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ORIGINAL RESEARCH ARTICLE

Can Cyprus Afford Luspatercept? A Budget Impact Analysis of the Reimbursement of Luspatercept for the Management of Thalassaemia in Cyprus

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Abstract

Objective This study aims to estimate the budget impact of luspatercept reimbursement as an adjuvant to the standard management of β-thalassaemia major in Cyprus, from a societal perspective, and assess the financial feasibility of its inclusion in the β-thalassaemia armamentarium.

Methods A 5-year horizon budget impact model was developed to determine the budget impact of reimbursing luspatercept for the management of β-thalassaemia major in Cyprus. Two treatment discontinuation scenarios were elaborated. In the first scenario, luspatercept is reimbursed complementary to best supportive care, and a dropout rate of 40% is assumed based on published real-world data, while for the second scenario a dropout rate of 25%, is assumed as per the clinical trial data. Input parameters were retrieved from the phase III clinical trial of luspatercept, literature, and expert opinion consensus. One-way sensitivity analyses were conducted for both scenarios.

Results The addition of luspatercept to the standard management of β-thalassaemia major in Cyprus imparted an incremental budget impact ranging from €21,300,643 to €25,834,368, depending on the drop-out rate scenario assumed. Results were sensitive to the number of eligible patients and dose per patient.

Conclusion The potential reimbursement of luspatercept will wield a substantial impact on Cyprus total pharmaceutical expenditure and it is therefore imperative to affix a reimbursement framework that will allow the payer to mitigate uncertainty stemming out of the scarce clinical data and the inherently complex therapeutic landscape of β-thalassemia management.

Key Points for Decision Makers

The high acquisition cost of luspatercept solicits further elucidation of its potential budget impact.

Based on our findings, its 5-year budget impact, under two dropout scenarios, is substantial.

The first scenario assumes a dropout rate of 40% based on published real-world data, while the second scenario assumes a dropout rate of 25% as per the clinical trial data.

Given the uncertainty that engulfs the anticipated benefits, coupled with the burgeoning budget impact, a Managed Entry Agreement could be the way forward.

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1 Introduction

B-thalassaemias comprise a heterogeneous group of inherited hemoglobinopathies which are defined by defects in the β-globin chains. β-thalassaemia major is an autosomal recessive hereditary blood disorder. Heterozygotes, while carriers of the trait, do not present with symptoms [1]. In homozygotes, the disease manifests as an imbalance in the α/β-globin chain ratio, ineffective erythropoiesis, chronic haemolytic anaemia, compensatory haemopoietic expansion, hypercoagulability, and increased intestinal iron absorption [2]. Left untreated, the prognosis of patients with β-thalassaemia major is poor and patients' survival primarily relies on frequent and lifelong blood transfusions, from an early age. Even though red blood cell transfusion (RBCT) constitutes the lifeline for these patients, the oxymoron is that it concomitantly comprises a reckoned risk factor due to the accumulation of iron, predominantly on the heart and liver [3, 4].

Consequently, iron chelation therapy (ICT) has emerged as the cornerstone of pharmaceutical management by eliminating the iron overload and thus decreasing complications stemming from it. The use of parenteral ICT has been compounded by the need to carry a special device. Nevertheless, the introduction of oral pharmaceutical forms, while exerting a beneficial effect in adherence, brought about added safety repercussions.

Cyprus has one of the highest prevalences of β-thalassaemia trait carriers in the world, at around 15% [5]. Therefore, the disease is considered endemic in Cyprus, in contrast to its orphan designation in most of the world, and it is often designated as a national disease.

Cyprus has implemented an array of measures to compound disease incidence quite early. Since the 1960s, thalassaemia has come to pass as a significant public health concern in Cyprus. During this period, patient survival rates began to improve, leading to an increased demand for blood donations and essential treatments, particularly iron chelation therapy. Concomitantly, a national screening program for carriers was launched in 1972 [6]. By 1976, high-risk couples were referred to the UK for a prenatal diagnosis, due to an absence of local infrastructure, until the advent of a national program in Cyprus in 1980 [7]. While the incidence was reduced, the need to expand services for an aging patient population remained overarching. The Pancyprian Antianaemic Society (PAS), established in 1970 as a patient support organization, played a pivotal role in advocating for comprehensive health coverage for all patients receiving treatment services. Their effective advocacy efforts led to the achievement of full public health coverage [8, 9]. PAS has also been an ardent advocate in raising awareness for blood donation, and they are credited for the preservation of voluntary blood donation. These actions safeguarded blood as a free public resource rather than a commodity, which also infers that donors are not incentivized. Within this backdrop, a major impediment, availability of blood, which of course serves other patients as well, was overcome. It is worth noting that Cyprus stands out as one of the few countries worldwide that maintains self-sufficiency in meeting its blood and blood product requirements [9].

The need for regular RBCT comprises one of the most prolific burdens of the disease. Apart from the need to constantly keep a certain reserve of blood, blood transfusion carries its own risks, both infectious and noninfectious. Early attempts to cure thalassaemia, and in particular, alleviate the transfusion burden, as in the case of gene therapies, were suitable only for a small number of patients, had a burgeoning cost and consequently, are winding down [10].

Reasonably, it was anticipated that a reduction in RBCT would reduce the use of iron chelating agents, apart from the blood volume required. The impact of blood transfusion on patients' lives was also considered, since regular transfusions are usually required every 2–5 weeks, with a total duration of 6 hours [10]. While no specific guidelines concerning the volume and rate of RBCT exist [11], the frequency and duration mentioned has been confirmed by a local expert panel. In fact, the proximity to a specific transfusion center is a major determinant of patients' housing decisions.

Luspatercept is a recombinant fusion protein which binds to select transforming growth factor β superfamily ligands and enhances late-stage erythropoiesis. A phase I trial demonstrated a statistically significant reduction in blood transfusion burden and increased hemoglobin levels in healthy postmenopausal women [12]. In the phase III trial, 21.4% of patients demonstrated a reduction in the transfusion burden of at least 33% from baseline during weeks 13–24 plus a reduction of at least two red-cell units compared with 4.5% in the placebo group ($p < 0.001$).

Furthermore, analysis of the randomized controlled trial (RCT) showed that the luspatercept group had a significantly lower mean serum ferritin level at week 48 compared with the placebo group. This suggested that luspatercept contributed to a decrease in serum ferritin levels, reflecting a reduction in iron overload [13].

However, it is important to note that luspatercept was associated with certain adverse events. These included transient bone pain, arthralgia, dizziness, hypertension, and hyperuricemia, which occurred more frequently in the luspatercept group compared with the placebo group [13].

As previously mentioned, β-thalassaemia major is an endemic disease in Cyprus. While disease incidence has been curbed due to the vigorous screening and educational programs, it is essential that innovative approaches

to disease management integrate with the reimbursed healthcare package. The prevalence of β-thalassaemia major, coupled with the price of luspatercept are anticipated to exert budgetary pressures on the National Health Insurance Service (NHIS) of Cyprus. At the time this paper was written, the product was not reimbursed through the NHIS. Luspatercept has received a positive reimbursement recommendation for the indication of β-thalassaemia management in a number of countries, including Greece, Italy, Germany and Canada. However, financial concerns were raised in health technology assessments. A forerunner of these concerns is the Canadian Agency for Drugs and Technology in Health (CADTH), who recommends reimbursement of the modality provided that the listed price is reduced by 85% [14].

Therefore, the scope of this publication is to estimate the budget impact of luspatercept, following its reimbursement in the NHIS in Cyprus [15].

2 Design and Methods of the Budget Impact Analysis (BIA)

A budget impact analysis (BIA) model was elaborated in MS Excel®. The model has a 5-year time horizon concordant with the principles of ISPOR, and it compares the 'current scenario' in which luspatercept is not reimbursed with a 'scenario with luspatercept reimbursement' in which luspatercept reimbursement is introduced and its market share increases over the 5-year time horizon [16]. A 5-year time horizon is often the maximum considered in a BIA and is concordant with the abovementioned ISPOR principles. The market share increase assumption was based on the local expert panel consensus. This panel consists of five specialists in thalassaemia and one patient representative. In both scenarios where luspatercept reimbursement was modeled, we assumed that the initial number of patients was 42, while by the 5th year, this number would reach 174 patients.

No discounting was applied and no adjustments were made for inflation, in line with ISPOR recommendations [16]. All costs refer to 2022.

2.1 Base Case and Scenario Design

Base case analysis included direct and indirect costs and outcomes associated with disease management. Due to the recent introduction of luspatercept in reimbursement systems, real-world data on its use and outcomes is limited. The abstract by Delaporta et al. [17], which indicates a disparity between the data gleaned from the BELIEVE trial and real-world data (RWD) drop-out rates, was used as a reference for the worst-case scenario analysis, while the best-case scenario was elaborated according to the dropout rate of the BELIEVE trial. Considering the uncertainty pertaining to dropout rates and the financial impact the dropout rate exerts on final outcomes, we deemed it necessary to develop both scenarios into full BIA, thus creating a worst- and best-case scenario analysis. These were the only two scenarios that could be based on some existing data, potentially rendering further non-data-based drop-out scenarios as less relevant. The scenario analysis was preferred in order to explore the impact of the structural assumptions of the dropout rate in the model. In the first scenario (Scenario RWD), a drop-out rate of 40% was assumed. The 40% dropout rate was assumed after talking with the local expert panel and taking into consideration published RWD from Greece [17]. For the second scenario, a 25% dropout rate was adopted in accordance with the BELIEVE trial dropout rate data [13].

Both BIA scenarios adopted a 5-year horizon. All other structural parameters of the BIA remained the same. Efficacy, dosage, and duration of treatment with luspatercept were extracted from the BELIEVE trial [13].

2.2 Model Inputs

Demographic data was obtained directly from the National Thalassaemia Registry. The number of eligible patients was specified by the expert committee, who used real-world data regarding the uptake of luspatercept in countries with similar disease prevalence. The costs of all medicinal products were calculated by multiplying their yearly consumption (doses and frequencies) by their prices. The doses and frequencies of administration were obtained from the respective Summary of Product Characteristics (SmPC). We used actual reimbursement prices for the Cyprus National Health Insurance Scheme (NHIS), except in cases that a confidential agreement was reached. Luspatercept is currently not reimbursed, and we therefore used its wholesale price.

Probabilities for adverse events were extracted from the BELIEVE trial. Costing of adverse events was calculated using data of the cost of the associated medical activity—Diagnosis Related Group (DRG) and Current Procedural Terminology (CPT)—as per the actual average reimbursement value of NHIS in 2022. The Cyprus healthcare sector is governed by a hard cap global budget [18]. Each activity is assigned a specific weight, and each month a base rate is calculated based on the number of medical activities submitted to Health Insurance Organization (HIO), which is the single payer of Cyprus NHIS.

The adherence to iron chelating agents was evaluated indirectly, based on actual data of prescriptions issued and prescriptions dispensed in 2022 for the entire β-thalassaemia major population of the island. The relevant data was extracted from reports issued by the HIO.

A table with all relevant values is included as in the Electronic Supplementary Material [19].

2.3 Clinical Inputs

Adherence to the disease management regimen was assumed at 95% for all modalities. Specifically, adherence pertinent to the iron chelating agents was deduced from HIO 2022 consumption data, while for luspatercept, the corresponding adherence rate was extracted from the phase III trial [13]. Dose was set at 1 mg/kg for all patients, which is the lowest therapeutic dose. No vial sharing was assumed as indicated by the product's SmPC [20]. The drug has been licensed for use only in adult patients with β-thalassaemia major. Therefore, all patients were assumed to be adults.

Transfusion burden was assumed to be 6–20 units per patient per 24 weeks according to the BELIEVE trial inclusion criteria. The distribution of patients per transfusion rate was extracted from the BELIEVE trial. The reduction in the transfusion load for patients receiving luspatercept was calculated according to the primary endpoint reduction data reported in the BELIEVE trial [13].

The percentage reduction in total blood units transfused per year on luspatercept treatment compared with best supportive care (BSC) was assumed to be equivalent to the percentage cost reduction in ICT costs per year.

2.4 Model Perspective

The social footprint of thalassaemia called out for the adoption of a societal perspective in this analysis. Despite blood donation not being incentivized and the fact that blood is considered a free public good in Cyprus, blood donation incurs several cost centers. These entail awareness campaigns, blood donation and relevant activities such as storage and preparation. Thus, the costs of blood were calculated as a composite of the above-mentioned cost centers. Administration costs of RBCT burdens the payer. In addition, transfusion is a lengthy process, and we therefore deemed fit to incorporate the indirect costs of the procedure in the analysis [9, 21].We defined the societal costs by taking into consideration the social ramifications of the disease. Considering the percentage of thalassemic patients in unemployment relying on social benefits as a source of income, and the percentage of thalassemic patients that are underemployed, Cyprus National Minimum Wage was deemed the optimum metric to deduce average hourly remuneration. Currently, the Cyprus National Minimum Wage is €1002 per month and has remained the same since 2022 [22]. The percentage of unemployment or underemployment of thalassaemia patients was obtained from the National Statistics Service [7]. Using the average amount of blood units transfused per visit as per the BELIEVE trial, and data available from the Thalassaemia International Federation on the time necessary to transfuse one unit of blood, we calculated the cost of absenteeism from work, or the number of productive hours lost per RBCT visit. We then used these data to calculate the total savings per year for the transfusion volume decrease on luspatercept therapy.

2.5 Sensitivity Analysis

A univariate deterministic sensitivity analysis was performed in order to assess the parameters exerting the most significant impact on the model's output. The magnitude of uncertainty associated with each parameter was visually translated as a Tornado chart in order to facilitate the comparative analysis. Each parameter was subjected to a range adjustment commensurate with the percentage budget impact of the corresponding scenario, relative to its baseline value. The resulting Tornado charts are represented as Figs. 1 and 2.

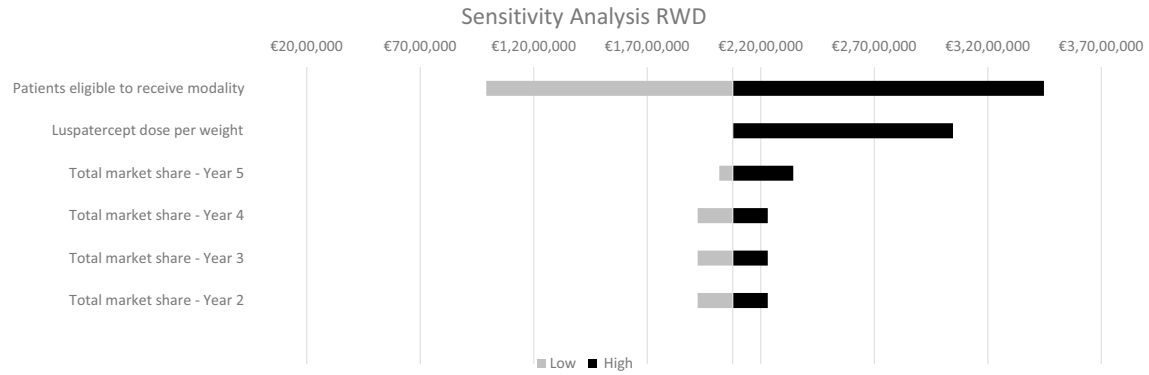

Fig. 1 Sensitivity analysis, real-world data (RWD)

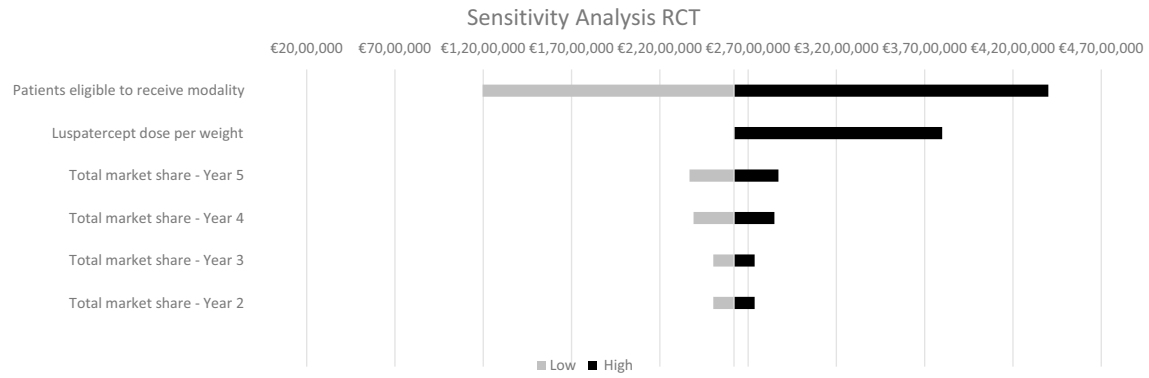

Fig. 2 Sensitivity analysis, randomized controlled trial (RCT)

2.6 Budget Impact Calculation

The per-member per-year (PMPY) costs were calculated taking into consideration the incremental difference in treatment costs for luspatercept reimbursement over the actual number of the NHIS beneficiaries, which is 943,978 [23]. Correspondingly, the per-member per-month (PMPM) costs were derived as the monthly equivalent of the PMPY. The per-treated-member per-month (PTMPM) costs were calculated using the corresponding number of eligible patients per year estimated at 526 according to the expert panel assessment, and the resulting value was then adjusted to represent a 1-month period.

3 Results of the BIA

According to the National Thalassaemia Registry and the local expert panel, 526 patients with transfusion-dependent β-thalassemia can be considered eligible to receive luspatercept. The patient pool is considered stable over the 5-year time horizon since the preventive measures have reduced the incidence of the disease.

In the scenario where a 40% dropout rate is assumed (Table 1), an incremental budget impact of €1,476,279 is forecasted in the first year following the introduction of luspatercept. This is expected to reach €6,309,351 by year 5 of luspatercept reimbursement. The annual cost following introduction of luspatercept is estimated at €18,538,390 in the first year and will escalate to €23,371,463 by year 5. The current scenario, where luspatercept is not reimbursed, assumes a steady expenditure of €17,062,111.

The total PMPY costs are estimated at €1.56 in first year and €6.68 by year 5. The PMPM costs are estimated at €0.13 in the first year and €0.56 by year 5.

The PTMPM costs are gauged at €233.88 in the first year and peak at €999.58 by year 5.

In the scenario where a 25% dropout rate is assumed (Table 2), an incremental budget impact of €1,845,312 is forecasted in the first year following the introduction of luspatercept. This is expected to reach €7,611,912 by year 5 of luspatercept reimbursement. The annual cost following introduction of luspatercept is estimated at €18,907,423 in the first year and will escalate to €24,674,023 by year 5. The current scenario, where luspatercept is not reimbursed, assumes a steady expenditure of €17,062,111.

The total PMPY costs are estimated at €1.95 in first year and €8.06 by year 5. The PMPM costs are estimated at €0.16 in the first year and €0.67 by year 5.

The PTMPM costs will begin at €292.35 in the first year and peak at €1205.94 by year 5.

Table 3 presents the budget impact of luspatercept reimbursement per year for both scenarios.

In terms of total budget impact, in the RWD scenario, the payer is anticipated to invest an additional 20% into the existing costs of thalassemia management over a 5-year period, solely for the introduction of luspatercept in the regimen. In absolute terms, this amount exceeds 21 million euro. The corresponding increase in the RCT scenario was estimated at 23%, which exceeds 25 million euro.

Regarding the overall expenditure over a 5-year period, we observed minor savings in RBCT and iron chelating agents' costs centers attributed to luspatercept reimbursement. Nevertheless, these savings fall short of making up for the steep acquisition cost of luspatercept. This is further corroborated by the other BIA metrics such as PMPY, PMPM and PTMPY. Although no explicit threshold applies for Cyprus, these metrics can cumulatively complement the incremental budget impact, aggregating into an informed health decision making.

While all acquisition costs burden the payer, any potential savings achieved by a reduction of RBCTs will not be capitalized upon, as blood is considered a public good in Cyprus. Nevertheless, we consider that is necessary to calculate the potential savings and include them in the analysis, as the

Table 1 RWD scenario

	Year 1	Year 2	Year 3	Year 4	Year 5	Total
NHIS beneficiaries	943,978	943,978	943,978	943,978	943,978	-
Eligible patients	526	526	526	526	526	-
Current scenario	0%	0%	0%	0%	0%	-
Scenario with luspatercept reimbursement	8%	16%	25%	30%	33%	-
Patients on luspatercept	42	84	132	158	174	-
Iron chelation agents						
Current scenario	€6,844,292	€6,844,292	€6,844,292	€6,844,292	€6,844,292	€34,221,460
Scenario with luspatercept reimbursement	€6,773,987	€6,773,987	€6,773,987	€6,773,987	€6,773,987	€33,869,937
RBC						
Current scenario	€10,072,387	€10,072,387	€10,072,387	€10,072,387	€10,072,387	€50,361,934
Scenario with luspatercept reimbursement	€9,968,923	€9,865,460	€9,749,063	€9,684,398	€9,645,600	€48,913,444
Adverse event costs						
Current scenario	€1946	€1946	€1946	€1946	€1946	€9728
Scenario with luspatercept reimbursement	€2091	€2236	€2400	€2491	€2545	€11,763
Monitoring costs						
Current scenario	€143,487	€143,487	€143,487	€143,487	€143,487	€717,434
Scenario with luspatercept reimbursement	€143,487	€143,487	€143,487	€143,487	€143,487	€717,434
Luspatercept cost						
Current scenario	€ 0	€ 0	€ 0	€ 0	€ 0	€ 0
Scenario with luspatercept reimbursement	€1,628,58	€3,257,168	€5,089,325	€6,107,189	€6,717,908	€22,800,174
Luspatercept administration costs						
Current scenario	€ 0	€ 0	€ 0	€ 0	€ 0	€ 0
Scenario with luspatercept reimbursement	€24,238	€48,476	€75,744	€90,893	€99,982	€339,333
Money saved from blood transfusions						
Current scenario	€ 0	€ 0	€ 0	€ 0	€ 0	€ 0
Scenario with luspatercept reimbursement	€292	€5841	€9126	€10,952	€12,047	€40,886
Total treatment cost						
Current scenario	€17,062,111	€17,062,111	€17,062,111	€17,062,111	€17,062,111	€85,310,556
Scenario with luspatercept reimbursement	€18,538,390	€20,084,973	€21,824,879	22,791,494	€23,371,463	€106,611,199
Incremental difference in treatment cost						
Current scenario	N/A	N/A	N/A	N/A	N/A	N/A
Scenario with luspatercept reimbursement	€1,476,279	€3,022,862	€4,762,768	5,729,383	€6,309,351	€21,300,643
PMPY cost	€1.56	€3.20	€5.05	6.07	€6.68	€22.56
PMPM cost	€0.13	€0.27	€0.42	0.51	€0.56	€1.88
PTMPM cost	€233.88	€478.91	€754.56	907.70	€999.58	€3374.63

N/A not-applicable, *PMPM* per member per month, *PMPY* per member per year, *PTMPM* per treated member per month, *RBC* red blood cells, *RWD* real-world data

classification of blood as a public good does not render it cost-free.

In addition to BIA, a deterministic sensitivity analysis was performed on both scenarios in order to elucidate the uncertainty encompassing model parameters.

According to the results of the sensitivity analysis, the main cost drivers for both scenarios were the number of eligible patients and the dose per weight. Since the number of eligible patients is only contingent to the reimbursement guidelines, the deterministic sensitivity analysis provides an appropriate backdrop to investigate the effect of model parameters on the total budget impact [24]. To this end, we decided to use a deterministic sensitivity analysis as we aimed to emphasize the quantitative relationship between changes in inputs and outputs [24].

Sensitivity analysis results for 'Scenario RWD' are presented in Fig. 1 and results for 'Scenario RCT' are presented in Fig. 2.

In our scenarios, we used the procurement prices of iron chelating agents. To balance out luspatercept' absence of financial agreement, we assessed the budget impact of introducing luspatercept in a reimbursement

Table 2 RCT scenario

	Year 1	Year 2	Year 3	Year 4	Year 5	Total
NHIS beneficiaries	943,978	943,978	943,978	943,978	943,978	-
Eligible patients	526	526	526	526	526	-
Current scenario	0%	0%	0%	0%	0%	-
Scenario with luspatercept reimbursement	8%	16%	25%	30%	33%	-
Patients on luspatercept	42	84	132	158	174	-
Iron chelation agents						
Current scenario	€6,844,292	€6,844,292	€6,844,292	€6,844,292	€6,844,292	€34,221,460
Scenario with luspatercept reimbursement	€6,756,411	€6,668,531	€6,569,665	€6,514,739	€6,481,784	€32,991,130
RBC						
Current scenario	€10,072,387	€10,072,387	€10,072,387	€10,072,387	€10,072,387	€50,361,934
Scenario with luspatercept reimbursement	€9,943,057	€9,813,728	€9,668,232	€9,587,401	€9,538,903	€48,551,322
Adverse event costs						
Current scenario	€1946	€1946	€1946	€1946	€1946	€9728
Scenario with luspatercept reimbursement	€2091	€2236	€2400	€2491	€2545	€11,278
Monitoring costs						
Current scenario	€143,487	€143,487	€143,487	€143,487	€143,487	€717,434
Scenario with luspatercept reimbursement	€143,487	€143,487	€143,487	€143,487	€143,487	€717,434
Luspatercept cost						
Current scenario	€ 0	€ 0	€ 0	€ 0	€ 0	€ 0
Scenario with luspatercept reimbursement	€2,035,730	€4,071,460	€6,361,656	€7,633,987	€8,397,386	€28,500,218
Luspatercept administration costs						
Current scenario	€ 0	€ 0	€ 0	€ 0	€ 0	€ 0
Scenario with luspatercept reimbursement	€30,298	€60,595	€94,680	€113,616	€124,978	€424,166
Money saved from blood transfusions						
Current scenario	€ 0	€ 0	€ 0	€ 0	€ 0	€ 0
Scenario with luspatercept reimbursement	€3651	€7301	€11,408	€13,690	€15,059	€51,108
Total treatment cost						
Current scenario	€17,062,111	€17,062,111	€17,062,111	€17,062,111	€17,062,111	€85,310,556
Scenario with luspatercept reimbursement	€18,907,423	€20,752,735	€22,828,711	€23,982,031	€24,674,023	€111,144,925
Incremental difference in treatment cost						
Current scenario	N/A	N/A	N/A	N/A	N/A	N/A
Scenario with luspatercept reimbursement	€1,845,312	€3,690,624	€5,766,600	€6,919,920	€7,611,912	€25,834,368
PMPY cost	€1.95	€3.91	€6.11	€7.33	€8.06	€27.37
PMPM cost	€0.16	€0.33	€0.51	€0.61	€0.67	€2.28
PTMPM cost	€292.35	€584.70	€913.59	€1096.31	€1205.94	€4,092.90

N/A not-applicable, *PMPM* per member per month, *PMPY* per member per year, *PTMPM* per treated member per month, *RBC* red blood cells, *RWD* real-world data

Table 3 Budget impact of luspatercept reimbursement

Budget impact of luspatercept reimbursement	Year 1	Year 2	Year 3	Year 4	Year 5	Total
Scenario with luspatercept reimbursement RWD	€1,476,279	€3,022,862	€4,762,768	€5,729,383	€6,309,351	€21,300,643
Scenario with luspatercept reimbursement RCT	€1,845,312	€3,690,624	€5,766,600	€6,919,920	€7,611,912	€25,834,368

RCT randomized controlled trial, *RWD* real-world data

model using the wholesale prices for all corresponding pharmaceuticals.

The weighted discount achieved among the iron chelating agents was 35%. Therefore, a 54% increase in the iron

chelating agents' prices indicates the expenditure of the therapies without financial agreements, based on wholesale prices.

The result of this change led to an anticipated total expenditure increase for the management of thalassemia. Nevertheless, the differences in incremental budget impact were barely distinguishable from the primary analyses. In the RWD scenario, the incremental budget impact changes from €21,300,643 to €21,114,336 (20% vs 17%). In the RCT scenario, the corresponding results are €25,834,368 vs €25,182,293 (23% vs 20%). This reinforces the robustness of the findings of the two primary scenarios regarding the modest effect of luspatercept on iron chelating agents' utilization.

4 Discussion

To our knowledge, this is the first BIA of luspatercept to be published. We believe that our model results could potentially be extrapolated to other thalassaemia-endemic countries. As we retrench, we should not sideline the overwhelming patient and social perspective of thalassaemia. Thalassaemia is an endemic disease in Cyprus and has been the exemplary stress test for the Cyprus health policy context.

The scenario analysis of this BIA further elucidated the fact that Cyprus will face substantial challenges in the process of reimbursing luspatercept for thalassaemia. As a result, in a time horizon of 5 years, the anticipated cumulative financial burden of thalassaemia management with luspatercept reimbursement is forecasted to exceed 100 million euros, while the accumulated acquisition cost of luspatercept is estimated at a range of 23–28 million euros pertaining to the respective scenarios (RWD–RCT). In order to put things into the payer perspective, the annual total pharmaceutical expenditure for Cyprus' NHIS is approximately 270 million [18]. Another area of budgetary concern is that all chelation agents are generics and procured through tendering, which further minimizes any potential for savings.

Additionally, we need to take into account the recent conditional approval granted by the EMA to a gene editing therapy targeting younger individuals with β-thalassaemia [25]. Although not yet priced, it is unlikely that the acquisition and administration costs will deviate from the soaring costs of other gene therapies. Reimbursement of a gene editing therapy will be a stress test for the sustainability of any health care system, let alone in countries where thalassemia is an endemic disease. Moreover, these advances, coupled with the substantial budget impact of luspatercept, call for a thorough analysis of the thalassemia management reimbursement framework and underscore the need for further research in the field. This accentuates the compelling need for evidence-based decision making, both clinically and pharmacoeconomically, and notes the exigency of linking reimbursement to outcomes.

A more aggressive uptake scenario, partially driven by induced demand—since this will be the first thalassemia management agent entering the reimbursement system after a long period of absence of new therapies—would bring about intense financial repercussions. The ingrained uncertainty imposes the need to control the uptake rate, presumably by the implementation of eligibility criteria, while any financial uncertainty should be equally socialized between the payer and the Marketing Authorization Holder (MAH). This is important since current evidence does not fully substantiate several aspects of the product's efficacy and safety profile. Therefore, authorities should consider, apart from any price reduction, a performance-based reimbursement scheme. To this end, a thoroughly designed and implemented Managed Entry Agreement (MEA) can extenuate financial burden, while concomitantly providing access to the right patients. The inclusion criteria of the BELIEVE trial [13] can demarcate a certain patient profile.

In addition, we should delineate the MEA endpoints. Various options exist here; for example, the interest could be in a shorter duration of transfusions, as primary indicators, or are we only aiming for an increased interval between transfusions? The former might, for example, face the consideration that any transfusion has certain fixed costs and pre-transfusion activity, which the patient must abide to. Therefore, if the patient is exposed to this procedure, despite the potentially shorter duration, this probably does not qualify as a substantial health gain and cost reductions may be limited.

The discontinuation rate poses further challenges and limitations concerning consistent data availability and evidence. By extrapolating data from the BELIEVE trial, we estimate that 25% of the patients will discontinue the product in any given year [13]. However, RWD suggest that the dropout rate is much higher [17]. Given the substantial discontinuation rate, in tandem with the uncertainty engulfing the results of the BELIEVE trial [13]—in particular the fluctuating reduction rate between the 12-week intervals—a MEA should consider the BELIEVE trial eligibility criteria, and incorporate the successful completion of a minimum of 24 weeks of treatment while exhibiting a discernible reduction in RBCT.

5 Limitations of the Study

While the cost-effectiveness analysis (CEA) and its instruments have been thoroughly examined, the landscape of BIA lacks the corresponding information pertinent to

the utilized tools, such as PMPM, PTMPM and PMPY, particularly concerning thresholds and their policy-related interpretation. We should underline that the evaluation of BIA and its ensuing relationship to affordability is not merely a technical health economic function but it also percolates in the public policy decision-making context.

Therefore, further data are required to methodologically bring BIA up to par with CEA.

Furthermore, each scenario was developed on one study (RCT and RWD, respectively). As is the case, bias could be attributed to the transferability of data from a single study. Moreover, we used the official price of luspatercept, which may deviate from a potential future confidential agreed-upon one.

6 Conclusion

Current BIA has intimated that reimbursement of luspatercept will wield a substantial impact on Cyprus pharmaceutical expenditure. Within this context, it is imperative to affix a reimbursement price which incorporates the multifaceted factors explored in this paper.

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Declarations

Ethics Approval and Consent to Participate Not applicable.

Consent for Publication Not applicable.

Availability of Data and Materials The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Code Availability The parameter values utilized in the model for this BIA are accessible in the published article (as well as its supplementary information files). The model is available from the corresponding author on reasonable request.

Competing Interests O. Pitsillidou (PhDc) and Dr P. Petrou are employees of Cyprus Health Insurance Organization (HIO). The views and opinions expressed in this publication are those of the authors. They do not purport to reflect the opinions or views of the HIO. The authors have no relevant affiliations or financial involvement with any organization or entity with financial interest in or financial conflict with the subject matter or materials discussed in this manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants, or patents received or pending, or royalties.

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Authors' Contributions OP and PP conceptualized and designed the model. OP designed and drafted the article. PP and MJP provided study material and revised the initial article. All authors read and approved the final manuscript.

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