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RESEARCH ARTICLE

Cost-effectiveness of gene therapy with etranacogene dezaparvovec versus factor IX prophylaxis in men with hemophilia B in Brazil

Juliana Alvares-Teodoro[1], Ana Clara Silva Mendes[1], Ricardo Mesquita Camelo[1,2], Augusto Afonso Guerra Júnior[1], Francisco de Assis Acurcio[1*]

[1]Faculdade de Farmácia, CCATES, Universidade Federal de Minas Gerais, Belo Horizonte, MG, Brasil. [2]Faculdade de Medicina, Universidade Federal de Minas Gerais, Belo Horizonte, MG, Brasil.

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ABSTRACT

Background: The high costs and uncertainties surrounding the effectiveness and safety of new health technologies necessitate continuous evaluation to balance access and sustainability within Brazil's Unified Health System.

Aims: Cost-effectiveness analysis comparing etranacogene dezaparvovec versus factor IX prophylaxis in people with hemophilia B from the Brazilian healthcare system perspective.

Methods: A cost-effectiveness analysis was conducted using TreeAge Pro software. A decision tree model compared the costs and effectiveness of etranacogene dezaparvovec versus factor IX prophylaxis in preventing bleeding in adult male with severe or moderately severe hemophilia B over a three-year horizon. A deterministic sensitivity analysis identified variables impacting incremental cost-effectiveness ratio.

Results: etranacogene dezaparvovec incurred a cost of USD 2,335,747 (BRL 10.810.993) versus USD 46,451 (BRL 232.256) for plasma-derived factor IX prophylaxis, with an incremental cost of USD 2,115,747 (BRL 10.578.737). The effectiveness (number of bleeding events) was 2.86 for etranacogene dezaparvovec and 10.95 for factor IX prophylaxis, with etranacogene dezaparvovec avoiding 8.09 additional bleeding events. The incremental cost-effectiveness ratio was USD 261,436 (BRL1.307.179) per bleeding event avoided. Sensitivity analysis revealed treatment duration as the most impactful variable on incremental cost-effectiveness ratio, contributing to 80% of model uncertainty.

Discussion: International studies suggest that etranacogene dezaparvovec is cost-effective and dominant in multiple contexts, particularly when compared to extended half-life recombinant factor IX (rFIX-EHL), offering greater quality-adjusted life years for people with hemophilia B at lower long-term costs. However, a lack of robust data underscores the need for ongoing monitoring and careful evaluation before incorporation by the health system. It should also be noted that high pricing of new treatments like etranacogene dezaparvovec poses challenges for Brazil's Unified Health System sustainability and equitable access.

Introduction

Hemophilia B (HB) is a hereditary coagulopathy caused by mutations in the *F9* gene located on the X chromosome, which encodes coagulation factor IX (FIX)[1]. Globally, an estimated 37,385 individuals live with hemophilia B, including 2,277 in Brazil[2]. Reduced residual plasma FIX activity elevates the risk of spontaneous bleeding, particularly hemarthrosis, which can lead to hemophilic arthropathy, reduced mobility, and impaired quality of life[3,4].

Standard treatment for hemophilia B involves intravenous replacement of exogenous FIX to prevent or manage bleeding episodes. Prophylaxis is the globally recommended approach to mitigate bleeds and associated complications[4-7].In Brazil, prophylaxis was incorporated into the SUS in 2012, with FIX procured by the Ministry of Health and distributed free of charge through Hemophilia Treatment Centers[8]. However, lifelong infusion requirements hinder treatment adherence[9] and FIX pharmacokinetic variability results in different degrees of protection between doses[10]. Expenses related to FIX concentrates and its administration account for over 99% of the total prophylactic treatment costs for people with hemophilia B. In Brazil, plasma-derived FIX (pdFIX) is the product provided by the SUS[11].

Gene therapy aims to achieve stable endogenous FIX activity through a single dose[12] and has been under investigation for over two decades[13]. Recently, two technologies have been approved for clinical use[14,15]. The first employs an adeno-associated virus serotype 5 (AAV5) vector containing a wild-type human F9 cassette (AMT-060)[16] resulting in stable endogenous FIX expression and reducing bleeding episodes for up to five years[17]. AAV5 targets hepatocytes, where the transgene is inserted, enhancing plasma FIX activity[18]. Building on this, an AAV5 vector with a mutated F9-Padua cassette was developed to improve thrombin generation[19]. Consequently, etranacogene dezaparvovec (AMT-061) was created, an AAV5 vector carrying the F9-Padua gene variant[20,21,22]. Since this technology had not been registered or priced in Brazil at the time of analysis, this study estimated its value based on another gene therapy available in the country, onasemnogene abeparvovec, used for treating spinal muscular atrophy[23].

The phase 3 HOPE-B study evaluated the efficacy and safety of etranacogene dezaparvovec compared to FIX prophylaxis in 54 adult people with hemophilia B with residual plasma FIX activity ≤ 2%[21]. Between 7 and 18 months post-treatment, annualized bleeding rates decreased by 64% (total bleeds), 77% (treated bleeds), 78% (treated or untreated hemarthroses), and 79% (treated hemarthroses). However, uncertainties remain regarding FIX expression durability[17,24] and long-term side effects. In the short-medium term, 42% developed drug-induced hepatitis, with 38% requiring corticosteroids[21].

The price of AMT-061, launched in 2022, was US$ 3.5 million (approximately BRL 17.5 million)[15]. International economic evaluations estimate costs ranging from US$ 1.8 to 2.0 million[25,26]. The high cost, coupled with uncertainties regarding effectiveness and safety, underscores the need for continuous assessments to balance access to new technologies with the sustainability of the Brazil's Unified Health System (SUS)[27].

So, this study aims to analyze the cost-effectiveness of etranacogene dezaparvovec compared to FIX prophylaxis in severe and moderately severe hemophilia B from the Brazilian healthcare system perspective.

Methods

COSTS

The cost calculation for prophylactic treatment was based on the dosage and acquisition price of pdFIX, as well as the cost of infusion procedures.[28] The price per IU for the latest national pdFIX procurement (April 27, 2023) was obtained from the Banco de Preços em Saúde[29] (Tables 1 and 2). Infusion procedure costs were retrieved from the Departamento de Informática do Sistema Único de Saúde[29] (Table 1).

The costs for people with hemophilia B treatment with etranacogene dezaparvovec included the price of the drug and hepatic monitoring exams. For therapy with onasemnogene abeparvovec, a 40% reduction in its launch price was observed prior to commercialization in Brazil. Similarly, the etranacogene dezaparvovec launch price of US$ 3.5 million[29] was reduced, yielding a model-based medication cost of US 2.1 million.

The costs included hepatic monitoring tests for aspartate aminotransferase (AST) and alanine aminotransferase (ALT), performed weekly for three months following infusion[21]. For patients treated with etranacogene dezaparvovec who experienced therapeutic failure, additional costs for resuming prophylaxis with pdFIX were incorporated (Table 2).

Bleeding treatment costs were estimated based on the required amount of pdFIX concentrate. The prices of pdFIX concentrates and infusion procedures were the same as those used for pdFIX prophylaxis[29,30] (Tables 1 and 2).

EFFECTIVENESS

Effectiveness data for etranacogene dezaparvovec were derived from the phase 3 clinical trial, which included 54 people whit hemophilia B, 52 of whom discontinued FIX prophylaxis after a single dose of etranacogene dezaparvovec, reflecting a 96% treatment success rate.[21] The annualized bleeding rates for treated bleeds with FIX prophylaxis (3.65) versus etranacogene dezaparvovec (0.84) were also sourced from the HOPE-B study[21]. The effectiveness of any FIX concentrate in this study was considered equivalent to that of pdFIX concentrate.

Table 1. Parameters used in the economic model

Parameters	Prophylaxis with pdFIX	Range (min.and max.)	AMT-061	Range (min.and max.)	References
Weight (kg))	74,6	65,3-74,6	74,6	65,3-74,6	IBGE*, 2008
Gene Therapy Success Rate (%)	NA	NA	96	NA	Pipe SW et al., 2023
Duration (years)	3	0-3	3	0-3	Pipe SW et al., 2023
pdFIX dose in prophylaxis (IU/kg)	25	20-30	NA	NA	
Frequency of pdFIX in prophylaxis (infusions/month)	9	7-10	NA	NA	
ABR for Treated Bleeds	3,7	2,8-4,7	0,8	0,4-1,7	Pipe SW et al., 2023
pdFIX dose in on-demand treatment (IU/kg)	49	29-79	9	9-39	Brasil. 2015 Manual de hemofilia
Frequency of pdFIX in On-Demand Treatment (days)	3	1-7	3	1-7	Premise
Total number of AST and ALT tests	NA	NA	24	NA	Cslbehring, 2023

1 US$ = 5 R$ (Reais)

min.: minimum; max.: maximum; NA: Not applicable; pdFIX: Plasma-derived factor IX; ABR: Annualized bleeding rate; IU/kg: International Unit/kilogram; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; AMT-061: etranacogene dezaparvovec

* IBGE: Instituto Brasileiro de Geografia e Estatística;(The Brazilian Institute of Geography and Statistics)

Table 2. Prices used in the economic model

Parameters	Prophylaxis with pdFIX	Range (min.and max.)	AMT-061	Range (min.and max.)	References
Price per infusion (R$)	5,39	NA	5,39	NA	Datasus**, 2023 proc. 030602002-5
Price of pdFIX (R$/IU)	0,33	NA	0,33	NA	BPS***, 2023 code 0450529
Price of AMT-061 (R$/dose)	NA	NA	10,8 million	2-15.millions	Premise
Price of AST and ALT tests (R$)	NA	NA	2,01	NA	Datasus**, 2023

1 US$ = 5 R$ (Reais)

min.: minimum; max.: maximum; NA: Not applicable; pdFIX: Plasma-derived factor IX; AMT-061: etranacogene dezaparvovec; IU/kg: International Unit/kilogram; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase;

** Datasus. Departamento de Informatica do SUS (Department of Informatics of the Unified Health System) - SIGTAP: Sistema de Gerenciamento da Tabela de Procedimentos, Medicamentos, Órteses, Próteses e Materiais Especiais do SUS;

*** BPS: Banco de Preços em Saúde. (Health Price Database) SIASG: Sistema Integrado de Administração de Serviços Gerais

COST-EFFECTIVENESS MODEL

A cost-effectiveness analysis was conducted using TreeAge Pro, LLC software (Williamstown, USA). A decision tree model was developed to compare the costs and effectiveness of etranacogene dezaparvovec versus FIX prophylaxis in preventing bleeding episodes in people with hemophilia B with severe or moderately severe conditions over a three-year horizon from the perspective of Brazilian Ministry of Health (Figure 1).

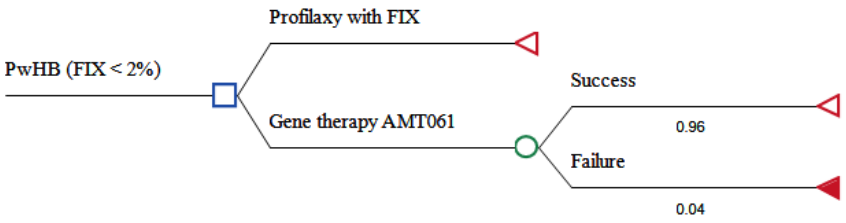

Figure 1. Decision tree of the economic cost-effectiveness analysis model of gene therapy with AMT-061 compared to prophylaxis with plasma-derived factor IX.

The modeled population consisted of adult male with hemophilia B with severe (residual FIX activity <1%) or moderately severe hemophilia (1% ≤ residual FIX activity ≤ 2%) undergoing regular FIX prophylaxis, as recommended by the World Federation of Hemophilia.[4] This cohort aligns with participants from the HOPE-B study[21]. The three-year time horizon was selected based on phase 2b trial data indicating a mean endogenous FIX activity of 36.9% (range: 32.3%-41.5%) three years post-treatment with etranacogene dezaparvovec[24]. As a novel technology, data on its efficacy or effectiveness beyond this period are not yet available.

FIX prophylaxis has a variable dosage depending on the product used and the bleeding phenotype of the people with hemophilia B[4]. Plasma-derived FIX (pdFIX) has a standard half-life of approximately 17 hours, with a dosage of 20–30 International Units (IU)/kg of body weight administered twice weekly, adjustable to individual needs[8]. This study assumed an average dosage of 25 IU/kg twice weekly for pdFIX, with 100% adherence.

For etranacogene dezaparvovec treatment, a single-dose administration was assumed. Reapplication of etranacogene dezaparvovec was

considered infeasible in cases of therapeutic failure due to immune responses to viral vectors[31] or cross-immunity to other AAV-based gene therapies[32]. People with hemophilia B experiencing significant reductions in AMT-061 expression were assumed to return to routine pdFIX prophylaxis, characterizing therapy failure.

The treatment of bleeding episodes varies based on the type of bleeding and the clinical condition of the people with hemophilia B[8]. This model considered the dosing for hemarthrosis, the most common bleeding event[1]. FIX dosage was calculated as:

FIX IU = weight (kg) × Δ,
where Δ = % factor needed − % endogenous residual factor.

To control hemarthrosis, the FIX activity increase required ranged from 30% to 80%,[8] then the average value of 50% was adopted. Endogenous FIX levels from the HOPE-B study showed 1.19% for people with hemophilia B on FIX prophylaxis and 41.48% for those on etranacogene dezaparvovec[21]. A median weight of 74.6 kg (IBGE, 2008)[33] was used, resulting in treatment regimens of 49 IU/kg for pdFIX prophylaxis and 9 IU/kg for etranacogene dezaparvovec, each lasting an average of three days (Table 1).

SENSITIVITY ANALYSES
A deterministic sensitivity analysis was conducted to assess model uncertainties and identify which variables had the greatest impact on the incremental cost-effectiveness ratio (ICER). The ICER represents the additional cost per bleeding event avoided with etranacogene dezaparvovec.[34] Variables analyzed included the duration of pdFIX prophylaxis, the cost of etranacogene dezaparvovec, and the annualized bleeding rates for each strategy. Minimum and maximum values for each variable (detailed in Table 1) were used. Results were illustrated using a tornado diagram. A discount rate was not applied due to the short time horizon.

Results

COST ANALYSIS: The total cost of etranacogene dezaparvovec was US$ 2,335,747 (BRL 10.810.993), compared to US$ 46,451 (BRL 232.256) for FIX prophylaxis. This resulted in an incremental cost of US$ 2,115,747 (BRL 10.578.737) over three years.

EFFECTIVENESS ANALYSIS: The number of bleeding episodes was 2.86 for etranacogene dezaparvovec and 10.95 for FIX prophylaxis, yielding an incremental benefit of 8.09 fewer bleeding events for etranacogene dezaparvovec.

INCREMENTAL COST-EFFECTIVENESS RATIO (ICER): etranacogene dezaparvovec demonstrated an ICER of US$ 261,436 (BRL 1.307.179) per bleeding event avoided.

SENSITIVITY ANALYSIS: Treatment duration was the most influential variable, accounting for 80% of the uncertainty in ICER estimates (Figure 2).

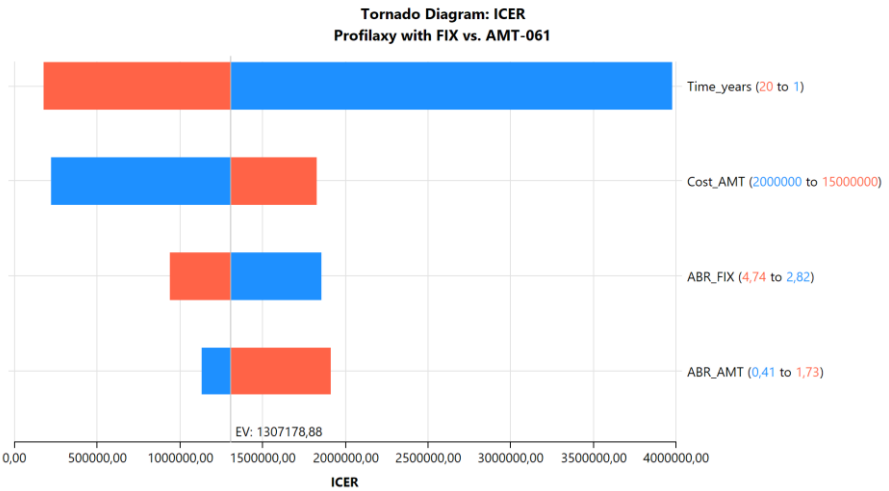

Figure 2. Deterministic Sensitivity Analysis

Extending the time horizon to 20 years reduced the ICER to US$ 34,400 (BRL 172.000) per bleeding event avoided (Figure 3).

Adjusting etranacogene dezaparvovec costs to US$ 400,000 (BRL 2.000.000) decreased the ICER to US$ 40,000 (BRL 200.000) per event avoided. Variations in bleeding rates had minimal impact on outcomes.

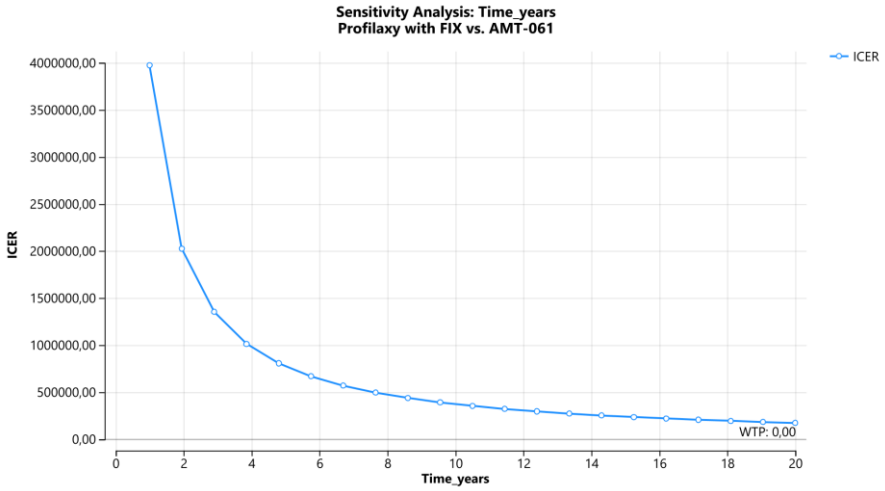

Figure 3. ICER versus Time

Discussion

Health Technology Assessment (HTA) is a multidisciplinary process that systematically evaluates the properties, effects, and impacts of health technologies. The primary goal of HTA is to inform policy and decision-making in healthcare by assessing the medical, social, economic, and ethical implications of the use of health technologies. HTA examines various dimensions of health technologies, including their clinical effectiveness, safety, cost-effectiveness, and broader social and ethical impacts. New technologies tend to be more expensive than older ones, often driving up healthcare costs. In this scenario, the HTA process ensures that new technologies are only adopted after their effectiveness has been demonstrated[35]. In this way, HTA is essential for balancing innovation with practical healthcare delivery. It ensures that health technologies provide value, improve patient outcomes, and promote equitable access to healthcare resources.

Through the cost-effectiveness analysis carried out in this study, etranacogene dezaparvovec reduced the annualized bleeding rate for treated bleeds by 26% compared to pdFIX prophylaxis for moderately and severely affected people with hemophilia B under the SUS perspective after three years. However, this reduction came at an additional cost of US$ 261,436 (BRL 1.307.179) per bleeding event avoided. Cost equivalency between treatments would only be achieved after 20 years of etranacogene dezaparvovec administration.

GENERAL CONSIDERATIONS

The current study highlights several important considerations. The development of neutralizing antibodies against the vector could hinder the efficacy of gene therapy. For instance, the first gene therapy trial in people with hemophilia B, published in 2006, showed no FIX expression among participants, likely due to an immune response elicited by the AAV2[13,36]. Subsequent studies with AAV2/8, AAVS3, and AAV8 excluded people with hemophilia B with positive serology for these vectors[37-39].

Interestingly, AAV5 does not elicit a significant immune response, making it a viable option for gene therapy in people with hemophilia B. A prior clinical trial found no correlation between pre-existing anti-AAV5 antibodies and the therapeutic efficacy of etranacogene dezaparvovec in 10

people with hemophilia B[18]. Consequently, the HOPE-B study did not select participants based on anti-AAV5 serology[21], and this criterion was not used in the current cost-effectiveness analysis.

Another key short-term side effect, drug-induced hepatitis, is believed to result from a cytotoxic immune response to the AAV capsid[40]. All AAV vector-based gene therapy trials for people with hemophilia B reported some degree of asymptomatic hepatotoxicity[12]. In certain cases, this was accompanied by a decline in FIX activity, which might or might not respond to immunomodulation with corticosteroids, typically observed within 12 weeks post-vector administration[13]. This finding supports the use of corticosteroid-based immunomodulation of variable duration.

The recent approval of etranacogene dezaparvovec is undoubtedly a landmark achievement in the field of gene therapy. However, significant challenges remain in expanding gene therapy for hemophilia to a broader population. For example, the durability of transgene expression is a crucial factor to address[41].

PHARMACOECONOMIC STUDIES / COST-EFFECTIVENESS ANALYSIS

A recent systematic review focusing cost-effectiveness analyses of gene therapies for hemophilia, was conducted using a structured approach to evaluate the validity, relevance, and potential weaknesses of the data and assumptions in the models. The review highlights that gene therapies for hemophilia represent a major medical breakthrough, offering significant quality-of-life improvements by eliminating the need for prophylactic factor replacement therapy. However, their high costs necessitate evaluating their lifetime value to assess their impact on patients, healthcare systems, and payers. Payer concerns about the durability and magnitude of treatment effects limit access and reimbursement. Proposed solutions include outcome-based agreements and finance-based models to address high upfront costs and long-term uncertainties[42].

Two independent studies used cost-effectiveness analysis to compare etranacogene dezaparvovec and FIX prophylaxis for lifetime treatment[25,26]. Boulos et al.[25] developed a Markov model with microsimulation to compare etranacogene dezaparvovec with recombinant FIX prophylaxis (rFIX-MVP and rFIX-MVE) from the payer's perspective in the U.S. Hospitalizations, surgeries, and mortality were included, with expenses estimated using a microcosting approach. The price of etranacogene dezaparvovec was $2,000,000 in the base scenario. The etranacogene dezaparvovec alternative was considered cost-effective at a threshold of US$150,000 per quality-adjusted life year (QALY). In sensitivity analyses, in most scenarios, etranacogene dezaparvovec was more effective and less costly. Considering only rFIX-MVP, which has pharmacokinetics and effectiveness similar to pdFIX[43], the costs were US$15,109,058 for prophylaxis with rFIX-MVP and US$6,293,502 for etranacogene dezaparvovec, with QALYs of 20.95 and 23.00, respectively[25]. According to the results of this study, gene therapy appears more cost-effective than prophylaxis or on-demand treatment for severe hemophilia B when analyzed from a U.S. third-party payer perspective, based on clinical data, real-world costs, and assumptions where evidence was limited. With additional clinical trial data and final pricing, gene therapy could offer substantial budget savings for healthcare systems while enhancing patient outcomes and quality of life.

Meier et al.[26] compared prophylaxis with rFIX-MVE and etranacogene dezaparvovec in a microsimulation model from the perspective of the German healthcare system. The price of etranacogene dezaparvovec was €2,000,000. The model included women, hospitalizations, surgeries, and mortality. Prophylaxis with rFIX-MVE cost €6,427,660, while etranacogene dezaparvovec cost €5,247,830. Etranacogene dezaparvovec was considered the dominant alternative. Sensitivity analysis indicated that people with hemophilia B treated with this alternative had a gain of 0.50 QALY and a cost reduction of €1,179,829. QALY was influenced by

the duration of maximum bleeding reduction after etranacogene dezaparvovec, the relative reduction in bleeding with rFIX-MVE prophylaxis, and the increase in bleeding over time after etranacogene dezaparvovec. The ICER was influenced by the duration of maximum bleeding reduction, relative bleeding reduction, and the increase in bleeding over time, all after etranacogene dezaparvovec[26]. The authors concluded that depending on its price, etranacogene dezaparvovec may offer cost savings and improved health outcomes for hemophilia patients compared to extended half-life factor IX prophylaxis, positioning it as a potentially cost-effective option. However, these findings are uncertain due to limited evidence on etranacogene dezaparvovec's long-term effectiveness.

Still in the United States a study, funded by the pharmaceutical company responsible for etranacogene dezaparvovec, developed a decision -analytic model to evaluate the long-term impact of introducing etranacogene dezaparvovec for people with hemophilia B over a 20-year time horizon. Factor IX prophylaxis comparator was a weighted average of different FIX prophylaxis regimens based on US market share data. The authors compared a scenario in which etranacogene dezaparvovec is introduced in the US versus a scenario without etranacogene dezaparvovec. Adopting etranacogene dezaparvovec incurred an excess cost of US$265 million over the first five years but achieved annual savings starting in year 6, totaling US$2.58 billion by year 20. The total cumulative 20-year cost savings of $2.32 billion began accruing in year 8. Therefore, initiating people with hemophilia B on etranacogene dezaparvovec sooner can produce greater and earlier savings and additional bleeds avoided[44].

FUTURE PERSPECTIVES

Recently, another gene therapy using F9-Padua with the recombinant AAV Rh74var vector was introduced to the global market[13]. In the phase 1/2a study, 10 people with hemophilia B received gene therapy with fidanacogene elaparvovec and were followed for 52 weeks[45]. Among the 7 people with hemophilia B who were on prophylaxis with FIX before gene therapy, FIX expression remained between 18% and 81%, and the annualized bleeding rate for treated bleeds reduced by 94%. In the phase 3 study, all 188 people with hemophilia B evaluated received FIX prophylaxis for at least 6 months before gene therapy and were followed for 15 months[46]. The annualized bleeding rate for treated bleeds reduced by 78%, with FIX expression ranging from 2% to 119%. Corticosteroid use occurred in 28 (62%) participants due to elevated ALT or decreased FIX expression.

Additionally, other technologies are being used for treatment. In some countries, people with hemophilia B are being treated with monoclonal antibodies that inhibit the tissue factor pathway inhibitor[47,48]. These medications can reduce bleeding via subcutaneous administration, while maintaining thrombin production by preventing the inactivation of the extrinsic tenase[49]. Finally, other forms of gene therapy are still under study, such as gene editing using AAV2/6 and zinc finger nucleases[50]. However, in this study, the only people with hemophilia B tested did not have sufficient FIX expression.

LIMITATIONS

An important limitation of this study was the time horizon considered. The duration of AMT-061 expression would not be a limiting factor, as there does not appear to be a significant reduction that would require a return to prophylaxis for at least 25.5 years[51]. Despite this, the current study did not consider the variability in FIX expression according to characteristics of people with hemophilia B. For example, expression is higher in individuals with a higher body mass index, older age, and those who did not experience an increase in ALT[41].

The 3-year time frame was adopted due to the uncertainty about what could occur over longer periods, as there is no available literature. Therefore, only short-term effects could be evaluated, such as drug-induced hepatitis[12]. However, despite hepatotoxicity screening being included in the cost-effectiveness analysis for all people with hemophilia B, the immunomodulation

performed in some participants was not assessed. In the HOPE-B study, 9 participants received corticosteroids for 51 to 130 days, but no side effects were reported[21]. In the long term, potential conditions such as insertion mutagenesis[12] and musculoskeletal health[52] should be evaluated.

Specifically regarding insertion mutagenesis, the recombinant AAV used in etranacogene dezaparvovec does not have the machinery to insert the FIX gene into the recipient's DNA[41]. One participant in the HOPE-B study developed hepatocellular carcinoma 12 months after treatment, but no relationship was established between etranacogene dezaparvovec and cancer[21]. An evaluation of people with hemophilia B treated in the first gene therapy trial in 2006 over 12-15 years did not show the development of cancer[13,53]. However, there are no studies with longer follow-up on gene therapy in people with hemophilia B.

Another important limitation is the lack of a national price for etranacogene dezaparvovec. In Brazil, the drug is not even in the process of being approved by ANVISA, the national regulatory agency. To conduct the current study, the price of an already incorporated gene therapy into the SUS was adopted: onasemnogene abeparvovec[23]. However, etranacogene dezaparvovec has been described as the most expensive therapy in the world[54], meaning the price may be even higher than what was considered in this analysis. In the United States, in 2023, the price of etranacogene dezaparvovec was 1.6 times higher than the price of onasemnogene abeparvovec[55].

Furthermore, although etranacogene dezaparvovec is a new therapy with potentially high effectiveness and low risks, the comparator used in this study from the perspective of the Brazilian reality is an outdated product. Worldwide, pdFIX still represents a large portion of FIX concentrates used in the treatment of people with hemophilia B. However, in countries where hemophilia investments are intensified, rFIX is now used, with greater attention to rFIX-MVE. There is evidence that prophylaxis with rFIX-MVE is more effective in both reducing bleeds and decreasing total FIX consumption[56]. Finally, the study did not take into account specific treatment approaches that are required for special people with hemophilia B like as acute on chronic liver failure due to hepatitis B, coinfection with hepatitis C or D, or human immunodeficiency virus, and hepatitis B infection in patients who are in immunosuppressive states due to specific therapies and liver transplant recipients[57].

Conclusions

In Brazil, the Federal Constitution guarantees all citizens the right to healthcare in a free and universal manner, establishing that access should be ensured by the State through social and economic policies. Additionally, it asserts that this State responsibility is shared with businesses and families.[58] However, ensuring access to healthcare, especially medications, has become an increasing challenge due to the high cost of innovative technologies launched on the market. This scenario is further aggravated by uncertainties related to these technologies, stemming from initial clinical studies that often do not include comparison groups, have short follow-up periods, and use surrogate outcomes.

The cost-effectiveness analysis conducted showed that the gene therapy etranacogene dezaparvovec provides significant benefits in reducing bleeds in patients with moderate to severe hemophilia B, but it comes with high costs that are only balanced over a 20-year time horizon. Limitations such as the still restricted time horizon, which prevents the analysis of long-term side effects, and the lack of a defined national price, among others, complicate the evaluation of the technology for its potential implementation in Brazil. International studies indicate that, despite the high cost, etranacogene dezaparvovec is cost-effective and dominant in various scenarios, especially when compared to prophylaxis with extended half-life recombinant products (rFIX-MVE), offering greater QALY to people with hemophilia B and lower long-term costs. However, the lack of more robust data reinforces the need for continuous monitoring and

careful evaluation before its incorporation. Additionally, the substantial pricing of innovative drugs like etranacogene dezaparvovec challenges SUS sustainability and equitable access.

Conflict of Interest Statement:

RMC received financial support as a speaker and to participate in scientific events from Bayer, NovoNordisk, Hoffman-La Roche, and Takeda, all unrelated to this study. JAT, ACSM, AAGJ, and FAA, declare that there are no conflicts of interest that could influence these results.

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