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ORIGINAL RESEARCH ARTICLE

Assessing the Value for Money of Enzyme Replacement Therapy in Gaucher Disease Types 1 and 3b: Can Expanded Coverage Be Justified?

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Abstract

Background and Objectives The Health Intervention and Technology Assessment Program was commissioned to conduct a cost–utility and budget impact analysis of enzyme replacement therapy (ERT) for Gaucher disease types 1 and 3b. The findings from this assessment are to support the decision-making process regarding the potential expansion of ERT coverage within Thailand's public health system.

Methods The analysis compared the current policy, which provides treatment with imiglucerase only for patients with Gaucher disease type 1, as listed in the National List of Essential Medicine, with a proposed policy that extends coverage to include Gaucher disease types 1 and 3b with either imiglucerase or velaglucerase. Cost–utility analysis of these policy options was performed using decision tree and Markov models over a lifetime horizon from a societal perspective. The financial implications for the relevant budgetary authority over 5 years were estimated. The research methodology adheres rigorously to Thailand's health technology assessment guidelines.

Results The study found that the incremental cost-effectiveness ratios for treating both Gaucher disease types 1 and 3b are 6,769,000 and 9,359,000 baht per quality-adjusted life year (QALY) for imiglucerase and velaglucerase, respectively, which is well beyond Thailand's cost-effectiveness threshold of 160,000 baht per QALY. Such an expansion would incur an additional budgetary burden of approximately 81 million baht for imiglucerase and 138 million baht for velaglucerase. Increasing the rate of hematopoietic stem cell transplantation (HSCT) can improve the cost-effectiveness of the expansion.

Conclusions The study concludes that expanding ERT with either imiglucerase or velaglucerase to treat both Gaucher disease types 1 and 3b is not cost-effective at current prices in Thailand; however, it could become cost-effective with a reduction of approximately 60% in drug prices or if all eligible patients undergo HSCT.

1 Introduction

Gaucher disease is a rare genetic disorder resulting from a deficiency in the enzyme glucocerebrosidase, causing the accumulation of fatty substances in organs such as the spleen, liver, and bone marrow. This progressive condition leads to symptoms that include organ enlargement, bone pain, fatigue, and neurological impairment, significantly affecting quality of life. In severe cases, it can result in early mortality [1, 2], underscoring the importance of early diagnosis and appropriate treatment to manage symptoms and improve survival outcomes.

Imiglucerase and velaglucerase are enzyme replacement therapies (ERT) approved by the Thai Food and Drug Administration (FDA) for the treatment of Gaucher disease. These therapies function by replacing the deficient enzyme responsible for the disease's symptoms, with velaglucerase being newly registered in Thailand as of January 2022. Owing to the rarity of the disease and the critical nature of the treatment, imiglucerase was listed in the Thai National List of Essential Medicines (NLEM) in 2013, making it part of the country's pharmaceutical reimbursement list for the treatment of Gaucher disease type 1 [3].

Recent scientific evidence has demonstrated the efficacy of ERT for Gaucher disease type 3 [4–9], and epidemiological data from Thailand have indicated a significant

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Key Points for Decision Makers

The rising number of patients with Gaucher disease type 3b in Thailand who experience neurological symptoms has revealed a treatment gap. Currently, enzyme replacement therapy (ERT) listed in the National List of Essential Medicines does not fully address the needs of this group, prompting this study to explore the expansion of ERT eligibility to include patients with type 3b.

Expanding treatment coverage with either imiglucerase or velaglucerase to include both Gaucher disease types 1 and 3b is not considered cost-effective in Thailand. However, a reduction in the price by approximately 60% could render treatment for types 1 and 3b cost-effective.

Increasing the rate of hematopoietic stem cell transplantation following ERT improves the cost-effectiveness of the treatment expansion and significantly reduces the overall budgetary burden.

prevalence of Gaucher disease type 3 [10]. In response, the National Expert Working Group on Drug Selection for Rare Diseases has provisionally supported expanding the indications for imiglucerase to include Gaucher disease type 3b. However, Gaucher disease types 2 and 3a were excluded owing to the severe neurological involvement and the reduced efficacy of ERT in these patient populations.

The NLEM undergoes regular reviews on the basis of health needs, safety, efficacy, cost-effectiveness, budget impact, and affordability [11]. For high-cost medicines such as ERT, further evidence regarding cost-effectiveness and budgetary implications for public health schemes is required before formalizing this policy. Previous economic evaluations of imiglucerase for Gaucher disease type 1 have indicated that it is not cost-effective within the Thai context. Nevertheless, its inclusion in the NLEM is justified by the low budgetary impact owing to the rarity of the disease, with only about five new cases reported annually [12]. To date, no studies have been identified concerning the economic impact of ERT for treating Gaucher disease type 3.

Hematopoietic stem cell transplantation (HSCT) offers a potential curative treatment for Gaucher disease types 1 and 3, although it is associated with higher morbidity and mortality compared with ERT [13, 14]. In addition, evidence suggests that HSCT may help stabilize neurological symptoms and prevent further progression in Gaucher disease type 3 [15]. In Thailand, HSCT for Gaucher disease types 1 and 3b has been included under the Universal Coverage Scheme, with matched related and matched unrelated donors used since 2015 and 2020, respectively. Although ERT is not a prerequisite for HSCT reimbursement, the general consensus among experts is that HSCT should not be the initial treatment. Instead, it is typically administered after at least 2 years of ERT. This strategy helps mitigate the morbidity and mortality associated with the high Gaucher cell burden, particularly in the spleen and bone marrow, as well as the elevated inflammatory cytokines seen in naïve patients. It also ensures that patients are in optimal health to undergo HSCT. While there is no formal minimum age requirement for HSCT, the ages of previous patients have ranged from 3.8 to 15.0 years, on the basis of our experience [16]. The upper age limit for HSCT in Gaucher disease and other non-malignant disorders is 20 years, in accordance with general practice in the country.

The Health Intervention and Technology Assessment Program (HITAP) was commissioned by the Thai FDA for the NLEM to undertake a cost–utility and budget impact analysis of ERT for Gaucher disease types 1 and 3b. The study aimed to address policy questions regarding the cost-effectiveness of expanding ERT to include Gaucher disease types 1 and 3b and to assess the associated budgetary implications. In addition, it determined which of the two drugs—imiglucerase or velaglucerase—was more cost-effective for treating Gaucher disease types 1 and 3b. The analysis also explored the potential role of HSCT as an adjunct to ERT, considering its potential to offer a permanent cure. The findings from this assessment could help inform potential ERT expansions within the public health scheme.

2 Methods

This study conducted a cost–utility analysis to estimate the expected costs and health outcomes, measured in terms of quality-adjusted life years (QALYs), associated with the current policy in Thailand, which provides imiglucerase treatment solely for patients with Gaucher disease type 1 as listed in the NLEM. The analysis compared this policy with a proposed alternative that extends treatment coverage to include both Gaucher disease types 1 and 3b, using either imiglucerase or velaglucerase. This study targeted both pediatric and adult patients.

We convened stakeholder meetings to involve all pertinent parties in the health technology assessment process. On 9 May 2023 [17], feedback was solicited on the research scope and proposal. Subsequently, on 16 May 2024 [18], additional feedback was obtained on the research findings and policy recommendations. The research team has integrated these recommendations to refine the research methodology, thereby enhancing its utility for policy decision-making.

A model-based economic evaluation was developed using Microsoft Excel® (Microsoft Corporation, Redmond, WA, USA) and the Plant-A-Tree add-in for decision trees [19, 20], following the National Health Technology Assessment

Guidelines of Thailand [21]. The analysis was performed from a societal perspective for the cost–utility analysis and from a public payer perspective for the budget impact analysis. Costs were converted to 2023 values, with a 3% discount rate, in accordance with the national guidelines [21] applied to estimate future costs and benefits.

2.1 Model Structure

The decision tree represents the policy options for treating Gaucher disease, while the Markov model simulates its natural progression. The model uses an initial diagnosis age of 6 years, as indicated by a Thai study [10].

Beginning with the decision tree (Fig. 1), the model evaluates the current policy in which ERT is provided free of charge to patients with Gaucher disease type 1 and compares it with a proposed policy that extends ERT coverage to patients with both Gaucher disease type 1 and type 3b. Under the current policy, some patients with Gaucher disease type 3b are initially classified as having type 1 owing to an ambiguous clinical presentation. However, during follow-up, some of these patients developed neurological symptoms that led to a later diagnosis of type 3b. Consequently, they had to transition from ERT to palliative (or symptomatic/supportive) care or discontinue the ERT. Clinical experts have indicated that once a patient is diagnosed with Gaucher disease type 3b, there is no possibility of subsequently changing the diagnosis to Gaucher disease type 1.

Following the diagnosis pathway, Markov models were employed to track disease progression over time. A lifetime horizon with a yearly cycle length was applied to model time progression. Four distinct Markov models (Figs. 2, 3 and 4) were used: one for patients not receiving ERT, two for patients receiving ERT (separately for type 1 and type 3b), and one for patients transitioning from ERT to discontinuation of ERT. These models were adapted from a previous study [12] to account for the new patient group (Gaucher disease type 3b), the new treatment (velaglucerase), and HSCT. All patients started in the "symptomatic" health state. Transitions between health states occurred on an annual basis.

Markov model A (Fig. 2) represents the progression of patients with Gaucher disease who do not receive ERT. In this model, patients have two possible health states: either continued presence of Gaucher symptoms ("symptomatic" state) or death. Markov model B (Fig. 3a, b) illustrates the progression of patients with Gaucher disease receiving ERT. This patient cohort encompasses five health states, starting with symptomatic patients. Following treatment with imiglucerase or velaglucerase, patients may either remain in the "symptomatic" state or achieve the treatment goal, subsequently transitioning to a "symptom-free" state for Gaucher disease type 1 or an "improved" state for Gaucher disease type 3b. Patients in the "symptom-free" or "improved" states may then be eligible for "HSCT," except for those over 20 years of age. After HSCT, patients enter a "recovery" phase during which ERT is no longer required following 4 weeks of HSCT. Patients in the "HSCT" and "recovery" states cannot revert to the "symptomatic" or "symptom-free/improved" states.

Lastly, Markov model C (Fig. 4) refers to patients who initially received ERT but, after an average follow-up period of 3 years, as per the clinicians' opinion, developed

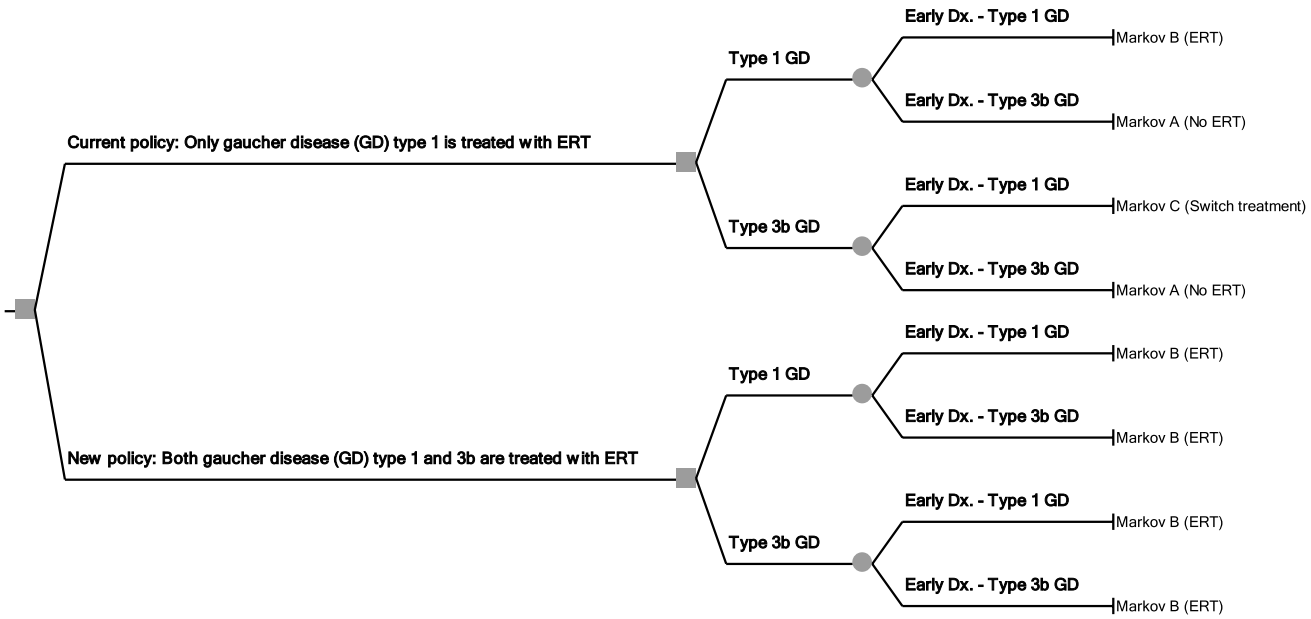

Fig. 1 Decision tree model representing the policy options for treating Gaucher disease. Dx, diagnosis

symptoms indicative of Gaucher disease type 3b, leading to the discontinuation of ERT. This occurs because their condition no longer meets the eligibility criteria for ERT under the NLEM. Following the cessation of ERT, patients in the "improved" state (or "symptom-free" at the time of diagnosis as type 1) or those remaining "symptomatic" after ERT may experience disease progression to the "symptomatic" state or death. In addition, patients in any health state within the Markov model are at risk of death owing to disease progression or other causes.

2.2 Data Collection

The retrospective cohort study was conducted at six participating hospitals (Ramathibodi Hospital, Srinagarind Hospital, Siriraj Hospital, Maharaj Nakorn Chiang Mai Hospital, King Chulalongkorn Memorial Hospital, and Phramongkutklao Hospital) to collect the variables related to the probability of health state transitions and costs. Utility values were collected by interviewing patients diagnosed with Gaucher disease types 1 and 3b, or their relatives, who received treatment at these six participating hospitals. These estimates were then applied in economic modeling to assess the cost-effectiveness and budget impact of treatments for Gaucher disease.

Data collection for the study was conducted between October and December 2023. Eligible participants included all patients with Gaucher disease types 1 and 3b who met the treatment criteria [22], as assessed by pediatricians at the participating hospitals. The data collection was organized into the following categories: (1) secondary data from the hospital database using case record forms to gather clinical indicators and treatment costs, and (2) interviews with patients and/or their relatives to assess their costs and quality of life. The study included 24 patients (10 with Gaucher type 1 and 14 with Gaucher type 3b). However, owing to the research team's inability to contact some patients, interviews were conducted with only 17 patients (9 with Gaucher type 1 and 8 with Gaucher type 3b). Since velaglucerase became available in Thailand only in 2023, all patients received imiglucerase, except for one patient who did not receive ERT. In total, five patients (5/24) underwent HSCT following certain years of ERT, including one with Gaucher disease type 1 and four with Gaucher disease type 3b.

Clinical indicators refer to the duration that patients achieved or remained in each health state, which was used to calculate the transitional probabilities between health states in the Markov models. The definitions of "symptom-free" for Gaucher type 1 and "improved" for Gaucher type 3b were based on the therapeutic indicators specified in the NLEM criteria [22]. This study considered both direct medical costs and direct nonmedical costs. These include expenses related to the diagnosis, treatment, and follow-up of Gaucher disease, covering both inpatient and outpatient care. In addition, the study accounted for travel costs, food expenses, accommodation, and the opportunity costs associated with the time lost by relatives traveling to the hospital. Utility values (quality of life) for patients in different health states were obtained through interviews using the EuroQol-5 Dimensions-Youth Version-3 Level (EQ-5D-Y-3L) or EuroQol-5 Dimensions-5 Level (EQ-5D-5L) questionnaires, developed by the EuroQoL group [23]. For children under the age of 8 years or in cases where patients could not complete the questionnaire themselves, information was collected from primary caregivers (proxy respondents).

This research study received ethical approval from the Central Research Ethics Committee (CREC) of Thailand on 7 September 2023, with certificate no. CREC075/2023.

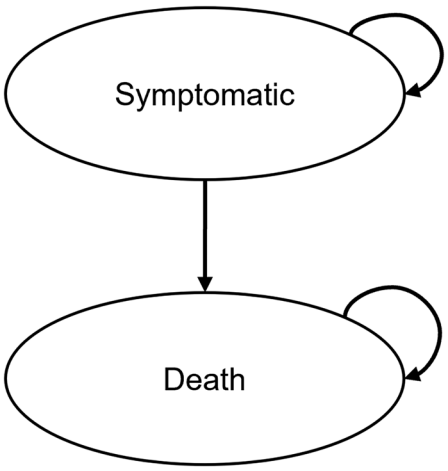

Fig. 2 Markov model A represents the progression of patients with Gaucher disease who do not receive enzyme replacement therapy

2.3 Model Input Parameters

All input parameters utilized in the models are presented in Table 1, summarized as follows:

The proportions of patients with Gaucher disease types 1 and 3b in the decision tree model were 31% and 69%, respectively, as derived from the study investigating clinical characteristics of Thai patients with Gaucher disease between 2010 and 2018 [10]. For the initial diagnosis proportion, we compared physician-diagnosed data from participating hospitals with the actual distribution of Gaucher disease types in Thailand [10]. It was revealed that 58% of patients with Gaucher disease type 3b were initially diagnosed as type 1, as their early symptoms did not align with those typical of type 3b. In contrast, all patients with Gaucher disease type 1 (100%) were accurately diagnosed as type 1 from the beginning.

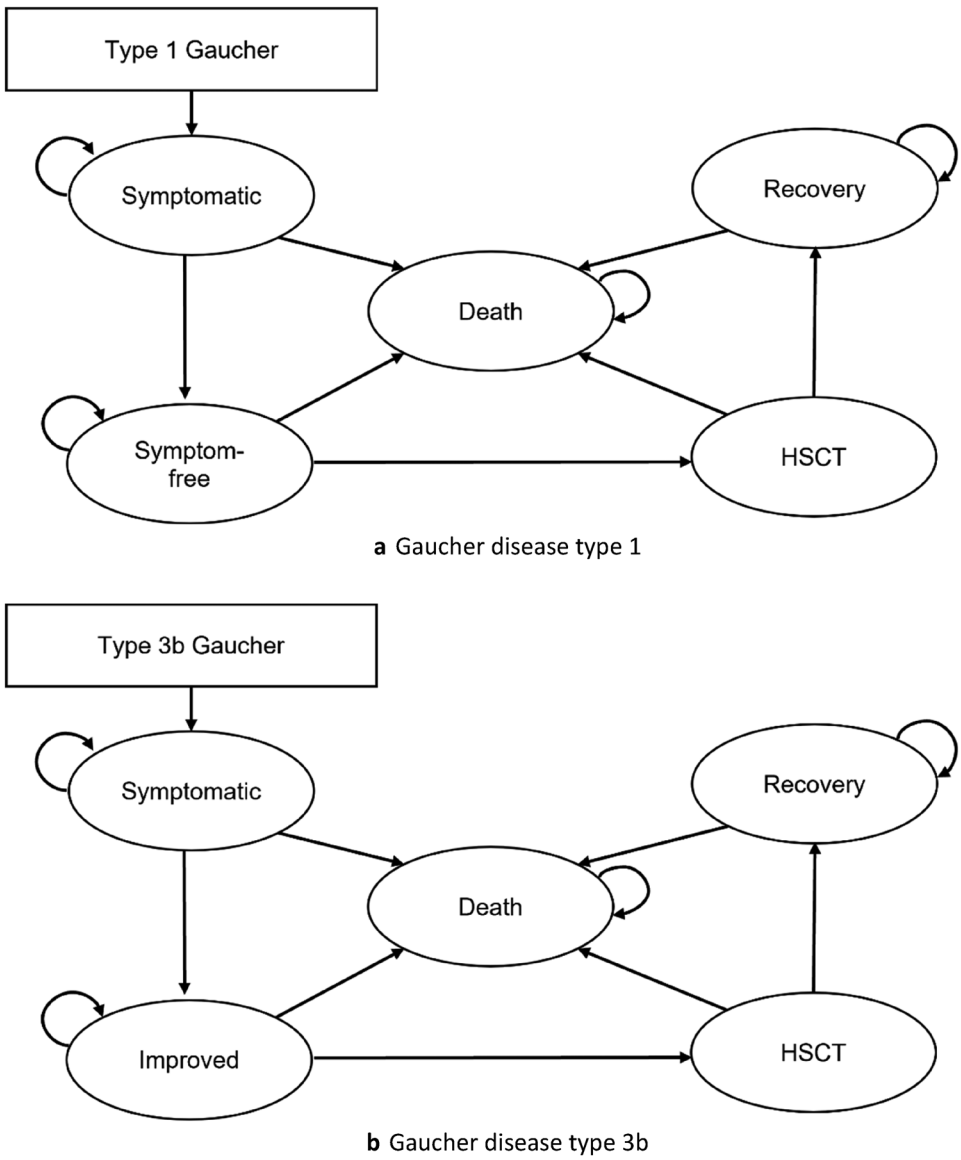

Fig. 3 Markov Model B illustrates the progression of patients with Gaucher disease receiving enzyme replacement therapy with imiglucerase or velaglucerase; the figure includes two separate models: **a** for Gaucher disease type 1 and **b** for Gaucher disease type 3b

The efficacy of ERT has been examined in a noninferiority trial by Turkia HB et al. [24], which directly compared the efficacy and safety of imiglucerase and velaglucerase in a head-to-head study. The study concluded that velaglucerase is noninferior to imiglucerase in terms of both efficacy and safety for treating Gaucher disease type 1. However, owing to the lack of comparative studies specifically examining the efficacy of imiglucerase and velaglucerase in patients with Gaucher disease type 3b, it is assumed (in the present study) that the efficacy of velaglucerase relative to imiglucerase in patients with type 3b is equivalent to that observed in patients with Gaucher disease type 1.

The probabilities of state transitions in the Markov models were derived from individual patient data collected retrospectively, as previously described. The time to event for each health state transition was calculated by subtracting the previous state's start date from the transition date to the subsequent state. Patients were censored if they missed a follow-up visit or if no transition occurred by the study end date, 31 December 2023. A parametric survival-time model with a Weibull distribution was applied to estimate the probability of outcomes.

Owing to the absence of data on ERT-treated patients who died from a symptomatic state in the retrospective secondary data of this study, the probability of death from a symptomatic state in ERT-treated patients was referenced from the previous study [12], which was based on expert opinion. In addition, the probability of transitioning from an

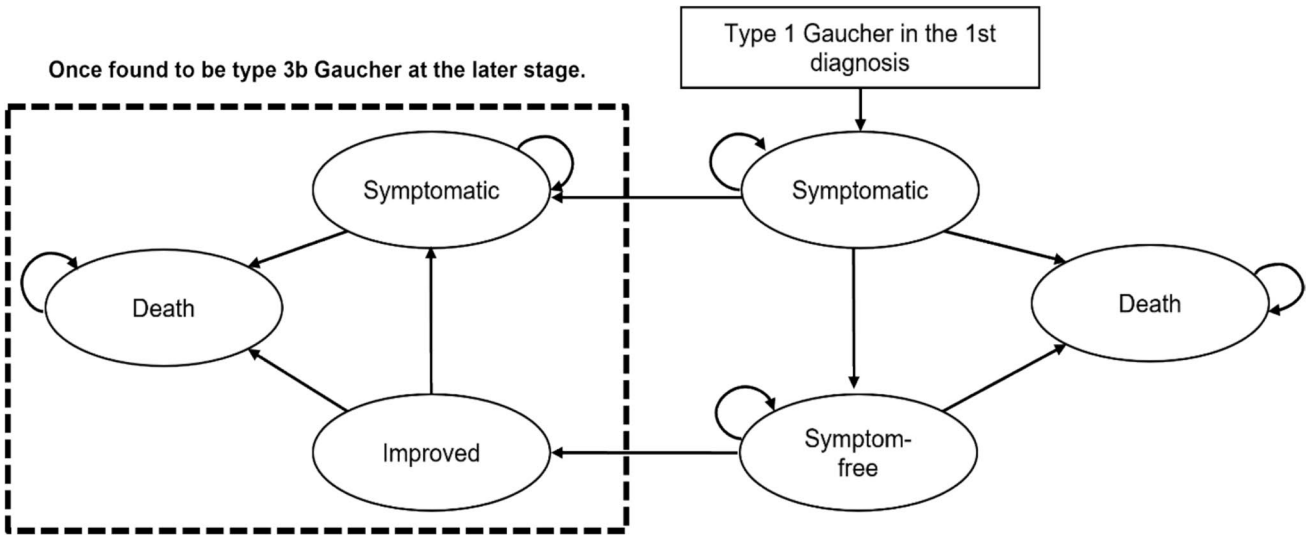

Fig. 4 Markov model C showing progression for patients initially treated with enzyme replacement therapy who develop symptoms indicative of Gaucher disease type 3b, leading to treatment discontinuation

improved state to a symptomatic state in patients with Gaucher disease type 3b who had discontinued ERT (Markov C) was assumed to be 100% [18]. Furthermore, the mortality rate for patients undergoing HSCT was 10% [25], and the mortality rate for the general population was derived from the 2014 Thailand Burden of Disease and Injury Study [26].

The analysis from a societal perspective included both direct medical and direct nonmedical costs. Direct medical costs were obtained from retrospective secondary data collected from the databases of six participating hospitals, while direct nonmedical costs were gathered from interviews with patients or their relatives. However, direct medical costs associated with the symptomatic state in patients with Gaucher disease type 1 who are not receiving ERT were referenced from a previous study [12], owing to the absence of primary data collected in this study. The opportunity cost of time for relatives accompanying patients to the hospital was estimated on the basis of the per capita gross national income of 219,796 baht, as reported by the Office of the National Economic and Social Development Council [27].

The price of imiglucerase, 40,164 baht per vial (400 U), was referenced from the procurement prices managed by the National Health Security Office under the Universal Coverage Scheme. The price of velaglucerase, 48,133 baht per vial (400 U), was based on the price proposed by the pharmaceutical company. The recommended dosage for treating Gaucher disease with ERT is 60 units per kg of patient body weight every 2 weeks. However, if the patient has undergone HSCT, ERT is administered for 4 weeks following the procedure, after which the treatment is discontinued. To adjust historical costs to current values, the consumer price index [28] was employed to convert these costs to the monetary value for the year 2023. United States Dollar (USD) was considered equivalent to 32.46 baht as per the exchange rates on 30 September 2024 [29].

Utility values for patients in various health states were obtained through interviews with patients or their primary caregivers using the EQ-5D-Y-3L questionnaire for those under 11 years of age and the EQ-5D-5L questionnaire for those aged 12 years and older. Responses from the EQ-5D-5L for patients over 12 years old were calculated using the Thai value set [30]. However, owing to the lack of a value set for the EQ-5D-Y-3L in Thailand, we examined available value sets from other Asian countries, including China [31], Indonesia [32], Japan [33], Malaysia, Singapore, Taiwan, and Vietnam. It should be noted that the value sets for Malaysia, Singapore, Taiwan, and Vietnam are unpublished data obtained through personal communication with an Associate Professor at the NUS Saw Swee Hock School of Public Health, National University of Singapore, based on ongoing research as of December 2023. An analysis using the Mann–Whitney *U* test and a comparison of absolute standardized mean differences in utility values between symptom-free and symptomatic states across available countries revealed that the value set from Vietnam had the highest absolute standardized mean differences, indicating the largest effect size or difference between the two groups (Supplementary Information Table S1) [34]. Consequently, this value set from Vietnam was selected for estimating the utility value of the EQ-5D-Y-3L in this study.

Table 1 Input parameters used in the models

Parameters	Base case value	Standard error	Parameter distribution	References
Transition probabilities in the Markov model with a yearly cycle length				
From symptomatic to symptom-free/improved state				a ($N = 23$)
Constant value for baseline hazard	− 0.2822	0.3419	LogNormal	
Gaucher type coefficient for baseline hazard	0.2996	0.4338	LogNormal	
Gamma (γ)	− 0.1882	0.1640	LogNormal	
Undergoing hematopoietic stem cell transplantation (HSCT)				a ($N = 5$)
Constant value for baseline hazard	− 4.1704	1.3285	LogNormal	
Gaucher type coefficient for baseline hazard	1.2004	1.1230	LogNormal	
Gamma (γ)	0.0220	0.3877	LogNormal	
Being in the recovery state after undergoing HSCT				a ($N = 5$)
Constant value for baseline hazard	13.3205	5.1433	LogNormal	
Gaucher type coefficient for baseline hazard	− 2.5552	1.6072	LogNormal	
Gamma (γ)	1.6460	0.3787	LogNormal	
Death from the symptomatic state in patients not receiving ERT				a, [12] ($N = 9$)
Constant value for baseline hazard	− 4.2032	1.5275	LogNormal	
Gaucher type coefficient for baseline hazard	0.3661	1.1959	LogNormal	
Gamma (γ)	0.7512	0.3562	LogNormal	
Death from the symptomatic state in patients receiving ERT	0.0410	0.0540	Beta	[12]
Death from the symptom-free/improved state				a ($N = 22$)
Constant value for baseline hazard	− 21.1699	5034.4410	LogNormal	
Gaucher type coefficient for baseline hazard	16.8661	5034.4400	LogNormal	
Gamma (γ)	0.0013	0.8751	LogNormal	
Death from undergoing HSCT	0.10	0.0179	Beta	[25]
Death from recovery state	Assumed to be equivalent to death from the symptom-free/improved state			
Mortality rate among the general population	Thailand Burden of Disease and Injury Study [26]			
Relative risk (velaglucerase versus imiglucerase)	1.00	Deterministic sensitivity analysis (0.7–1.3)		[24]
Price of enzyme replacement therapy (ERT) in baht				
Imiglucerase, per 1 vial (400 U)	40,164	Deterministic sensitivity analysis (± 20%)		National Health Security Office
Velaglucerase, per 1 vial (400 U)	48,133	Deterministic sensitivity analysis (± 20%)		Drug company
Direct medical costs excluding ERT per year for patients with Gaucher disease type 1 in baht				
Symptomatic state in patients not receiving ERT				[12]
1st year	187,579	93,789	Gamma	
From the 2nd year onward	182,069	91,034	Gamma	
Direct medical costs dependent on patient weight (per kilogram)	11,360	5680	Gamma	
Symptomatic state in patients receiving ERT	14,454	7227	Gamma	a ($N = 1$)
Symptom-free state	36,181	12,060	Gamma	a ($N = 9$)
Undergoing HSCT	260,649	130,324	Gamma	a ($N = 1$)

Table 1 (continued)

Parameters	Base case value	Standard error	Parameter distribution	References
Recovery state after undergoing HSCT				a ($N = 1$)
1st year	83,025	41,512	Gamma	
From the 2nd year onward	34,143	17,072	Gamma	
Direct medical costs excluding ERT per year for patients with Gaucher disease type 3b in baht				
Symptomatic state in patients not receiving ERT	1,437,961	718,981	Gamma	a ($N = 1$)
Symptomatic state in patients receiving ERT	14,454	7227	Gamma	Assumed to be equivalent to type 1
Improved state	22,626	8000	Gamma	a ($N = 8$)
Undergoing HSCT	1,919,366	959,683	Gamma	a ($N = 4$)
Recovery state after undergoing HSCT				a ($N = 4$)
1st year	439,534	219,767	Gamma	
From the 2nd year onward	351,124	175,562	Gamma	
Direct non-medical costs per year include travel expenses, food, accommodation, and loss of income for relatives in baht				
Gaucher patients not receiving ERT	93,334	b	Gamma	a, c
Gaucher patients receiving ERT	95,869	b	Gamma	a, c
Gaucher patients undergoing HSCT	604,011	b	Gamma	a, c
Gaucher patients in the recovery state following HSCT				a, c
1st year	109,842	b	Gamma	
From the 2nd year onward	35,101	b	Gamma	
Utility				
Symptomatic state in patients with Gaucher disease type 1	0.51	0.17	Beta	c ($N = 9$)
Symptomatic state in patients with Gaucher disease type 3b	0.53	0.19	Beta	c ($N = 8$)
Symptom-free state in patients with Gaucher disease type 1	0.87	0.23[d]	Beta	c ($N = 7$)
Improved state in patients with Gaucher disease type 3b	0.94	0.18[d]	Beta	c ($N = 6$)
Undergoing HSCT	0.79	0.36	Beta	Assumed to be equivalent to recovery state
Recovery state after undergoing HSCT	0.79	0.36[d]	Beta	c ($N = 3$)

[a]Retrospective secondary data collected from six participating hospitals

[b]The calculation is an aggregate of variables, including the number of outpatient department (OPD) and inpatient department (IPD) visits, length of stay, travel expenses per visit, accommodation costs, and income loss for relatives

[c]Data collection from interviews with patients or their primary caregivers

[d]Owing to the small sample size, the standard error is wide, which places the random variables outside the Beta distribution range. Consequently, the research team has set the standard error as wide as possible to ensure that the random variables remain within the Beta distribution range

2.4 Cost–Utility Analysis and Sensitivity Analysis

The cost-effectiveness was evaluated on the basis of incremental costs and incremental quality-adjusted life years (QALYs). The incremental cost-effectiveness ratio (ICER) was compared with the official cost-effectiveness threshold in Thailand, which is set at 160,000 baht per QALY [35]. Sensitivity analyses were conducted to assess the robustness of the results in the face of parameter uncertainty. A probabilistic sensitivity analysis (PSA) was conducted with

1000 simulations, and the results were illustrated using cost-effectiveness acceptability curves. For the one-way sensitivity analysis, parameters were varied within their 95% confidence intervals, and the most influential variables were presented in a tornado diagram. In addition, a scenario analysis was performed to assess the impact of key parameters on the ICER. A threshold analysis of the ERT price was also carried out to identify the maximum price at which the drug would remain cost-effective.

2.5 Budget Impact Analysis

The budget impact analysis adheres to the Thai guideline [21]. The estimated number of new Gaucher disease cases is 5 per year, based on research by Tim Phetthong and colleagues [10], which reports 3.7 cases annually, representing only 80% of the total patient population in Thailand. The budget impact analysis encompasses only direct medical costs associated with Gaucher disease treatment, as determined by the Markov model, and is projected over a 5-year period from the public payer's perspective with no discounting.

2.6 Model Validation

Face validity was assessed by evaluating the reasonableness of the model structure, parameter values, and assumptions through consultations with clinical experts who treat patients with Gaucher disease and through two rounds of stakeholder meetings [17, 18]. It was concluded that the model and input data were appropriate and consistent with current practices for diagnosing and treating Gaucher disease. Internal validity was tested by verifying the accuracy of the formulas used to calculate the number of cohorts in the economic model. As this study employed a closed model, the research team ensured that the total number of cohorts across all health states equaled the initial total number of cohorts.

Lastly, predictive validity was examined by comparing the model's predictions of average life expectancy for patients with Gaucher disease type 1 and 3b with clinical or epidemiological data. For a patient starting at age 6 years, the model predicted that patients with Gaucher type 1 would have an average life expectancy of 7 years without ERT and 63 years with ERT. These predictions are comparable to the estimates by van Dussen et al. [36], who reported that treated patients with Gaucher disease type 1 had a life expectancy of 61.7 years free from end-organ damage and 62.13 QALYs. However, no economic evaluations or studies have projected life years or QALYs for patients treated with Gaucher disease type 3b in literature. In the present study, the projected life expectancy for patients with Gaucher type 3b was 6 years without ERT and 41 years with ERT. Clinical experts confirmed that these estimates were consistent and aligned with clinical and epidemiological data.

3 Results

3.1 Cost–Utility Analysis

Table 2 presents the cost–utility analysis results of ERT for treating Gaucher disease types 1 and 3b. The findings demonstrate that expanding treatment coverage to include patients with Gaucher disease types 1 and 3b using either imiglucerase or velaglucerase results in higher lifetime costs but also yields improved health outcomes in terms of life years and QALYs. This is in contrast to the current policy, which provides treatment with imiglucerase only for patients with Gaucher disease type 1. However, the ICER indicates that expanding treatment coverage for these patient groups is not cost-effective at a threshold of 160,000 baht per QALY gained.

3.2 Sensitivity Analysis

The probabilistic sensitivity analysis (PSA) results, depicted in the cost-effectiveness acceptability curve in Fig. 5, show that at a threshold of 160,000 baht per QALY, the policy extending treatment to include patients with Gaucher disease types 1 and 3b using imiglucerase or velaglucerase is not cost-effective compared with the current policy, which covers only Gaucher disease type 1 with imiglucerase under the NLEM. As the cost-effectiveness threshold increases, the probability of the new policy being deemed cost-effective also rises. At a threshold of 13,500,000 baht per QALY, there is a 50% chance that the expanded coverage is considered cost-effective.

The one-way sensitivity analysis of the model variables identifies the discount rate for costs and health outcomes as the primary factor affecting the cost-effectiveness of expanding treatment coverage for patients with Gaucher disease types 1 and 3b using imiglucerase or velaglucerase. This is illustrated in Figs. 6 and 7 of the tornado graphs for imiglucerase and velaglucerase, respectively. In addition, other significant variables include the utility values for patients in the recovery, improved, and symptomatic states for Gaucher disease type 3b, as well as the prices of imiglucerase and velaglucerase.

Given that the prices of imiglucerase and velaglucerase significantly influence the cost-effectiveness of expanding treatment for Gaucher disease types 1 and 3b, the threshold analysis indicates that this expansion becomes cost-effective at a threshold of 160,000 baht per QALY if the price per vial of both drugs is below 19,826 baht. In addition, the sensitivity analysis varied the starting age of

Table 2 Lifetime costs and health outcomes of each policy option using societal perspective

	Current policy (ERT for Gaucher type 1 only)	New policy (Gaucher type 1 and 3b)	
		Imiglucerase	Velaglucerase
ERT lifetime costs (baht)	62,648,000	128,305,000	153,764,000
Other costs[a] (baht)	3,782,000	4,666,000	4,666,000
Total lifetime costs (baht)	66,430,000	132,971,000	158,430,000
Total life years	12.11	22.33	22.33
Total QALYs	9.15	18.98	18.98
Difference in total costs (baht)		66,541,000	92,000,000
Difference in QALYs		9.83	9.83
ICER per QALY gained		6,769,000	9,359,000

ERT enzyme replacement therapy, *ICER* incremental cost-effectiveness ratio, *QALY* quality-adjusted life-year

[a]Other costs include direct medical costs, excluding enzyme replacement therapy, and direct non-medical costs, such as travel, food, accommodation, and the opportunity cost of time for relatives accompanying patients to the hospital

patients with Gaucher disease from the base case age of 6 years to 3 years and 18 years. This adjustment accounts for the real-world scenario where patients with Gaucher disease type 3b may be diagnosed younger than 6 years, and patients with type 1 and 3b may be adults. The analysis shows that a younger starting age slightly improves the cost-effectiveness ratio by reducing the ICER, though it remains above Thailand's threshold of 160,000 baht per QALY.

The sensitivity analysis, which adjusts the hypothesis for HSCT rates from the base case analysis (17% for Gaucher disease type 1 and 43% for type 3b), indicates that increasing the HSCT rate leads to a reduction in the ICER for expanding treatment coverage for both Gaucher disease types. As shown in Fig. 8, if the HSCT rate increases to 50%—meaning that 50% of patients who achieve a symptom-free status (for Gaucher disease type 1) or an improved status (for Gaucher disease type 3b) after ERT undergo HSCT—the ICER for the new policy, which includes treatment with imiglucerase and velaglucerase, decreases by 37% and 32%, respectively. Despite these reductions, the ICER remains above Thailand's cost-effectiveness threshold of 160,000 baht per QALY. In addition, Fig. 8 demonstrates that increasing the HSCT rate enhances cost-effectiveness and could make the expansion of ERT coverage cost-effective if all patients who show improvement after ERT ultimately undergo HSCT. Under this scenario, the ICER becomes cost-saving.

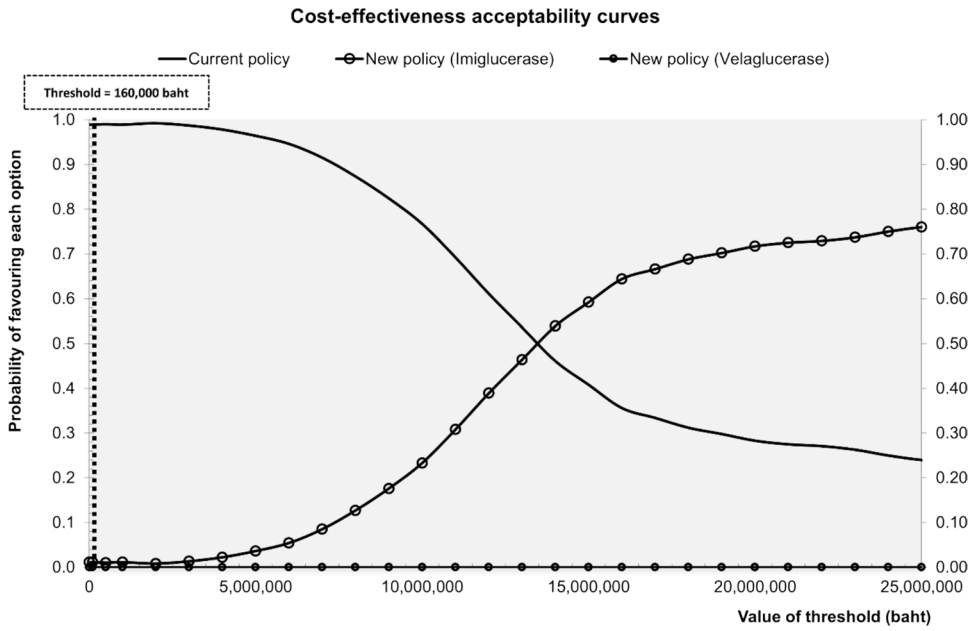

Fig. 5 Acceptability curves of the cost-effectiveness at the different ceiling thresholds of both the current policy and the proposed new policy for treating patients with Gaucher disease types 1 and 3b

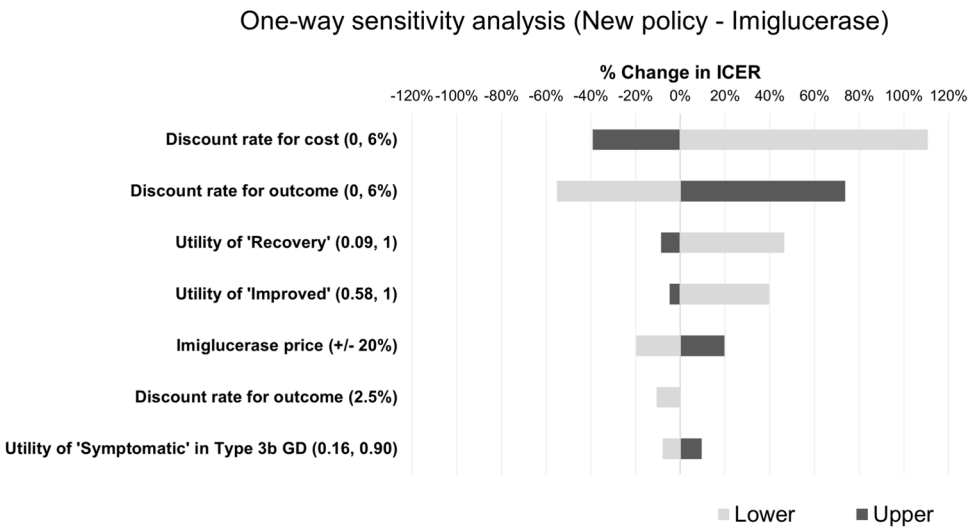

Fig. 6 Results of one-way sensitivity analysis for the cost-effectiveness of expanding treatment coverage for patients with Gaucher disease types 1 and 3b using imiglucerase

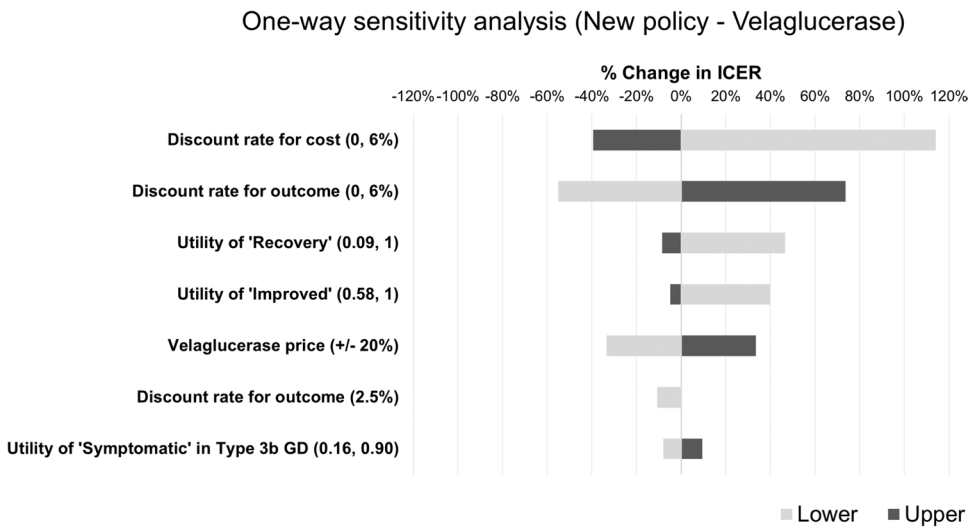

Fig. 7 Results of one-way sensitivity analysis for the cost-effectiveness of expanding treatment coverage for patients with Gaucher disease types 1 and 3b using velaglucerase

Lastly, the average HSCT cost for patients with Gaucher disease type 3b is significantly higher than that for patients with Gaucher disease type 1. This discrepancy is primarily attributed to the fact that only one patient with type 1 underwent HSCT, and this patient received partial financial support from a charity, resulting in an artificially lower provider cost. Since the subsidized cost was not reported in the hospital database, the actual cost could not be accurately estimated. To assess the impact, a one-way sensitivity analysis was conducted by increasing the HSCT cost for the patient with type 1 Gaucher disease from 260,649 to 1,082,201 baht (adjusted to 2023 values)—the cost incurred by a patient with type 3b who underwent a matched-sibling donor HSCT, a method similar to that used for the patient with type 1. However, the cost-effectiveness results remained unchanged. This is because, although HSCT costs influence cost estimations in the Markov model, they cancel each other out when comparing alternative policy options in the decision tree model. As a result, these costs do not affect the overall ICERs between policy alternatives.

3.3 Budget Impact Analysis

On the basis of an estimate of five new cases of Gaucher disease per year, expanding treatment coverage to include imiglucerase or velaglucerase for both Gaucher disease types 1 and 3b would incur an additional budgetary burden of 81 million and 138 million baht, respectively, over the next 5 years. In addition, increasing the HSCT rate would reduce the overall budgetary impact over this period compared with the current situation, as outlined in Table 3.

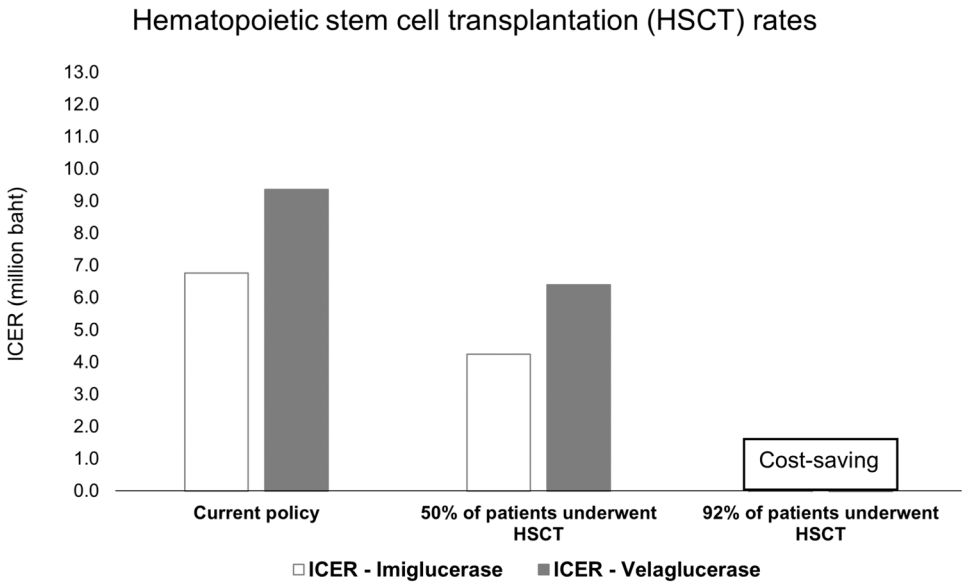

Fig. 8 Results of the sensitivity analysis when adjusting the hematopoietic stem cell transplantation (HSCT) rates in the cost-effectiveness model from a societal perspective

4 Discussion

Expanding the indications for ERT to treat patients with Gaucher disease type 3b in Thailand, in addition to patients with type 1, is not cost-effective at the current ERT price proposed by pharmaceutical companies to the NLEM. However, if these companies reduce the price of ERT by approximately 60%, expanding treatment coverage for both types 1 and 3b with either imiglucerase or velaglucerase would meet Thailand's cost-effectiveness threshold of 160,000 THB per QALY. International literature suggests that ERT production costs represent about 10% of their selling price [37, 38], making such a reduction feasible through negotiations and some types of agreement that can be mutually beneficial for all parties involved. This proposed suggestion aligns with discussions from the stakeholder meeting in May 2024, where representatives from both pharmaceutical companies noted that a price reduction would be consistent with their global strategies to increase access to treatments for rare diseases [18].

Given that no significant differences in efficacy and safety between imiglucerase and velaglucerase have been established, the decision on which ERT to include in the NLEM should primarily depend on the price offered to the Thai government. The first option is to select a single drug, consistent with the NLEM Subcommittee's policy of "choosing one policy." This approach involves selecting one price and accepting all drugs that can meet that price or choosing one specific drug without necessarily opting for the lowest-priced option. Clinical experts have indicated that either ERT could be used, despite limited experience with velaglucerase among Thai patients [18]. This approach encourages competitive pricing from pharmaceutical companies but may require special consideration for patients already responding well to imiglucerase, particularly those with Gaucher disease type 3b. Switching from imiglucerase to velaglucerase without robust evidence may pose risks, as no head-to-head

Table 3 Budget impact analysis of expanding treatment coverage for Gaucher disease types 1 and 3b with imiglucerase or velaglucerase, based on an estimate of five new cases of Gaucher disease per year

	Current policy	New policy	
		Imiglucerase	Velaglucerase
Current situation			
5-year budgetary impact (million baht)	208	289	346
Additional budget required (million baht)		81	138
50% of patients who achieve a symptom-free/improved status after ERT undergo HSCT			
5-year budgetary impact (million baht)	208	286	342
Additional budget required (million baht)		78	134
All patients who achieve a symptom-free/improved status after ERT undergo HSCT			
5-year budgetary impact (million baht)	208	215	254
Additional budget required (million baht)		7	46

ERT enzyme replacement therapy, *HSCT* hematopoietic stem cell transplantation

studies are comparing the two drugs in this subgroup. The second option is to include both ERTs in the NLEM, designating the lower-priced ERT as the first-line treatment for patients newly diagnosed with type 1 and 3b Gaucher disease. The other ERT would be reserved for cases where the first-line therapy proves ineffective. This approach offers greater flexibility for physicians and patients, allowing existing patients to continue their current therapy, even if it is not the lowest-priced option. However, this dual-ERT approach may reduce the incentive for pharmaceutical companies to offer the lowest price and increase the administrative burden associated with managing two drugs within the NLEM. In addition, it would be necessary to evaluate whether switching patients who demonstrate nonresponse to one treatment would incur additional costs.

Ultimately, if the price of ERT is not reduced to a level that renders the new policy cost-effective, policymakers may opt to implement the policy on the basis of equity considerations. This is particularly relevant given that ERT for Gaucher disease type 1 has not been demonstrated to be cost-effective within the Thai context [12], and its inclusion in the NLEM was influenced by policy decisions driven by the need for life-threatening intervention and minimal budgetary implications.

In addition to ERT pricing, this study highlights the importance of expanding access to HSCT, which offers a potential cure for Gaucher disease. HSCT eliminates the need for lifelong ERT and biweekly hospital visits, improving cost-effectiveness in the long term. However, barriers to accessing HSCT in Thailand include limited availability of medical personnel, the concentration of services in a few large hospitals, challenges in finding matching donors, and a lack of incentives for patients to opt for HSCT, particularly for type 1 Gaucher disease, where ERT is effective in the short term and publicly funded. Stakeholders have proposed establishing a new committee under the National Expert Working Group on Drug Selection for Rare Diseases to coordinate comprehensive care for patients with Gaucher disease and explore ways to increase access to HSCT [18].

Notably, this study compared the cost-effectiveness of policy choices for treating different groups of patients with Gaucher disease, rather than evaluating the treatments themselves, as is common in most economic evaluations. Using a hybrid model, each policy option encompasses both diagnosis and treatment over patients' lifetime. As a result, the cost-effectiveness and budget impact analyses are presented for each policy option (i.e., current versus new policy) rather than being segmented by patient group (i.e., Gaucher types 1 and 3b). This approach accounts for the possibility that some patients initially diagnosed with type 1 may later experience disease progression, resulting in diagnosis change to type 3b. Therefore, disaggregated data on the number of patients and lifetime treatment costs for each type of Gaucher disease cannot be reported in this study. Furthermore, based on our experience conducting cost-effectiveness analyses for rare diseases to inform coverage decision in Thailand [39], the results often suggest that high-cost treatments for rare diseases are cost-ineffective. Consequently, budget impact analysis provides policy-relevant information to complement cost-effectiveness results when making coverage decisions. As outlined in the new policy recommendation [39], life-saving interventions for rare diseases with low budget impact may be included in Thailand's benefit package.

This study is the first to address the policy issue of expanding treatment access from type 1 to type 3b Gaucher disease. A review of international cost-effectiveness studies revealed no research specifically on this expansion. Katsigianni and Petrou's systematic review [40] found that, as of 2012, only one study by van Dussen et al. evaluated the cost-effectiveness of ERT for Gaucher disease type 1, with an ICER of approximately 432,000€ per QALY, highlighting the significance of drug prices as a major cost driver [36]. This work represents an example of how research can be used to support policy-making process, specifically how this study was used to support the decision-making process for NLEM in Thailand.

The study has limitations owing to the small sample size, reflecting the rarity of Gaucher disease. However, the 24-patient sample represents the most comprehensive dataset available in Thailand. In addition, long-term data on ERT and HSCT efficacy for patients with Gaucher disease are limited both domestically and internationally. Establishing a patient registry in Thailand to track long-term outcomes and enhance the understanding of factors affecting cost-effectiveness is recommended and could be overseen by the proposed committee.

Currently, no high-quality studies are comparing the head-to-head efficacy of imiglucerase and velaglucerase for Gaucher disease type 3, which complicates direct cost-effectiveness comparisons. This study assumes that both drugs have identical safety and efficacy on the basis of clinical trial data for Gaucher disease type 1. If future evidence contradicts this assumption, new cost-effectiveness analyses will be required to reassess the policy recommendations. Scenario analysis of the efficacy parameter for Gaucher disease type 1 indicates that increasing the effectiveness of velaglucerase relative to imiglucerase reduces the ICER for expanding treatment to both Gaucher disease types 1 and 3b. Furthermore, the analysis suggests that velaglucerase would be as cost-effective as imiglucerase if its relative risk were 4.5. In addition, non-ERT medical costs were derived from retrospective secondary data from six hospitals, on the basis of charges rather than actual costs, as no reference for cost-to-charge ratios was available for patients with Gaucher disease. However, since drug costs dominate overall

medical expenses, this limitation is unlikely to affect the study's conclusions.

The input parameters for utility data were derived from both patients and proxies, reflecting the mixed population in the study, which includes individuals ranging from 3 to 37 years of age. In addition, since value sets for calculating utility values for children in Thailand are not available, this study employed the EQ-5D-Y-3L value sets from Vietnam, as they were considered most relevant to the Thai context. These factors may introduce variation and uncertainty in the estimates. However, these issues were discussed and acknowledged by stakeholders during the consultation meeting as unavoidable limitations. Given that three of the utility parameters are among the seven most important factors influencing the study's results, future research is needed to refine these utility parameters.

HSCT involves multiple types—matched related donor, matched unrelated donor, and haploidentical transplantation—each with varying costs, complications, and outcomes. This study used average costs and results for HSCT, and further research is needed to evaluate the cost-effectiveness of each HSCT type individually. Lastly, cost-effectiveness data are context-specific; therefore, applying evidence from this study to other settings should be done with caution. The approach presented here is likely generalizable across settings but may require further adaptation to ensure transferability.

5 Conclusions

This study concludes that, under current drug prices, expanding treatment coverage for Gaucher disease types 1 and 3b with imiglucerase or velaglucerase is not cost-effective in Thailand. The additional budget would be approximately 81 million baht for imiglucerase and 137 million baht for velaglucerase. However, through negotiation and agreements, if pharmaceutical companies were to reduce the drug prices to around 20,000 baht per vial—a 60% reduction from current levels—the expansion of treatment coverage for both types of Gaucher disease with either drug would meet Thailand's cost-effectiveness threshold of 160,000 baht per QALY. In addition, increasing the rate of HSCT could further improve the cost-effectiveness of expanding treatment coverage, potentially making it viable if all patients who benefit from imiglucerase or velaglucerase subsequently undergo HSCT. Nevertheless, enhancing HSCT rates presents ongoing challenges that necessitate collaborative efforts among stakeholders to improve comprehensive care and access to HSCT for patients with Gaucher disease.

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Declarations

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Conflicts of Interest The authors declare no conflicts of interest.

Availability of Data and Materials The individual patient data from six participating hospitals cannot be made publicly available for privacy and confidentiality reasons. The economic model is fully replicable from the information reported in this paper.

Ethics Approval This research study received ethical approval from the Central Research Ethics Committee (CREC) of Thailand on 7 September 2023, with certificate no. CREC075/2023.

Consent to Participate Informed consent was obtained from all patients and/or their caregivers prior to their participation in the study.

Consent for Publication Not applicable.

Code Availability The executable model is available from the authors upon request.

Author Contributions All authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship of this article and have approved its publication. All authors contributed to the conception and design of the study. D.W., T.T., K.W., A.S., P.C., K.S., and C.T. collected patient data from six participating hospitals. W.R., T.A., and W.I. analyzed the input parameters. W.R. developed the model, reviewed input parameters, and conducted the economic evaluation. W.R. and Y.T. prepared the manuscript. All authors reviewed and approved the final version.

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