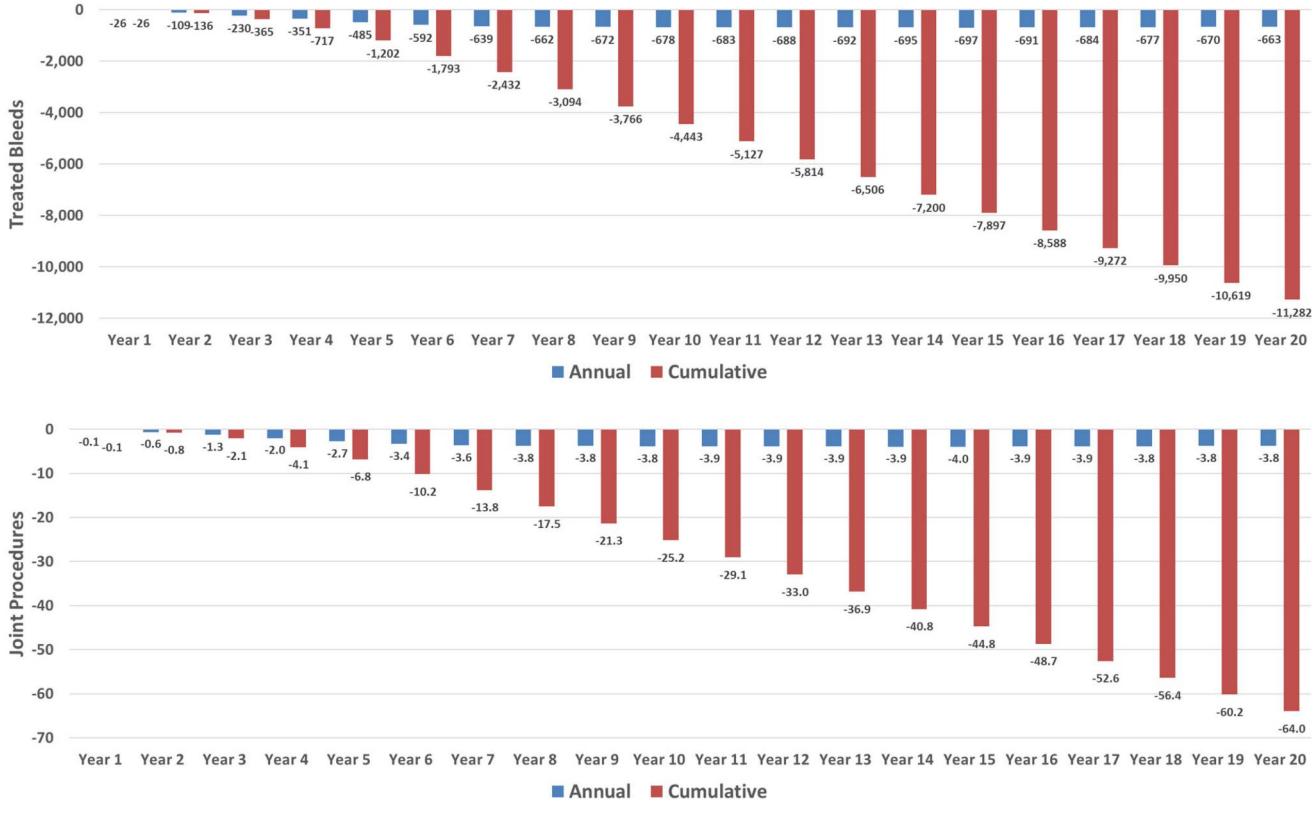

Figure 1. Incremental impact of introducing etranacogene dezaparvovec on outcomes over 20-year horizon.

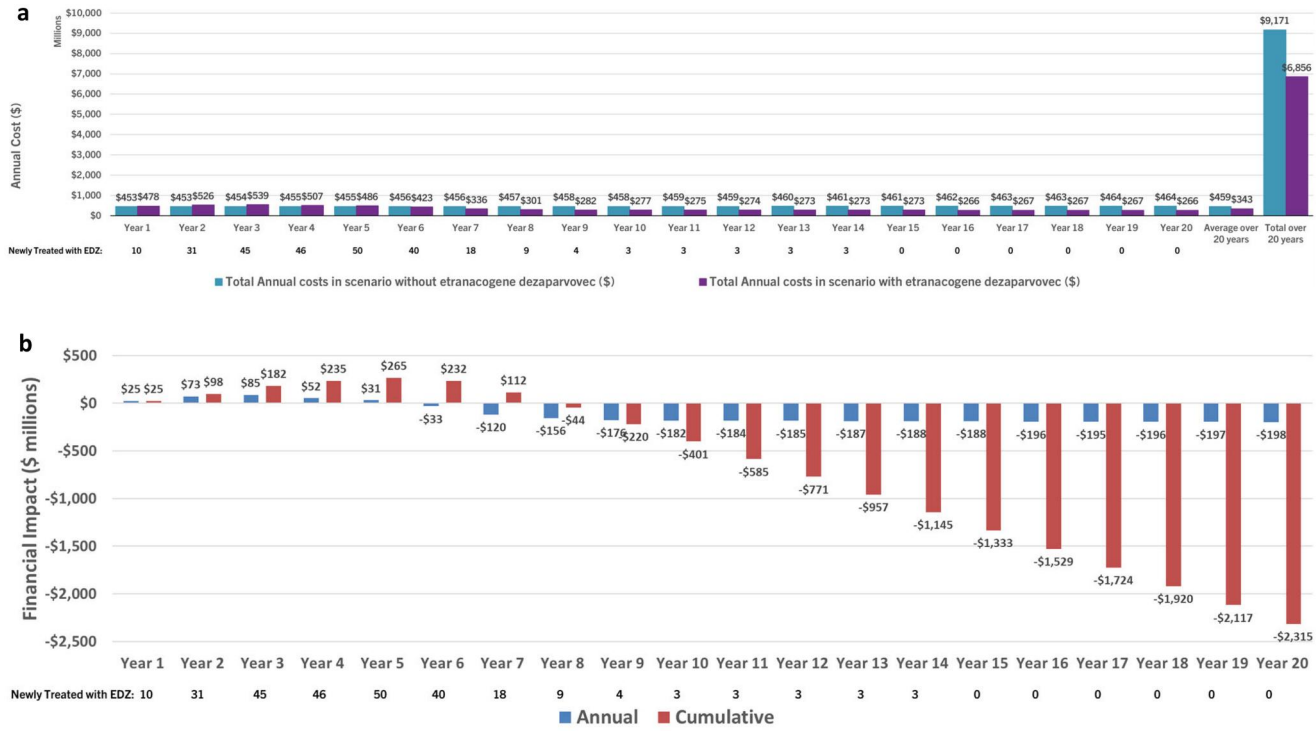

Figure 2. (a) Total annual costs over 20-year horizon. (b) Annual and cumulative cost impact of introducing etranacogene dezaparvovec over 20-year horizon. Results estimated for a total modeled population of 596 PwHB in year 1, increasing to a population of 611 PwHB in year 20.

a return to FIX prophylaxis to <3 IU/dL or <5 IU/dL FIX level resulted in slightly lower cumulative cost-savings compared to the base case ($2.27 billion savings and $2.17 billion savings for an assumption of <3 IU/dL and <5 IU/dL FIX levels, respectively, compared to $2.32 billion savings in the base case) over 20 years. With the assumption of a 50%, 70%, and 90% uptake in years 1, 2, and 3-20, the model estimated that the uptake of EDZ would result in substantially more bleeds (26,729) and joint procedures (152) prevented than in the base case (11,282 and 64, respectively). The scenario assuming 50%, 70%, and 90% uptake of EDZ in years 1, 2, and 3-20, respectively also resulted in higher excess costs in year 1 ($758.63 million) but was cost saving thereafter. The resulting 20-year cost savings were substantially greater in this scenario analysis ($5.62 billion) compared with the base case analysis ($2.32 billion). Average annual cost savings increased from $115.74 million in the base case to $281.15 million in this scenario analysis. Reducing the average annual cost of FIX prophylaxis input to $546,000 reduced the cumulative savings over 20 years to $1.541 billion. Considering only product costs instead of total medical costs reduced the benefit of EDZ, but only slightly ($2.06 billion cumulative savings). Conversely, assuming the average weight of the PwHB population equal to the US male population average resulted in greater cost savings for EDZ ($2.62 billion cumulative savings).

Discussion

In this study, we estimated the long-term impact on clinical outcomes and costs resulting from the introduction of EDZ as a treatment for PwHB in the US. Within the US population, approximately 596 individuals were estimated to be eligible for EDZ, with the population increasing to approximately 611 individuals by year 20. Under the base case uptake assumptions, the analysis found that EDZ would avert 11,282 bleed events and 64 joint procedures over the 20 years. Unlike with costs, where there is an up-front cost of gene therapy, PwHB would begin accruing reductions in bleeds within the first year of introduction. According to the CHESS US study which collected real-world disease burden and cost data for individuals with severe hemophilia B, results showed nearly 30% of bleeds in PwHB required hospitalization[15]. This finding, in combination with the bleeds averted suggest that EDZ may also result in approximately 3,473 fewer hospitalizations. When combined with the elimination of need for regular administration of FIX prophylaxis in the vast majority of patients, these benefits suggest a substantial humanistic value added by EDZ in improving the quality of life of PwHB.

Along with the expected clinical benefit, the maximum annual excess cost during years 1 to 5 would be $84.94 million, and EDZ would become cost-saving annually beginning in year 6 and cost-saving cumulatively beginning in year 8. The total cost savings in the US would be $2.32 billion over a 20-year period. A scenario analysis found that increasing uptake of EDZ to 50%, 70%, and 90% in years 1, 2, and 3-20 respectively would result in 26,729 bleed events averted and 152 joint procedures avoided and $5.6 billion in savings over the 20 years.

Limited literature exists estimating the economic impact of prophylaxis in PwHB in the US. A recent, non-peer-reviewed budget impact analysis was conducted for EDZ[16], however this study considered only a 5-year time horizon

Table 3. Scenario analysis results: Cumulative costs and outcomes along with impact of etranacogene dezaparvovec for each scenario.

	Cumulative Costs (millions $)			Annual Costs (millions $)	Total events over 20 years	
Scenario	Year 1	Year 10	Year 20	20-year Average	Bleeds	Joint procedures
Base case	**$25.01**	**−$401.45**	**−$2,315**	**−$115.74**	**−11,282**	**−64**
With EDZ	$477.73	$4,153	$6,856	$342.79	32,753	186
Without EDZ	$452.72	$4,555	$9,171	$458.53	44,035	250
FIX activity level threshold 3 IU/dL	**$25.01**	**−396.34**	**−$2,267**	**−$113.37**	**−11,093**	**−63**
With EDZ	$477.73	$4,158	$6,903	$345.16	32,942	187
Without EDZ	$452.72	$4,555	$9,717	$458.53	44,035	250
FIX activity level threshold 5 IU/dL	**$25.01**	**−$378.63**	**−$2,166**	**−$108.28**	**−10,688**	**−61**
With EDZ	$477.73	$4,176	$7,005	$350.25	33,348	189
Without EDZ	$452.72	$4,555	$9,171	$458.53	44,035	250
Accelerated uptake scenario*	**$758.63**	**−$1,968**	**−$5,623**	**−$281.15**	**−26,729**	**−152**
With EDZ	$1,211	$2,587	$3,548	$177.39	17,306	98
Without EDZ	$452.72	$4,555	$9,171	$458.53	44,035	250
Including product costs only	**$25.42**	**−$315.16**	**−$2,061**	**−$103.01**	**−11,282**	**−64**
With EDZ	$438.28	$3,838	$6,303	$315.15	32,753	186
Without EDZ	$412.86	$4,154	$8,363	$418.16	44,035	250
Assuming annual cost of FIX prophylaxis = $546,000	**$26.79**	**−$98.92**	**−$1,541**	**−$77.06**	**−11,282**	**−64**
With EDZ	$371.65	$3,371	$5,445	$272.23	32,753	186
Without EDZ	$344.87	$3,470	$6,986	$349.29	44,035	250
US male population 40–49 years of age average weight	**$24.30**	**−$521.19**	**−$2,621**	**−$131.06**	**−11,282**	**−64**
With EDZ	$519.72	$4,463	$7,414	$370.71	32,753	186
Without EDZ	$495.42	$4,984	$10,035	$501.77	44,035	250

EDZ = etranacogene dezaparvovec.

The results show the cumulative costs over time (with or without EDZ in plain text and the impact of EDZ in bold text) over one year, 10 years, and 20 years following introduction of EDZ in the United States. Differences between the "with and without" scenarios (i.e. the cost and outcomes impact) are presented in bold rows. The total modeled population was 595.6 PwHB in Year 1 and increased to 610.9 PwHB in Year 20. FIX activity thresholds (e.g. <2 IU/dL; <3 IU/dL; <5 IU/dL) are assumed as a proxy for return to FIX prophylaxis.

*The "accelerated uptake scenario" assumes 50% of eligible PwHB are treated with EDZ in Year 1, 70% are treated in Year 2, and 90% are treated thereafter. All other parameter estimates are assumed the same as in the base case analysis.

post treatment and as such underestimates the long-term value of the gene therapy.

The study has limitations to note. First, there is limited duration of FIX activity efficacy data for EDZ from the HOPE-B trial. As such, estimating longer-term effect requires extrapolation and is subject to uncertainty. Based on HOPE-B 3-year data, a patient-level modeling analysis projected the percentage of PwHB who will maintain FIX level at ≥2%, ≥3% and ≥5% each year for up to 25.5 years after EDZ administration[10]. Our study estimates that it would take only 5 years of FIX prophylaxis to offset the one-time cost of EDZ. This suggests that EDZ is likely to be cost-saving overall. However, it is recognized that the percentage of PwHB free from FIX prophylaxis needs to be substantiated with long-term data as it accumulates over time. Another limitation is that there is substantial heterogeneity in annualized bleed rate within the PwHB population. Cost savings will be greater when EDZ is given to PwHB with higher bleed risk. The choice of FIX prophylaxis regimen will also affect the results, as annual prophylaxis costs vary by product and associated annualized bleed rate outcomes. The expected average annual cost of FIX prophylaxis may be highly variable, and this variation could substantially affect the time needed for EDZ implementation to achieve cost savings. We calculated FIX prophylaxis cost based on currently available WAC (wholesale acquisition cost) pricing data and market research of the distributions of the FIX products and their dosing regimens. However, the percentages of PwHB receiving each FIX product and dosing schedule may vary over time, and any such resulting changes in costs would affect the financial impact of EDZ.

In the US, common practice of budget impact analysis considers a shorter time horizon because health plan members typically switch plans within 5 years. However, a recent study showed that people with hemophilia A remain with the same commercial health plans longer than expected[17]. In addition, this study takes a different perspective from budget impact analysis, i.e. the total US population and aggregate costs from all insurance payers. Hence, the long-term analysis is appropriate in that the "one's loss is the other's gain" scenarios of insurance plan switching are inherently taken into account. It also provides a more holistic view of the unique properties of gene therapy *via* the long-term durable effect, high up-front costs and sustained improvement in bleeding episode outcomes. Real-world data will confirm these long-term impacts of EDZ.

Conclusion

This analysis estimated the clinical and cost impact of introducing EDZ in the US. The introduction of EDZ eliminates FIX prophylaxis in almost all PwHB, substantially reduces bleed events requiring FIX prophylaxis and long-term complications requiring joint procedures. Treatment with EDZ was also found to save costs annually beginning in year 6, after introduction, and generate cumulative cost savings beginning in year 8. Though a faster uptake of EDZ will lead to greater up-front costs, the subsequent reductions in bleed events and FIX prophylaxis use will lead to substantially more bleeds and joint procedures avoided and greater long-term cost savings.

Transparency

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Declaration of financial interest

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Author contributions

KT, MW, CM, and SY contributed to the study conception and design. Material preparation, data collection and analysis were performed by CM, MW, and SY. The first draft of the manuscript was written by MW, and all authors provided feedback on drafts of the manuscript. All authors reviewed and approved the final manuscript.

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