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ORIGINAL RESEARCH ARTICLE

Cost-Effectiveness of RefluxStop Versus Nissen Fundoplication and Proton Pump Inhibitors for Refractory Gastroesophageal Reflux Disease: A Spanish Healthcare Perspective

Sam Harper[1] · Khanh Ha Bui[2] · Stuart Mealing[1] · Daniel Sanchez[3] · Pablo Priego Jiménez[4] · Carlos Moreno Sanz[5]

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Abstract

Background Gastroesophageal reflux disease (GERD) affects 6.8 million individuals in Spain, incurring €56 million/year in healthcare costs. Standard-of-care treatment (SOC) in Spain includes medical management with proton pump inhibitors (PPIs) and laparoscopic Nissen fundoplication (LNF) in selected cases. The limitations of PPIs, including high rates of unresponsiveness, adverse events (AEs) associated with long-term use, and nonindicative misuse, increase the economic strain on European healthcare systems. The durability of LNF treatment is hindered by reoperation and postoperative complications. RefluxStop, a novel implantable device, restores the anti-reflux barrier without encircling the esophagus and confers long-term efficacy and safety in the treatment of GERD.

Objective This study assessed the cost-effectiveness of RefluxStop compared with medical (PPI-based) and surgical (LNF) SOC for refractory GERD in Spain.

Methods The cost-effectiveness of RefluxStop versus PPI-based medical management and LNF was assessed from the Spanish National Health System (SNS) perspective over a lifetime horizon (monthly cycles, 3.0% annual discount rate). A Markov model adapted from a published UK National Health Service (NHS) cost-effectiveness analysis of this device was used. Quality-adjusted life years (QALYs) and total costs were calculated for each intervention, while inter-arm differences were evaluated using incremental cost-effectiveness ratios (ICERs).

Results RefluxStop yielded ICERs of €557 and €2393 per QALY gained compared with medical management and LNF, respectively. At the cost-effectiveness threshold of €30,000 per QALY gained for Spain, the probability of RefluxStop being cost-effective was 100% compared with medical management and 93% compared with LNF. Over a lifetime horizon, the per-patient cost differences and QALY gains for RefluxStop were €1472 and 2.64 versus medical management and €2111 and 0.88 versus LNF, respectively. The model results remained robust to sensitivity analysis.

Conclusions RefluxStop was estimated to be cost-effective relative to SOC in Spanish healthcare settings for the treatment of adult patients with refractory GERD, consistent with recently published findings in the UK, Switzerland, Sweden, and Norway. It is acknowledged that the model has limitations, including its reliance on single-arm trial data and indirect comparisons using heterogeneous literature sources, which limit the precision and generalizability of its findings.

✉ Khanh Ha Bui
khanhha.bui@implantica.com

1 York Health Economics Consortium, York, UK

2 Implantica AG, Zug, Switzerland

3 Hospital Universitario Infanta Sofía, Madrid, Spain

4 Hospital Universitario La Paz, Madrid, Spain

5 Hospital General La Mancha Centro, Ciudad Real, Spain

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Key Points for Decision Makers

RefluxStop was cost-effective compared with PPIs and LNF, with ICERs below Spain's accepted threshold for viable healthcare interventions—indicating meaningful health gains within acceptable costs for the healthcare system.

Markov model estimates showed RefluxStop, compared with standard of care for refractory GERD in Spain, led to better clinical outcomes (fewer surgical failures, reoperations, and dilatations) and enhanced patient health benefits (increased QALYs and life expectancy).

Findings aligned with evaluations from the UK, Switzerland, Sweden, and Norway, reinforcing the cost-saving potential for European payers.

1 Introduction

Gastroesophageal reflux disease (GERD) is a widespread and chronic disease characterized by the retrograde flow of gastric contents into the esophagus or oral cavity, causing persistent and troublesome symptoms, primarily heartburn and regurgitation [1]. Prevalence rates of GERD across different continents range from 8 to 33%, with European estimates between 9 and 26%, presenting a significant healthcare challenge worldwide [2, 3]. The reported prevalence of GERD in Spain ranges from 15 to 32%, affecting an estimated 6.8 million individuals and surpassing an annual economic burden of €56 million [4–7]. While the average GERD prevalence in Spain is lower than that in the USA (18–28%), the relatively higher consultation rates for GERD symptoms indicate a proportionally greater healthcare burden in Spain than in the USA [3, 8]. Healthcare resource utilization in Spain is severely impacted by the burden attributed to GERD-related physician consultations, radiographic studies, and endoscopies [9]. Indeed, patients treated for GERD in Spain have reported a higher number of emergency room visits, increased primary care consultations, and longer hospitalizations than those in other European countries [10]. Among patients with GERD seeking primary care, the rates of cardinal GERD symptoms such as heartburn and regurgitation are notably high, ranging from 82 to 90% [11]. One of the most concerning long-term complications is Barrett's esophagus (BE), a well-established precursor condition for esophageal adenocarcinoma (EAC) [1, 12]. Clinical oversight of BE necessitates expensive measures, such as stringent surveillance, frequent endoscopies, and oncological treatments for patients progressing to EAC [7, 13–15]. Given that nearly 30,000 inadequately treated patients with GERD in Spain advance to BE, these interventions likely impose an additional financial burden on a potentially strained Spanish healthcare system [7, 15, 16].

The Asociación Española de Gastroenterology (AEG) guidelines, aligning with multicountry consensus recommendations, endorse a stepwise GERD management approach: initially with lifestyle modifications, then pharmacological treatment with proton pump inhibitors (PPIs) as the primary therapy, and surgical interventions for refractory or selected cases [17–19]. However, up to 42% of patients with GERD are partially or fully unresponsive to PPIs while still facing increased risks from their long-term use, including osteoporosis, nutritional deficiencies, chronic kidney disease (CKD), and infections [17, 20]. Following a course of optimized PPI therapy lasting at least 8–12 weeks, a substantial percentage of patients continue to experience troublesome GERD symptoms with objective evidence of ongoing reflux, a condition termed refractory GERD. Despite suboptimal response rates and increasing recognition of long-term adverse effects, PPI prescriptions have surged globally, with 25% of adults using them regularly and often for up to 3 years [21, 22]. The chronic nature of the disease necessitates substantial PPI use in Spain, with more than 9000 treatment days per 1000 inhabitants annually [9]. Consistent with alarming global trends in PPI usage [21–24], the consumption of this drug class in Spain has increased two- to fourfold since 2000 [23, 25], with 18–28% of the Spanish population estimated to be using these medications [11, 21, 26]. Notably, PPIs are used at higher than recommended doses and for a longer than advised duration in many countries, including Spain, where a hospital cohort study revealed inappropriate use in 61–80% of cases [24, 25]. From a payer perspective, the long-term pharmacological management of GERD, the treatment of PPI-associated adverse events, and the limited durability of treatment effect collectively contribute to impose an undue burden on the Spanish healthcare system [11, 16, 21–26].

In the case of laparoscopic Nissen fundoplication (LNF), the standard of care (SOC) for anti-reflux surgery, postoperative complications (e.g., dysphagia) and reoperations following surgical failure are recognized issues that diminish the clinical durability of the procedure [27–30]. RefluxStop, a novel, nonactive, implantable device, used for treatment of GERD reinstates the anatomical integrity of the anti-reflux barrier without encircling and compressing the esophagus, thereby substantially reducing the risks of postoperative complications [31–33]. The device has demonstrated long-term safety and effectiveness in treating GERD, conferring near-complete cessation of PPI and reoperations [31–33]. In contrast, 12–14% of patients with GERD fail to achieve independence from PPIs and 8–15% require reoperations at

5 years following LNF, indirect comparisons notwithstanding [29, 34]. In addition, RefluxStop has demonstrated cost-effectiveness compared with LNF and PPIs in the UK [35], Switzerland [36], Norway [37], and Sweden [38]. The objective of the present study was to assess the cost-effectiveness of RefluxStop for patients with refractory GERD, compared with PPI-based medical management and LNF, from the perspective of the Spanish Healthcare system.

2 Methods

This cost-effectiveness analysis was adapted from previous Markov model-based analyses conducted to in the UK [35], Switzerland [36], Norway [37], and Sweden [38]. Specifically, this study adjusted the model parameters to examine the cost-effectiveness of RefluxStop versus PPI-based medical management and LNF for adult patients with refractory GERD treated in Spain as the only available treatment options at the time of this analysis. GERD being a chronic condition, clinical performance and costs were examined over a lifetime horizon from the perspective of the Spanish National Health System (SNS), focusing only on direct medical expenditures and excluding indirect societal costs such as loss of productivity due to illness-related absenteeism. Clinical outcomes were measured using quality-adjusted life years (QALYs), an established metric for cost-effective analysis. In alignment with standard practices in Spanish health economic evaluations, all costs and QALYs were discounted at an annual rate of 3% [39]. The model utilized a cycle length of 1 month and assigned a half-cycle correction.

2.1 Model Structure

The state transition model employed in this study provides a systematic framework for simulating transitions of a hypothetical patient cohort through a series of four distinct health states based on the possible outcomes of the assessed GERD treatments. Two variations of the model structure were employed to distinguish medical (Fig. 1A) and surgical (Fig. 1B) management of GERD. Across both approaches, health states considered the impact of standard- and high-dose medical management, PPI resistance, primary surgery and reoperations, progression to BE, development of esophageal carcinoma, and mortality. The model also incorporated adverse events (AEs) associated with both medical and surgical treatments.

Consistent with the previously mentioned consensus GERD treatment guidelines, all patients initiated standard-dose PPI therapy and entered the medical management arm in the "medical management well" state [17, 18]. A prespecified monthly risk of GERD was assigned to the patients in the model. Patients that experienced relapse transitioned to a double-dose PPI regimen ("medical management relapse") and may either revert to standard-dose PPI or proceed to surgery. The model included LNF as the preferred surgical intervention, which is a widely accepted gold standard for treatment of refractory GERD when medical management by pharmacological or lifestyle approaches is considered insufficient or not feasible [30]. Post-surgical outcomes included either successful recovery ("surgery well") or failure ("surgery fail"). In cases of surgical failure, patients either underwent reoperation ("surgery re-op") or transitioned to lifelong double-dose PPI therapy ("medical management high dose").

In the model's surgical treatment arms (LNF and RefluxStop), as shown in Fig. 1B, all patients entered at the point of the initial surgery. The initial surgery may be either successful (placing patients in the "surgery well" state) or unsuccessful (resulting in a "surgery fail" state). For patients in whom the initial surgery failed, options included reoperation ("surgery re-op") or treatment with standard-dose PPI therapy ("medical management well"). Of the patients whose surgery failed and were placed on medical management, those experiencing relapse were assigned a double dosage of PPIs, maintained over their lifetime ("medical management high dose"). In the event of reoperation, patients in the surgical arms were assumed to have undergone the same surgical procedure as their initial treatment (i.e., LNF or RefluxStop). If reoperation failed, patients reverted to medical management with standard-dose PPI therapy ("medical management well"). In addition, mortality linked to specific health states and general population mortality was incorporated into the model, as detailed below.

2.2 Model Inputs

2.2.1 Clinical and Quality of Life Inputs

Demographic data: The model tracked a hypothetical cohort of 1000 patients with refractory GERD. The cohort characteristics included a mean age of 52 years and 56% male representation, consistent with the RefluxStop Conformité Européenne (CE) mark trial [31]. These demographics align with major GERD treatment trials, such as the UK REFLUX trial and a recent randomized controlled trial (RCT) comparing medical and surgical treatments for refractory GERD in the USA [40, 41]. The clinical and quality-of-life inputs used in the model are listed in Table 1.

Efficacy and safety: Data for RefluxStop effectiveness and safety were derived from the prospective, single-arm, multicenter CE mark trial [31] and updated with a recent follow-up of this study [42]. Efficacy and safety data for PPI-based management and LNF were obtained from literature

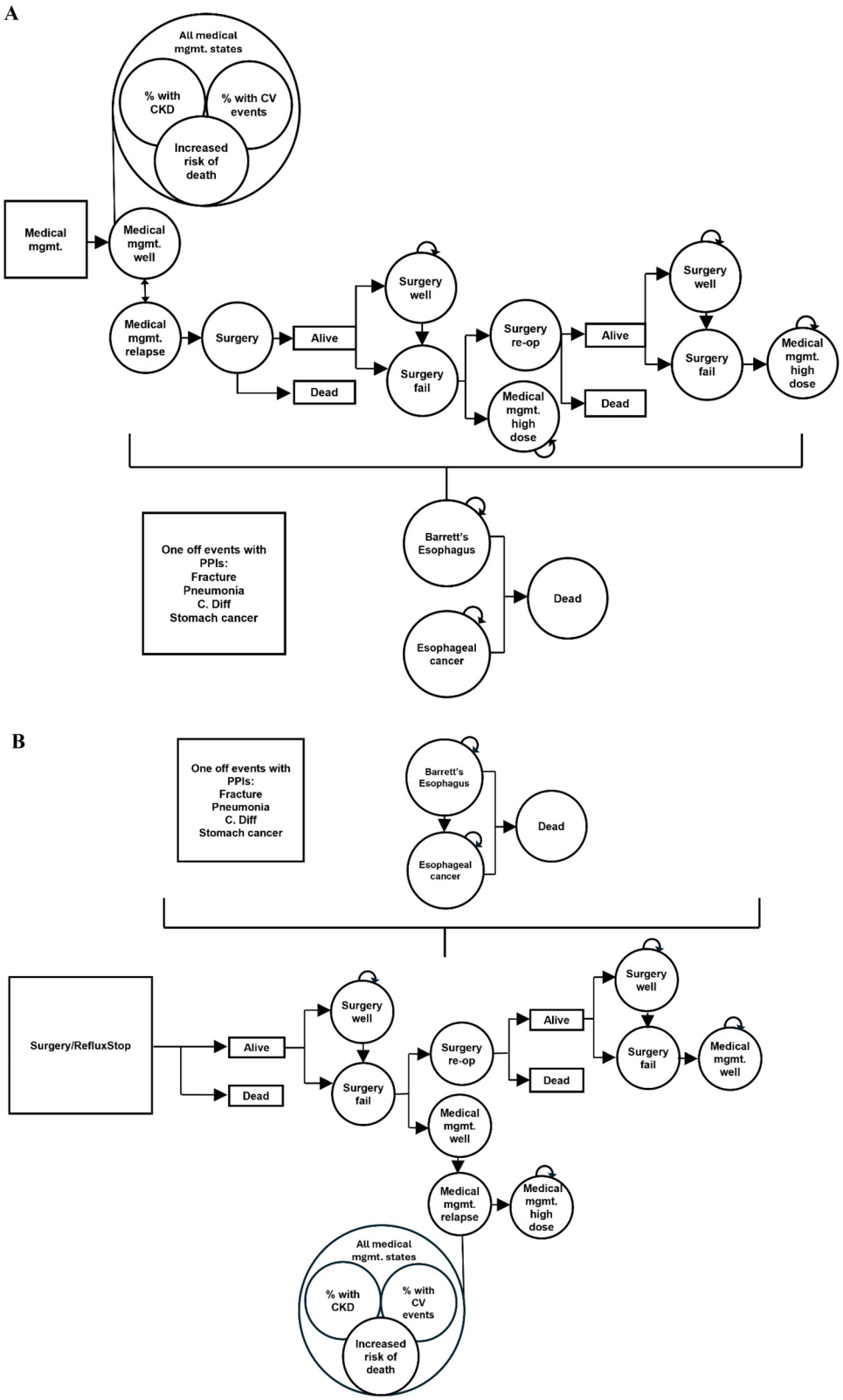

Fig. 1 Model structure applied to medical management (**A**) and surgical treatment options (**B**). *C. Diff Clostridium difficile*, *CKD* chronic kidney disease, *PPI* proton pump inhibitor, *reop* reoperation

[30, 43, 50]. The monthly probability of surgical failure was divided into two periods: the first-year post-surgery and the period after 1 year.

AEs: Intraoperative complications and postoperative AEs for all surgical interventions, including reoperations, were incorporated on the basis of a recent review of LNF

Table 1 Clinical and quality of life inputs used in the model

Parameter	Input	Source
Relapse of GERD symptoms with medical management	2.65%	Bojke et al. [52]
Reoperation following unsuccessful surgery	10.3%	
Surgery following a relapse of medical management	10.3%	Assumed to be the same as the probability in a case of reoperation
Probability of surgical failure up to 1-year post-surgery		
LNF	1.8%	Zehetner et al. [30]
RefluxStop	0.3%	Harsányi et al. [42]
Probability of surgical failure ≥ 1-year post-surgery		
LNF	1.8%	Zehetner et al. [30]
RefluxStop	0.1%	Harsányi et al. [42] Zehetner et al. [30]
Probability of surgical failure for reoperation or second-line treatment		
LNF	0.31%	Calculated on the basis of treatment failure rates up to 1 year and post-1-year provided above
RefluxStop	0.17%	Calculated on the basis of treatment failure rates up to 1 year and post-1-year provided above
Monthly probability of BE		
All treatment arms	0.083%	NICE model developed to support clinical guidance development in dyspepsia and GERD [49]
Risk of PPI-associated-AEs		
CV events (myocardial infarction (MI) or stroke)	0.01%	Calculated on the basis of World Health Organization (WHO) cardiovascular disease (CVD) risk chart working group [67] and Shiraev et al. [51]
CKD	0.01%	Calculated on the basis of Collins et al. [68] and Hussain et al. [69]
Fracture	0.02%	Calculated on the basis of Kanis et al. [70] and Zhou et al. [71]
Pneumonia	0.08%	Calculated on the basis of Sun et al. [72] and Lambert et al. [73]
Clostridium difficile	0.001%	Calculated on the basis of *Clostridium difficile* infection: mandatory surveillance 2017/18 report [74] and Janarthanan et al. [75]
Stomach cancer	0.002%	Brusselaers et al. [76]
Intraoperative AEs related to surgery		
Conversion to open surgery	RefluxStop: 2.1% LNF: 1.7%	Harsányi et al. [42] Zehetner et al. [30]
Splenic injury	RefluxStop: 0.0% LNF: 0.9%	
Gastro-esophageal injury	RefluxStop: 0.0% LNF: 1.0%	
Liver injury	RefluxStop: 0.0% LNF: 1.4%	
Post-operative AEs related to surgery		
Endoscopic esophageal dilatation	RefluxStop: 0.0% LNF: 0.3%	Harsányi et al. [42] Skubleny et al. [77]
Major complications requiring additional surgery	RefluxStop: 0.0% LNF: 1.4%	Bjelovic et al. [31]
Endoscopic device removal	RefluxStop: 0.0% LNF: N/A	Harsányi et al. [42] Alicuben et al. [78]
Utility decrement: stable medical management	0.12	Based on Bojke et al. [52] and Spanish population norms [53]
Utility decrement: medical management of GERD relapse	0.28	Bojke et al. [52] and Spanish population norms [53]
Utility decrement: medical management high dose	0.12	Assumed equal to stable medical management

Table 1 (continued)

Parameter	Input	Source
Post-surgery utility decrements (applied for 1 month)		
RefluxStop	0.24	Based on Bojke et al. [52], originally sourced from Ainslie et al. [79] and Spanish population norms [53]
LNF	0.24	
Utility decrements applied ≥ 1 month following successful surgery in the "surgery well" state		
RefluxStop	0.00	Calculated on the basis of utility decrement for dysphagia from Bouvy et al. [66] and the proportion reporting dysphagia from Harsányi et al. [42]. Applied to Spanish population norms [53]
LNF	0.01	Calculated on the basis of utility decrement for dysphagia from Bouvy et al. [66] and the proportion reporting dysphagia at 5 years from Zehetner et al. [30]. Applied to Spanish population norms [53]
Unsuccessful surgery utility decrements		
RefluxStop	0.16	Assumed equal to LNF
LNF	0.16	Based on Grant et al. (2008) and Spanish population norms Szende et al. [53]
Utility decrements associated with BE and EAC		
BE	0.10	Pollit et al. [56] and Spanish population norms [53]
EAC	0.44	NICE model developed to support clinical guidance development in dyspepsia and GERD [49] and Spanish population norms [53]

BE Barrett's esophagus, *C. Diff Clostridium difficile*, *CKD* chronic kidney disease, *CV* cardiovascular, *CVD* cardiovascular disease, *EAC* esophageal adenocarcinoma, *GERD* gastro-esophageal reflux disease, *MI* myocardial infarction, *NICE* National Institute for Health and Care Excellence, *PPI* proton pump inhibitor, *WHO* World Health Organization

outcomes [30]. Patients undergoing long-term PPI therapy in the medical management state were considered at risk for AEs such as *Clostridium difficile* (*C. Diff*) infection [43], osteoporosis-related fractures [44], community-acquired pneumonia [45], gastric cancer [46], chronic kidney disease (CKD) [47], and cardiovascular (CV) events [48]. Fractures, pneumonia, gastric cancer, and *C. diff* infection were modeled as isolated events, whereas CKD and CV events were modeled using a proportion-in-state method, assuming that a percentage of patients experienced these conditions at any given time.

Risk of BE and esophageal cancer: Chronic GERD is the main risk factor for BE, affecting 5–15% of patients [13]. Consistent with the model employed to instruct the National Institute for Health and Care Excellence (NICE) guidelines for dyspepsia and GERD, a monthly probability of 0.083% for developing BE was applied across all treatment arms [49]. Patients diagnosed with BE were assigned an additional 0.06% monthly risk of progression to EAC, a rate based on a meta-analysis that reported pooled estimates for BE incidence [50].

Mortality risks: The model accounted for excess mortality risks associated with surgery, esophageal cancer, and long-term PPI use, in addition to the general population mortality rates. Surgical mortality was modeled as a minor risk, with a 0.05% [31] chance of intraoperative death during the initial surgeries and a doubled risk for reoperation. Mortality estimates were balanced across all treatment arms without bias toward any specific treatment arm. To address the mortality risk of chronic PPI use, a relative risk of 1.57 was applied to patients in medical management states, based on a systematic review by Shiraev et al. [51].

Health-related quality of life (HRQoL): Utility decrements were used to assess the impact on quality of life. Utility decrements for patients with successful surgery were based on the percentage of patients experiencing persistent dysphagia, which is recognized as one of the most frequent and troublesome long-term complications of anti-reflux surgery [27, 28]. A utility decrement of 0.24 per month was assigned following both the initial surgeries and reoperations across all treatment arms. This assignment was on the basis of the quality-of-life impact associated with laparoscopic cholecystectomy, a procedure that confers comparable improvement in this parameter [52]. Utility decrements for PPIs were derived from a cost-effectiveness analysis comparing PPI therapy and LNF in the treatment of GERD, based on the NHS-funded REFLUX trial [40]. This clinical trial was previously used to determine the utility decrement for failed LNF, and the same assumption was applied to RefluxStop [40, 52]. Similarly, the corresponding utility decrements were applied to patients who developed BE or EAC. The utility decrements were applied to the Spanish

population norms [53]. The health-related quality of life (HRQoL) inputs used in this study are presented in Table 1.

2.2.2 Cost Inputs

The cost inputs for this analysis were obtained from the published literature through targeted literature search and the Spanish Diagnosis-Related Group (DRG) whenever possible [54]. To adjust for inflation in 2024, cost data from older studies were corrected using a web-based tool that utilizes gross domestic product (GDP) indices and purchasing power parity (PPP) rates from the Organization for Economic Cooperation and Development (OECD) [55]. Table 2 provides a summary of the key cost inputs used in this analysis.

PPIs: The model included costs for PPI medications (omeprazole, lansoprazole, pantoprazole, rabeprazole, and esomeprazole) [56]. PPI-associated AEs incurred different cost allocations: monthly costs were applied for chronic conditions such as CKD and CV events, while isolated events such as fractures, pneumonia, and *C. diff* infections were assigned nonrecurring costs. For those that developed gastric cancer, the model incorporated lifetime costs including supportive care and chemotherapy. The published prices for each drug formulation were retrieved and converted into unit

Table 2 Key cost inputs applied in the model

Parameter	Input	Source
Medical and surgical treatment costs		
Monthly cost of PPI medication (standard dose)	€74.01	Taken from the General Counsel of the Association of Pharmacists (Spanish Agency for Medicines and Health Products (AEMPS) 2024) website (BOT Plus—available at: https://botplusweb.farmaceuticos.com/) [56]
Monthly cost of PPI medication (high dose)	€76.01	Similar as above [56]
Procedure cost—all surgical treatments	€7551	Weighted average of the DRG codes for "Fundoplicatura gástrica" NS1, NS2, NS3, NS4 [54]
Device—RefluxStop	€5900	Implantica data on file
Training—RefluxStop	€16.31	Calculated based on Chaudhary et al. [80] and Palser et al. [81]
BE		
Diagnostic endoscopy	€1376.82	Based on Esteban et al. [82]
Treatment (EMR and RFA)	€3535.95	Based on Esteban et al. [82]
Monthly monitoring cost	€2217.08	Endoscopy assumed to be the same cost as EMR unit cost Patients with BE assumed to be prescribed PPI medication
EAC		
Initial diagnostic and treatment	€30,931.90	Sum of cost of GP visit, cost of diagnostic endoscopy, and cost of eshophagectomy. Based on Esteban et al. [82] and NICE model developed to support clinical guidance development in dyspepsia and GERD [49]
Palliative care	€24,998.20	Based on Corral et al. [83]
AEs associated with PPIs		
CKD monthly cost (including costs of treatment, hospitalization, and end-stage renal disease)	€189.87	Based on Kerr et al. [84] López Seguí et al. [85] Escobar et al. [86] Lamas Barreiro et al. [87] Villa et al. [88]
Monthly cost of CV events (MI or stroke)	€178.83	Based on Escobar et al. [89]
Fracture (event cost)	€4839.70	Based on Naranjo et al. [90]
Pneumonia (event cost)	€3015.66	Based on Shiri et al. [91]
C.diff. infection (event cost)	€4837.87	Based on Asensio et al. [92]
Stomach cancer (lifetime cost)	€8020.17	NICE technology appraisal of ramucirumab (TA378) [93]
AEs associated with surgery		
Conversion to open surgery	€2214.63	Based on Laudicella et al. [94]
Esophageal dilatation	€2143.01	Assumed to be similar to EMR cost
Additional surgery for major complications	€7551	Assumed to be equal to cost of initial procedure
Device removal	€7551	Assumed to be equal to cost of initial procedure

C. diff Clostridium difficile, *CKD* chronic kidney disease, *CV* cardiovascular, *DRG* diagnosis-related group, *EAC* esophageal adenocarcinoma, *EMR* endoscopic mucosal resection, *GERD* gastro-esophageal reflux disease, *MI* myocardial infarction, *NICE* National Institute for Health and Care Excellence, *PPI* proton pump inhibitor, *RFA* radiofrequency ablation

costs according to their respective packaging sizes. Using documented daily dosing requirements, monthly therapy costs were subsequently estimated for each formulation. Finally, a weighted mean cost was calculated to derive the overall estimated expenditure for PPI therapy.

Surgery: For surgical treatments, costs covered the procedure itself, with additional expenses for the RefluxStop device and required training. The procedural costs for LNF were assumed to be like those for RefluxStop, as both employ a standard laparoscopic technique. Costs for surgical AEs included costs pertaining to the conversion of laparoscopic procedures to open surgery, esophageal dilatation, significant surgical complications, and device explantations. Intraoperative injuries involving spleen, liver, or gastroesophageal area were assumed to be included in the general procedure costs.

BE and EAC: Patients that progressed to BE were assigned initial diagnostic and treatment costs, along with monthly management expenses, consistent with the treatment approach described in the cost-effectiveness analysis of endoscopic eradication therapy (EET) for BE [57]. Diagnostic endoscopy was assumed for all patients, with those diagnosed with dysplasia receiving endoscopic mucosal resection (EMR) and radiofrequency ablation (RFA), followed by biennial endoscopic surveillance and PPI therapy [57]. Nondysplastic patients only incurred the costs of PPI therapy and regular endoscopic surveillance. For patients with advanced esophageal cancer, the care pathway followed the model used in the NICE clinical guidance for dyspepsia and GERD, including initial diagnostics and treatment costs (such as general practitioner visits, esophagectomy, and chemotherapy), ongoing monthly PPI costs, and terminal care for those that did not survive the disease [49].

2.3 Economic Analysis

Lifetime per patient estimates for QALYs, life-years (LYs), and total costs for each treatment arm, along with the corresponding inter-arm incremental differences, were calculated. Specifically, incremental differences across treatments were assessed using three indicators: (1) the incremental cost-effectiveness ratio (ICER) for cost per QALY gained; (2) the incremental net health benefit (NHB), measuring the intervention's overall health impact; and (3) the incremental net monetary benefit (NMB) for financial value. In conducting this economic analysis, we followed the Consolidated Health Economic Evaluation Reporting Standards 2022 (CHEERS 2022), aligning with the latest guidelines for reporting in health economic evaluations [58]. In the context of healthcare in Spain, a cost-effectiveness threshold of €30,000 per QALY gained is widely accepted on the basis of a frequently cited economic analysis of expenditure variations across 17 regional health services over a 5-year period [59]. When evaluating healthcare interventions against this threshold, positive NHB or NMB values indicate health and monetary benefit respectively, with larger positive values signifying greater economic benefits within SNS.

2.4 Sensitivity Analyses

At the first instance, all the assumptions, model structure, and parameters were validated and corroborated by at least four clinical experts specialized in GERD treatment in Spain, to validate appropriateness and relevance to the Spanish population. In this model, parameters were sourced from relevant literature with similar clinical and geographical settings. This leads to potential heterogeneity in the parameters on clinical effectiveness, epidemiological data (i.e., risks of death associated with surgery, reoperation, and PPIs, as well as demographic information such as age and sex), costs, or health utilities. Remaining uncertainties were explored with deterministic and probabilistic sensitivity analyses.

Deterministic sensitivity analyses were conducted to evaluate the inherent uncertainties associated with the model results. Specifically, each model parameter was modified individually and the impact of these variations on the model outputs was documented to identify the most dominant parameters. Parameter variation ranges were based on reported confidence intervals (CIs) or assumptions when the data were unavailable.

Probabilistic sensitivity analysis involved sampling uncertain model inputs from plausible distributions (e.g., beta for clinical parameters and gamma for cost and utility parameters) and running 1000 iterations, each using a discrete set of values. Where available, standard errors for the probabilistic values were derived from the reported CIs; when not available, a standard error equal to 10% of the mean was assumed.

3 Results

3.1 Base-Case Results

RefluxStop conferred lifetime gains of 2.64 QALYs (14.20 versus 11.56) and 0.88 QALYs (14.20 versus 13.32) per patient compared with medical management and LNF, respectively, albeit at a higher cost (€20,296.66 versus €18,825.03 for medical management and €18,185.25 for LNF) (Table 4), resulting in an incremental cost difference of €1471.63 compared with medical management and €2111.41 compared with LNF. Reducing PPI-induced AEs contributed to per patient savings of €239.48 and €64.44 against medical management and LNF, respectively. Savings were also obtained through reductions in surgical complications. Compared with medical management,

RefluxStop generated per-patient cost savings of €27.41 for intraoperative events and €322.80 for endoscopic dilatations. Corresponding per-patient savings compared with LNF were €105.80 and €1120.85, respectively. Patients in the RefluxStop group demonstrated increased life expectancy compared with the assessed comparators, accumulating 1.64 years over medical management and 0.73 years over LNF throughout their lifetime (Table 3).

RefluxStop was cost-effective compared with both medical management and LNF, yielding ICERs of €557.12 and €2392.83 per QALY, respectively—both substantially lower than the €30,000.00 per QALY threshold set for economically viable medical interventions in Spain (Table 4). The NHB for RefluxStop was positive for both treatments, accruing 2.62 and 0.86 QALYs per patient over medical management and LNF, respectively (Table 4). Similarly, the NMB for RefluxStop was positive, yielding a per-patient benefit of €223,056.63 and €72,891.58 over the patient's lifetime compared with medical management and LNF, respectively.

Compared with LNF, RefluxStop demonstrated better surgical outcomes, including fewer surgeries (1.03 versus 1.05), surgical failures (0.26 versus 0.51), and endoscopic dilatations (0 versus 0.84) per 1000 patients (Table 3).

3.2 Sensitivity Analyses

Deterministic sensitivity analyses identified that the cost-effectiveness model was most sensitive to the probability of surgical failure post-RefluxStop and the probability of surgery after medical relapse (Supplementary Figs. 1 and 2). Regardless, the results of the model remained largely resilient to variations in input parameters. Only the monthly surgical failure rate for RefluxStop compared with LNF altered the directionality of the model's results. Overall, long-term cost-effectiveness remained stable across various cost estimates and AE risks.

On the basis of the commonly used Spanish cost-effectiveness threshold of €30,000 per QALY gained [60], probabilistic sensitivity analysis demonstrated that RefluxStop had a 100% probability of being cost-effective compared with medical management and a 93% probability against LNF (Fig. 2A). Most iterations from the probabilistic sensitivity analysis remained below this prespecified cost-effectiveness threshold (Fig. 2B). The average ICERs from 1000 iterations were €829.18 per QALY gained compared with medical management and €3128.13 per QALY gained compared with LNF, aligning closely with the base-case ICERs for RefluxStop versus each comparator.

Table 3 Clinical outcome estimates in the base-case analysis (per 1000 patients unless otherwise stated)

Clinical outcomes	RefluxStop	Medical management	Incremental versus medical management	LNF	Incremental versus LNF
Number of people developing BE	0.26	0.25	0.01	0.25	0.01
Number of people developing esophageal cancer	0.03	0.03	0.00	0.03	0.00
Number of surgeries	1.03	0.53	0.05	1.05	−0.02
Number of surgical failures	0.26	0.25	0.01	0.51	−0.25
Number of endoscopic dilatations	0.00	0.30	−0.30	0.84	−0.84
Number of device removals	0.00	0.00	0.00	0.00	0.00
Average life expectancy, years (per patient)	35.45	33.82	1.64	34.73	0.73

BE Barrett's esophagus, *LNF* laparoscopic Nissen fundoplication

Table 4 Cost-effectiveness outcomes estimated in the base case analysis, per patient

Summary results	RefluxStop	Medical management	Incremental versus medical management	LNF	Incremental versus LNF
Cost	€20,296.66	€18,825.03	€1471.63	€18,185.25	€2111.41
QALYs	14.20	11.56	2.64	13.32	0.88
Life years (undiscounted)	30.64	29.05	1.59	29.99	0.65
Life years (discounted)	18.24	17.59	0.65	18.00	0.24
Incremental cost-effectiveness ratio (ICER)		€557.12		€2392.83	
Net monetary benefit (NMB)		€223,056.63		€72,891.58	
Net health benefit (NHB)		2.62 QALYs		0.86 QALY	

ICER incremental cost effectiveness ratio, *LNF* laparoscopic Nissen fundoplication, *NHB* net health benefit, *NMB* net monetary benefit, *QALY* quality-adjusted life year

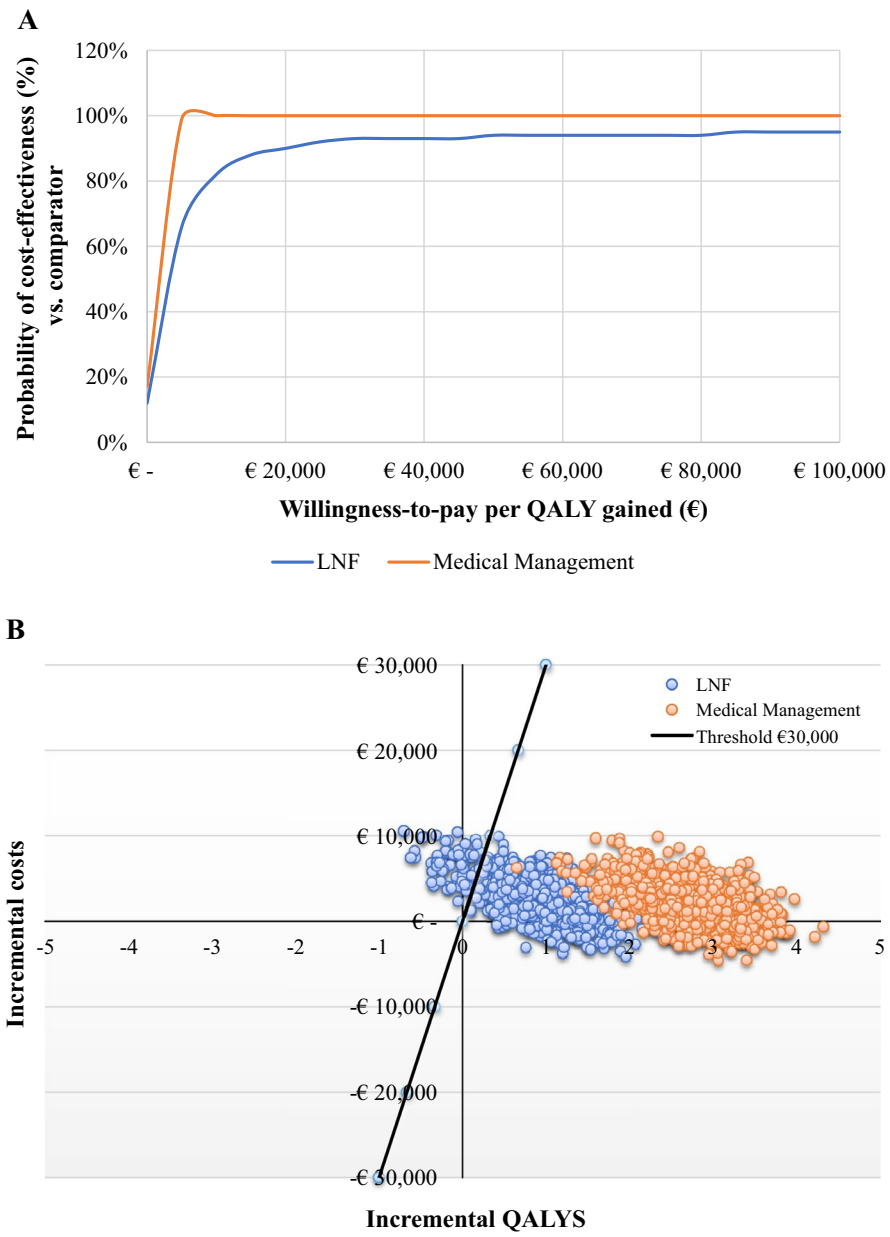

Fig. 2 Probabilistic sensitivity analysis results of RefluxStop versus both comparators, showing cost-effectiveness acceptability curves (**A**) and cost-effectiveness plane illustrating the spread of model iterations (**B**). The black line in panel **B** indicates a cost-effectiveness threshold of € 30,000 per QALY gained. The points lying to the right of this line indicate iterations in which RefluxStop was cost-effective versuss. the assessed comparator (marked by the color of the individual points), and the points lying to the left of the black line indicate those iterations in which RefluxStop was not cost-effective. *QALY* quality-adjusted life year, *LNF* laparoscopic Nissen fundoplication

4 Discussion

The findings of this cost-effectiveness analysis demonstrate that RefluxStop confers three key advantages relative to LNF and PPI-based medical management in the Spanish healthcare setting: (1) improved QALYs; (2) enhanced clinical outcomes, evidenced by substantially fewer surgical failures, reoperations, and endoscopic dilatations; and (3) a high probability of being a cost-effective intervention for treatment of refractory GERD, with ICERs considerably below the country's cost-effectiveness threshold of €30,000 per QALY gained set for economically acceptable medical interventions. The favorable NHB value of RefluxStop compared with the assessed treatments suggests that the health benefits of introducing the device would outweigh any deficits from resource reallocation, resulting in a net gain in population health. Consistently, positive NMB values suggest that the financial gains from health improvements relative to LNF and medical management would exceed the costs associated with introducing RefluxStop in Spain. The cost-effectiveness findings for RefluxStop in Spain are closely aligned with the corresponding analyses conducted in the UK [35], Switzerland [36], Norway [37], and Sweden [38]. In these studies, RefluxStop consistently showcased its value as a cost-effective option for treatment of refractory GERD relative to comparator treatment approaches, as evidenced by: (1) ICERs substantially lower than the respective national cost-effectiveness thresholds and a high probability of being

cost-effective at these benchmarks, (2) an increased number of QALYs and life-years per patient, and (3) favorably positive NHB and NMB. Overall, these findings suggest a broad economic viability across diverse healthcare settings in Europe.

The estimated lifetime savings from RefluxStop, conferred by reducing the need for long-term PPI treatment and managing PPI-induced AEs, are particularly relevant in the context of PPI misuse in Spain [11, 21, 23, 26]. Importantly, the recent CE trial results on RefluxStop showed nearly complete and sustained independence from PPI use for up to 4 years, further emphasizing the potential long-term cost benefits of RefluxStop. PPIs constitute one of the most frequently prescribed pharmacological classes in Spain [26], accounting for 3.4% of the national pharmaceutical expenditure (2016 estimates), 7.4% of the total drug packages, and daily utilization by 18–28% of individuals [11, 21, 23, 26]. Among these, omeprazole has emerged as one of the top-selling drugs in the past decade, accounting for 5.5% of the total drug packages invoiced [23]. The introduction of generic PPIs in the 2000s led to a two- to fourfold increase in PPI prescriptions, highlighting their significant financial impact on the healthcare system [23, 25]. Notably, Spain has one of the highest rates of PPI use in Europe, with 85 per 1000 persons using PPIs daily, greatly exceeding countries such as Norway (30 per 1000) and Italy (27 per 1000) [25]. A study conducted in a Spanish hospital revealed a high frequency of PPI overuse, with approximately 75% of prescriptions at admission, 61% during hospitalization, and 80% at discharge being inappropriate [24, 25]. Given these concerns, cost-effective alternatives that can reduce or eliminate long-term PPI dependence would be highly beneficial for any healthcare system. For instance, even simple measures such as resident-centered educational interventions in US primary care clinics have been shown to reduce PPI expenditure by up to 38% [61]. Lifetime savings from reduced PPI use and management of PPI-related AEs have been similarly demonstrated in cost-effectiveness analyses of RefluxStop conducted in the UK [35] and three European countries [36, 38]. This is noteworthy because widespread and inappropriate PPI prescribing practices are not unique to Spain and have been observed in numerous countries [21, 24]. This overprescription [11, 21, 23, 26], often linked to prophylactic use in low-risk patients and continuation without valid indications, exposes them to the risk of AEs, such as infections [43, 45], bone fractures [44], and nutritional deficiencies [20]. In the USA, Australia, the UK, Greece, and Spain, over half of primary care patients and 81% of hospitalized patients prescribed PPIs lack a valid indication for their use [22]. In this context, the demonstration of RefluxStop as a cost-effective alternative to a lifelong PPI regimen across various European payor settings underscores a key advantage of the device [36, 38].

Traditionally considered the benchmark surgical treatment for chronic or refractory GERD, LNF may be recommended when PPI therapy fails owing to adverse effects, lack of patient preference, or nonadherence [17, 22, 62]. Although generally considered cost-effective, the long-term outcomes of LNF are compromised by post-surgical complications such as dysphagia and a less than favorable frequency of reoperations (8–15% within 5 years), which gradually diminish its treatment durability and overall economic value [29, 34]. When properly positioned, RefluxStop restores the natural function of the lower esophageal sphincter without encircling or compressing the esophagus [31, 32]. Aligned with its design to minimize surgical complications and obviate the need for reoperation [31, 32], our cost-effectiveness analysis revealed an almost 50% reduction (0.26 versus 0.51 per 1000 patients) in surgical failures compared with LNF, and no endoscopic dilatations in the modeled patient cohort. In an actual clinical setting, the long-term results are demonstrably better, with no device-related AEs, esophageal dilatations, migrations, or explants over the duration of the study [32]. Although the reduction in the total number of surgeries was modest (1.03 versus 1.05 per 1000 patients), improvement in the reoperation rate is not negligible when one considers the impact of incremental gains on the population level over long-term time horizons. This was demonstrated in recent budget impact models conducted in the UK [63] and Italy [64], where the introduction of RefluxStop into the SOC led to a notable reduction in surgical failures, reoperations, and endoscopic dilatations in the GERD-treated population over a 5-year period compared with scenarios without the introduction of the device in the population. Notably, these clinical improvements were achieved with minimal perturbation to the healthcare budgets of the respective countries [63, 64].

In assessing the strengths and limitations of this study, a key advantage of this cost-effectiveness analysis is the use of clinical parameters for RefluxStop derived from a prospective, multicenter, single-arm CE mark trial [31, 42]. However, we must acknowledge the key limitations of this study, as with any cost-effectiveness analysis. First, an inherent limitation of the model concerns the underlying clinical data sources. The effectiveness inputs for RefluxStop were derived from a single-arm clinical trial, whereas those for the comparators came from published literature. This discrepancy in evidence sources introduces uncertainty, where differences in study populations, designs, and outcome measures may influence the comparability of the results. The absence of a direct comparator arm in the RefluxStop trial also limits the ability to account for confounding factors or establish relative treatment effects with confidence. Nonetheless, this limitation reflects a common challenge in surgical research, where randomized controlled trials are less frequently undertaken than in pharmacological studies [65]. Second, although effectiveness and

safety data for comparator treatments were extracted from literature sources, they were based on heterogeneous populations with variations in baseline characteristics, such as age, sex, and esophagitis status, resulting in a naive indirect comparison. However, no model is sufficiently equipped to fully capture the heterogeneous clinical care pathways of individual patients, and thus, the outcomes generated from health economic modeling should be regarded as representative of an "average" patient care context. Third**,** regional and individual health and/or socioeconomic variances were not integrated into this analysis despite acknowledged approaches to confront this critical issue. Fourth, the analysis in this model had necessarily simplified the clinical care pathway for patients with refractory GERD. In clinical practice, the management of GERD varies widely according to symptom severity, prior response to medical therapy, or patient preferences [17, 19]. The model, however, adopted a standardized treatment pathway to enable comparability across interventions, including RefluxStop and surgical alternatives. This simplification may not fully reflect real-world variations in diagnostic work-up, postoperative follow-up, or the sequencing and timing of interventions. Fifth, utility inputs were obtained from studies conducted in other European countries, as country-specific estimates are seldom available for all parameters [40, 52, 57, 66]. For this analysis, Spanish population norms were applied, with appropriate decrements derived from the most comparable published sources. This approach aligns with established health-economic practice when local utility data are lacking. Uncertainty associated with these utility estimates was examined through sensitivity analyses. Finally, a commonly acknowledged challenge in cost-effective analysis is the necessity to formulate assumptions owing to the lack of data for certain parameters. These assumptions introduce a degree of imprecision in the results of the model, which was expected; however, they are largely counterbalanced by the strength of the model estimates shown during sensitivity analyses when the inputs were adjusted. The parameters and results were validated with clinical experts and published studies, and the economic model underwent independent technical evaluation and quality assurance using a bespoke validation checklist, confirming the plausibility of the findings. Despite these limitations, the findings of this analysis provide robust evidence supporting RefluxStop as a potentially cost-effective treatment for GERD in Spain, demonstrating its value in the context of the Spanish healthcare system.

5 Conclusions

RefluxStop is highly likely to be cost-effective compared with medical management (PPIs) and LNF in Spain. Sensitivity analysis confirmed the sustained cost–utility benefits of RefluxStop compared with SOC medical and surgical therapy, underscoring its long-term value to payers as a cost-effective treatment option for adults with GERD in Spain.

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Declarations

Conflict of Interest Sam Harper and Stuart Mealing are employed by a consultancy company (York Health Economics Consortium at the University of York, UK) that was commissioned by Implantica to develop the model. Khanh Ha Bui is an employee of Implantica. Daniel Sanchez, Pablo Priego Jiménez, and Carlos Moreno Sanz do not have personal conflicts to declare.

Ethics Approval Since no individual patient level data was collected, and the Markov model was built using aggregated data from published literature, there was no ethical approval required.

Consent to Participate Not applicable.

Consent for Publication Not applicable.

Data Availability All data supporting the findings of this study are available within the paper.

Code Availability The model is not available as open source because it contains confidential scientific and business information and supports ongoing regulatory and commercialization efforts. The authors anticipate being able to share further details in the future once these activities conclude. The corresponding author is available to assist readers with any further inquiries pertaining to methodological, data, and analytical aspects of the manuscript.

Author Contributions Sam Harper, Khanh Ha Bui, and Stuart Mealing designed and developed the model. Daniel Sanchez, Pablo Priego Jiménez, and Carlos Moreno Sanz contributed to the design of the economic model and provided clinical perspective to validate the results. All authors contributed to the manuscript and approved the final version of the manuscript.

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