Cost Effectiveness of Romiplostim for the Treatment of Chronic Immune Thrombocytopenia in Ireland

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Abstract

Background Romiplostim, a thrombopoietin receptor agonist (TPOra), is a second-line medical treatment option for adults with chronic immune thrombocytopenia (ITP). Clinical trials have shown that romiplostim increases platelet counts, while reducing the risk of bleeding and, in turn, the need for costly rescue medications.

Aims The objective of this study was to assess the cost effectiveness of romiplostim in the treatment of adult ITP in Ireland, in comparison with eltrombopag and the medical standard of care (SoC).

Methods A lifetime treatment-sequence cost-utility Markov model with embedded decision tree was developed from an Irish healthcare perspective to compare romiplostim with eltrombopag and SoC. The model was driven by platelet response (platelet count $\geq 50 \times 10^9/L$), which determined effectiveness and progression along the treatment pathway, need for rescue therapy (e.g. intravenous

immunoglobulin [IVIg] and steroids) and risk of bleeding. Probability of response, mean treatment duration, average time to initial response and utilities were derived from clinical trials and other published evidence. Treatment sequences and healthcare utilization practice were validated by Irish clinical experts. Costs were assessed in € for 2011 and included drug acquisition costs and costs associated with monitoring patients and management of bleeding, as available from published Irish reimbursement lists and other relevant sources. Deterministic and probabilistic sensitivity analyses were conducted.

Results Romiplostim treatment resulted in an average of 20.2 fewer administrations of rescue medication (IVIg or intravenous steroids) over a patient lifetime than eltrombopag, and 29.3 fewer rescue medication administrations than SoC. Romiplostim was dominant, with cost savings of €13,258 and €22,673 and gains of 0.76 and 1.17 quality-adjusted life-years (QALYs), compared with eltrombopag and SoC, respectively. Romiplostim remained cost effective throughout a variety of potential scenarios, including short-term TPOra treatment duration (1 year). One-way sensitivity analysis showed that the model was most sensitive to variation in the cost of IVIg and use of romiplostim and IVIg. Probabilistic sensitivity analysis showed that romiplostim was likely to be cost effective in over 90 % of cases compared with eltrombopag, and 96 % compared with SoC at a willingness-to-pay threshold of €30,000 per QALY.

Conclusions Use of romiplostim in the ITP treatment pathway, compared with eltrombopag or SoC, is likely to be cost effective in Ireland. Romiplostim improves clinical outcomes by increasing platelet counts, reducing bleeding events and the use of IVIg and steroids, resulting in both cost savings and additional QALYs when compared with current treatment practices.

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Key Points for Decision Makers

- Results of the cost-effectiveness analysis showed that treatment with romiplostim was dominant, with cost savings compared with both eltrombopag and standard of care, including rituximab, whether given before or after rituximab in the Irish immune thrombocytopenia treatment pathway.
- Savings are achieved through higher response rates, driving a reduction in bleeding and the use of intravenous immunoglobulins and steroids.

1 Introduction

Primary immune thrombocytopenia (ITP; previously termed idiopathic thrombocytopenic purpura), an acquired immune-mediated disorder characterized by low peripheral blood platelet counts ($<100 \times 10^9/L$), is attributed to increased platelet destruction and suboptimal platelet production [1, 2]. In adults, ITP is typically a chronic condition (>12 months), with spontaneous remissions relatively uncommon. A review of published literature, based mainly on Western European data, found that the annual incidence of ITP has been estimated at approximately 3–4 per 100,000 person-years in adults, while in children, estimates ranged from 1.9 to 6.6 per 100,000 person-years [3]. While precise epidemiology estimates for Ireland are lacking, an incidence of 3.9 per 100,000 person-years has been reported in the UK population-based General Practice Research Database [4].

Chronic ITP can have serious clinical and economic consequences, particularly linked to bleeding and impaired quality of life (QOL). While many patients may present with no symptoms or with minor bruising, others experience serious bleeding, including gastrointestinal bleeds, extensive skin and mucosal bleeds and/or intracranial haemorrhage [2]. Physical symptoms are a primary driver of diminished QOL, and ITP patients score poorly on QOL scales such as bother, psychological impact, fear, social activity and work [5]. The economic burden of chronic ITP has been examined in several studies [6]. An annual cost of €26,581 (year 2007 values) per hospitalized patient has been reported in France, with rescue medication accounting for a substantial proportion of costs [6]. In the USA, ITP drug therapy alone is estimated to account annually for hundreds of millions of dollars [7], with mean annual per-patient costs estimated at approximately \$US28,000 (year 2000–2003 values) [8]. Studies that have examined the costs associated with ITP consistently reveal that adults with chronic ITP incur substantial per-patient medical

costs, primarily due to hospitalization required to manage bleeding events, drug costs and costs of surgical intervention [6–9], as well as having lower work productivity [7].

Active treatment is recommended for adult ITP patients with platelet counts $<30 \times 10^9/L$, or $30\text{--}50 \times 10^9/L$ with bleeding or risk of bleeding [1, 2]. First-line treatment typically consists of a short course of glucocorticoids, intravenous immunoglobulin G (IVIg) or anti-D (Rho) immunoglobulin (anti-D), all of which target platelet destruction [2]. These treatments generally provide relatively short-lived platelet responses, with many patients requiring repeated high doses of corticosteroids to maintain a safe platelet count, at the risk of undesirable adverse effects. Second-line options include surgical splenectomy and various treatments based on immune suppression, including off-label treatment with the anti-CD20 monoclonal antibody rituximab [2].

The thrombopoietin receptor agonists (TPOra) romiplostim and eltrombopag offer a different approach to treatment of ITP, by increasing platelet production [1, 2]. In Europe, both TPOra are approved for use in splenectomized adult patients who are refractory to other treatments (e.g. corticosteroids, IVIg), and as second-line treatment for those who are not candidates for splenectomy [10, 11]. As noted in an International Consensus Report, TPOra are the only ITP treatments with evidence of efficacy and safety from randomized controlled trials [2].

Health technology assessment is becoming increasingly required in the decision-making process in Ireland. We therefore conducted a cost-effectiveness analysis of romiplostim for the treatment of chronic ITP in adult patients in Ireland, from an Irish national payer perspective. In line with the guidelines for economic evaluation in Ireland [12], we considered only direct costs.

2 Methods

2.1 Patient Population and Model Structure

A treatment-sequence cost-utility model was developed to assess the cost effectiveness of romiplostim within its licensed indication for adult chronic ITP splenectomized patients who are refractory to other treatments (e.g. corticosteroids, IVIg), and as second-line treatment for adult non-splenectomized patients where surgery is contra-indicated. The patient cohort that was modelled had similar characteristics to patients from the romiplostim phase III trials [13] and individuals participating in an Irish survey [14]. A total of 50 % of patients were assumed to be splenectomized and 50 % non-splenectomized. The median age was 52 years, and 65 % were women [13]. Three treatment strategies were compared (Fig. 1):

Fig. 1 Model treatment pathways for adult immune thrombocytopenia (the proportions of patients represent patient treatment flow after the failure of the previous treatment based on the findings of a 2008

survey of 169 UK clinicians [16] updated and validated to match Irish practice [17]). *SOC* standard of care

- romiplostim followed by current medical standard of care (SoC);
- eltrombopag followed by SoC;
- SoC, including rituximab.

As rituximab use in ITP is off-label, the base-case analyses assumed that TPOra were received before rituximab in this pathway. However, as some patients might receive romiplostim or eltrombopag after rituximab, this treatment pathway was tested in sensitivity analysis. After failing rituximab, patients moved on to azathioprine followed by mycophenolate mofetil and finally cyclosporine. The SoC pathway comprised rituximab (80 % of patients), azathioprine (59 %), mycophenolate mofetil (37 %) and cyclosporine (4 %).

A Markov model with embedded decision tree was used with a 4-week cycle and a lifetime time horizon, developed from the perspective of the Irish national healthcare payer. A lifetime time horizon was deemed to be the most appropriate, since adult ITP tends to be a chronic disease; the 4-week cycle was used to match the evaluation schedule used in the long-term extension study [15]. Costs and outcomes were discounted at a 4 % annual rate, as recommended by the Health Information and Quality Authority (HIQA) in Ireland [12]. The treatment sequence used in the model was based on the findings of a 2008 survey of 169 UK clinicians [16], and was updated by two Irish clinicians to be applicable for Ireland [17].

The model was driven by platelet response (platelet count $\geq 50 \times 10^9/L$), which determined effectiveness and progression along the treatment pathway, need for rescue

therapy (IVIg and steroids) and risk of bleeding (Fig. 2). Patients started on the first treatment in the pathway and progressed to the next treatment if they did not have an initial response or if they relapsed (platelet count $< 50 \times 10^9/L$) after responding. Each relapse on active treatment, determined by platelet count $< 50 \times 10^9/L$, was followed by a period of ‘watch and rescue’ before initiating the next active treatment. Long-term treatment (keeping patients on active therapy for as long as they had a continued response) was modelled in the base case, and short-term treatment (1 year only) with romiplostim and eltrombopag was tested in a sensitivity analysis.

2.2 Clinical Inputs

Clinical efficacy data and utilities were derived from clinical trials, an International Consensus Report [2] and other published evidence.

The efficacy of each treatment within the model was characterized by three parameters (Table 1):

- probability of initial platelet response ($\geq 50 \times 10^9/L$);
- average time to initial response;
- treatment duration after initial response (treatment failure defined as platelets $< 50 \times 10^9/L$ for 4 consecutive weeks) [i.e. durability of response].

Efficacy data for romiplostim were taken from the pivotal phase III trials reported by Kuter et al. [13] and a subsequent long-term extension study [15]. The parallel, multicentre, double-blind, placebo-controlled phase III trials were conducted in splenectomized and non-

Fig. 2 Markov model with embedded decision tree overview (health states [platelets $\geq 50 \times 10^9/L$, platelets $< 50 \times 10^9/L$, dead] evaluated in 4-week cycles). *GI* gastrointestinal, *W&R* watch and rescue, *Tn* current treatment, *Tn + 1* next treatment in sequence

splenectomized patients. Patients were randomized to receive romiplostim or placebo over a 24-week period, with dosages adjusted according to weekly platelet counts.

In order to facilitate a comparison with eltrombopag, an odds ratio calculated by Bayesian meta-regression [18] was used to derive relative response rates for eltrombopag versus romiplostim (using romiplostim data from the clinical studies mentioned above) [13], as shown in Online Resource 1, Table 1A. The Bayesian meta-regression used a logit model to indirectly compare the two TPOra, accounting for differences in study effect, treatment effect and the effect of splenectomy. In a sensitivity analysis, use of the unadjusted response rate of 57 % for eltrombopag [18] was also tested. The response rates for all other treatments were obtained from published literature (see Table 1). The time to response for each intervention was assumed to be equal to the maximum response time cited in the International Consensus Report (see Table 1) [2].

It was assumed that all patients who initiated therapy received treatment throughout this time-to-response period, with the exception of rituximab, which was given as a single course. Treatment duration (time to platelets $< 50 \times 10^9/L$) was modelled for all treatments by retrospectively fitting survival curves to available data. For romiplostim, this was based on the reported number of patients who were still on-treatment (or withdrew from the study for reasons other than treatment failure) at each 12-week interval in the 24-week trial and subsequent long-term, open-label, extension study (using data for up to 288 weeks and taking censoring into account) [13, 15]. Weibull, log-Normal, log-logistic, exponential and Gompertz survival curves were fitted to these data to allow extrapolation. The mean duration of romiplostim treatment was estimated by calculating the mean of the log-Normal function, which was the best-fitting curve according to the Akaike Information Criterion (AIC) (Table 2A, Figure 1A, Online Resource 1). A similar analysis was conducted for the

Table 1 Clinical model inputs

Treatment	Probability of response (%)	Mean response duration (cycles)	Time to initial response (cycles) [2]
Romiplostim	83 [13]	140.86 [15]	1
Eltrombopag—adjusted response rate	35 [18]	89.66 [19]	1
Eltrombopag—unadjusted response rate	57 [18]	89.66 [19]	1
Rituximab	58 [39, 40]	18.87 [41–43]	2
Azathioprine	56 [44–46]	20.34 [47]	6
Mycophenolate mofetil	50 [48–50]	5.68 [49]	2
Cyclosporine	57 [45, 51–53]	14.54 [53]	1
IVIg	81 [54–65]	1 [66]	0
IV steroids	46 [57, 67]	1 [66]	0

IV intravenous, IVIg intravenous immunoglobulin

mean treatment duration for eltrombopag, using the results of the ongoing EXTEND (eltrombopag extended dosing) study [19]. Based on the reported number of patients who were still on-treatment or who dropped out for reasons other than treatment failure, assuming a constant rate of patient dropout and taking censoring after 2 years into account, the log-Normal function was used to estimate the mean treatment duration [20]. Again, the log-Normal function was also the best-fitting curve based on the AIC (Table 2A, Figure 1A, Online Resource 1). For all other treatments, treatment duration was modelled by fitting exponential curves through any available data points from papers identified within the literature review that reported the proportion of patients still responding over time.

While adverse events play a significant role in the treatment of ITP, they were not included in the model due to limited evidence available on the rates of events and their impact on costs and QOL.

2.2.1 Bleeding Events and Rescue Medication Use

In the phase III romiplostim clinical trials, a proportion of non-responders (i.e. patients with a platelet count $<50 \times 10^9/L$) received rescue medication. It is noteworthy that whilst a platelet count of $\geq 50 \times 10^9/L$ was targeted in these trials, no clinically significant bleeding occurred when platelet counts were $>20 \times 10^9/L$ [21]. The probability of experiencing bleeding was based on clinical trial data: patients who had a platelet count $\geq 50 \times 10^9/L$ were assumed to have a 12.64 % per-cycle probability of an outpatient bleed (i.e. not requiring hospitalization) and a 0.30 % per-cycle probability of an inpatient bleed

(requiring hospitalization) [21]. Corresponding per-cycle probabilities for patients with a platelet count $<50 \times 10^9/L$ were calculated as 40.77 and 3.69 %, respectively [21]. Among patients with an inpatient bleed, it was assumed that 7 % experienced intracranial haemorrhage, 21 % experienced a gastrointestinal bleed and 71 % experienced another type of bleed [21]. Similarly, for each cycle, it was assumed that 40 % of patients with a platelet count $<50 \times 10^9/L$ would receive IVIg, while 8 % would receive intravenous corticosteroids, for treatment of inpatient or outpatient bleeding, or for bleeding prevention [21]. As anti-D is not available in Europe, all patients who received anti-D were assumed to receive IVIg (which has a similar response rate to that of anti-D) [2].

2.2.2 Mortality

The model included combined mortality resulting from serious bleeding and all-cause mortality. All-cause mortality for patients was based on Irish life tables [22]. The mortality risks associated with each type of bleed were based on an analysis of the American Nationwide Inpatient Sample (NIS) from 2003 to 2006 [9].

2.2.3 Utility

Utilities were taken from a time trade-off (TTO) survey [23] conducted in the UK. The survey used TTO analysis to directly measure the utility values for patients with ITP, as perceived by 359 members of the general public, and defined by five health states:

1. sufficient platelets ($\geq 50 \times 10^9/L$) with no outpatient bleed;
2. sufficient platelets with an outpatient bleed;
3. low platelets ($<50 \times 10^9/L$) with no outpatient bleed;
4. low platelets with an outpatient bleed;
5. intracranial haemorrhage.

An outpatient bleed refers to bleeding treated at a clinic, health centre or general practice. For the remaining health states used within the model (platelets $<50 \times 10^9/L$ and gastrointestinal bleeding and platelets $<50 \times 10^9/L$ and other bleeding), a utility value of 0.54 was used [24]. The utilities were derived from cardiovascular patients who experienced stroke, as ITP-specific data were not available. EQ-5D utility values were available from the phase III romiplostim clinical trials [13], with data from 117 patients pooled across placebo and romiplostim arms, under the conservative assumption that there is no treatment effect on utility [25]. The TTO utility values [23] were used in the base case (due to the larger sample size) and use of EQ-5D values ($n = 117$) was investigated in sensitivity analysis (Table 2).

Table 2 Immune thrombocytopenia patient utilities

State	Time-trade off utilities [23]	EQ-5D utilities [25]
Platelets $>50 \times 10^9/L$ and no bleeding	0.863	0.790
Platelets $>50 \times 10^9/L$ and bleeding managed in outpatient care	0.734	0.730
Platelets $<50 \times 10^9/L$ and no bleeding	0.841	0.840
Platelets $<50 \times 10^9/L$ and bleeding managed in outpatient care	0.732	0.730
Platelets $<50 \times 10^9/L$ and intracranial haemorrhage	0.038	0.038
Platelets $<50 \times 10^9/L$ and GI bleeding [24]	0.540	0.540
Platelets $<50 \times 10^9/L$ and other bleeding [24]	0.540	0.540

GI gastrointestinal

2.3 Costs and Resource Use

Costs were assessed in €, year 2011 values, from the perspective of the Irish health service, exclusive of value added tax (VAT), as per HIQA guidelines [12]. The model considered drug acquisition and costs associated with monitoring patients and management of bleeding. Resource use and costs were derived from the International Consensus Report [2], published Irish reimbursement lists, individual summaries of product characteristics (SPCs) [10, 11], real-life observational data [26] and other relevant sources (Table 3). Healthcare utilization, such as frequency

of physician and nurse visits, was validated by Irish clinicians [17]. The cost of bleeds was estimated by taking a weighted average of the relevant cost with and without complications. The base-case model assumed that patients received each treatment that they initiated for as long as they continued to respond, with the exception of rituximab, which was assumed to be given for a single course only. Where 2011 values were not available, costs were inflated using the health inflator derived from Central Statistics Office Ireland [12].

The cost of IVIg was assumed to be €45 per g based on Irish clinical practice [17]—this is lower than the list price

Table 3 Healthcare utilization and costs

Treatment	Drug cost [27]	Dose [2]	Physician appointments including tests (€160.60) [68–70]	Nurse appointments (€9) [12]	IV admins (€300) [71]	Total costs
Romiplostim	€602.50/250 µg vial	3 µg/kg = 1 × 250 µg vial weekly ^a [13]	4 (1 st 8 weeks); 1 (>8 weeks)	4	—	€2,967.42 (1 st 8 weeks); €2,485.62 (>8 weeks)
Eltrombopag	€2,043.58 (28 × 50 mg) [72]	55 mg/day [11]	4 (1 st 8 weeks); 1 (>8 weeks)	—	—	€2,865 (1 st 8 weeks); €2,380 (>8 weeks)
Rituximab	€277.58 (100 mg)	1 course 4 × 375 mg/m ²	4 (1 st 8 weeks); 1 (>8 weeks)	—	4	€9,896
Azathioprine	€36.75 (56 × 50 mg)	2 mg/kg/day	2	—	—	€377
Mycophenolatemofetil	€164.84 (50 × 500 mg)	2 g/day	2	—	—	€714
Cyclosporine	€151.11 (30 × 100 mg)	3 mg/kg/day	2	—	—	€682
Rescue medications						
IVIg	€45/g [17]	1 g/kg for 2 days			2	€7,776
IV methylprednisolone	€0.15/mg	4 × 40 mg			4	€1,224
Hospitalization costs [68]						
Intracranial haemorrhage						€6,854
GI bleed (inpatient)						€2,913
Other inpatient bleed						€2,913
Outpatient bleed						€149

^a Cost of full 250-µg vial was included in the analysis

GI gastrointestinal, IV intravenous, IVIg intravenous immunoglobulin

of €70.01 per g (based on a weighted average of the different available pack sizes) [27]. Uncertainty around the price of IVIg was tested within the model (€37.60–52.40). Although 70 % of patients self-administered romiplostim in the open-label extension study [15], self-administration was not included in the model.

2.4 Model Outputs

For each of the three treatments (i.e. romiplostim, eltrombopag and SoC), the model calculated the following over the patient's lifetime:

- average number of administrations of rescue medication (IVIg or intravenous steroids);
- average number of bleeds;
- average number of hospitalizations.

Corresponding total costs, quality-adjusted life-years (QALYs) and life-years (LYs) per patient, and the incremental cost-effectiveness ratio (ICER) for romiplostim, were calculated.

2.4.1 Sensitivity Analysis

Scenario analyses were conducted to test alternative scenarios in the model, addressing structural uncertainty. These included the following:

- treatment duration of TPORa for 1 year instead of life-long;
- placing TPORa after rituximab in the treatment pathway;
- response rate of eltrombopag (impact of using the unadjusted response rate taken directly from the clinical trial vs. the adjusted response rate taken from the indirect comparison);
- use of the EQ-5D as a source for utilities.

Deterministic sensitivity analysis was performed to identify the parameters to which the model was most sensitive, within their upper and lower bounds as defined by 95 % confidence intervals where possible, or with plausible variation around the base-case values. The deterministic sensitivity analysis was based on incremental net benefit, which was calculated as the incremental QALYs multiplied by the willingness-to-pay threshold, minus incremental costs. Probabilistic sensitivity analysis (PSA) was conducted using 1,000 iterations to examine parameter uncertainty over the entire model. The following parameters were included in sensitivity analyses: response rates, durations, bleeding and rescue medication use, utilities, the proportion of patients using each SoC treatment, drug, resource use and bleed costs, and patient demographics (Table 3A, Online Resource 1).

3 Results

3.1 Base Case

The base-case (lifetime time horizon) model results (Table 4) indicated that romiplostim treatment resulted in an average of 20.2 fewer administrations of rescue medication (IVIg or intravenous steroids) over a patient lifetime than eltrombopag and 29.3 fewer administrations than SoC. The mean cost saving resulting from the reduction in rescue medications associated with romiplostim was €148,118 when compared with eltrombopag and €214,565 when compared with SoC. Additionally, romiplostim was associated with an average of 6.7 fewer bleeds and 1.7 fewer hospitalizations than eltrombopag and 8.7 fewer bleeds and 2.4 fewer hospitalizations than SoC. The mean cost saving resulting from the reduction in bleeds (including hospitalizations) was, on average, €6,888 when compared with eltrombopag and €10,296 when compared with SoC.

In total, the introduction of romiplostim into the beginning of the current treatment sequence resulted, on average, in a cost saving of €13,258 versus eltrombopag and €22,673 versus SoC and was also associated with a QALY gain of 0.76 versus eltrombopag and 1.17 versus SoC. Romiplostim was therefore the dominant treatment, i.e. more effective at a lower cost, and associated with cost savings and QALY gains versus both eltrombopag and SoC.

3.2 Scenario Analyses

Several scenario analyses were conducted (Table 5). In the short-term (1 year) TPORa treatment scenario, romiplostim was associated with an average cost saving of €335 and a QALY gain of 0.10 versus eltrombopag; hence, the use of romiplostim remained dominant. When compared with SoC, romiplostim was, on average, associated with an additional cost of €895 and a QALY gain of 0.22. This resulted in an ICER of €4,155, indicating that the use of romiplostim remained cost effective.

The use of romiplostim after rituximab resulted in similar cost savings and QALY gains compared with both SoC and eltrombopag, the average cost saving increasing to €16,279 and €27,022 compared with eltrombopag and SoC, respectively.

Additional scenario analysis tested the effect of using the response rate of eltrombopag derived from the eltrombopag clinical trial (instead of the response rate from the Bayesian meta regression of romiplostim and eltrombopag) [18]. Romiplostim remained dominant over eltrombopag, despite using a higher eltrombopag response rate (57 vs. 35 %) [Table 5].

Using the EQ-5D utility values resulted in a dominant ICER for romiplostim compared with both eltrombopag and SoC (Table 5).

Table 4 Base-case cost effectiveness of romiplostim compared with eltrombopag and standard of care

	Romiplostim	Eltrombopag	SoC
Cost of rescue therapy	€365,485	€537,617	€580,050
Cost of bleeds	€17,126	€24,617	€27,422
Other costs ^a	€216,092	€74,345	€13,904
Total costs	€598,704	€611,962	€621,376
LY gained	14.70	13.97	13.57
QALYs gained	12.08	11.32	10.91
		Romiplostim vs eltrombopag	Romiplostim vs SoC
Incremental total costs	–	–€13,258	–€22,673
LYs gained	–	0.73	1.13
QALYs gained	–	0.76	1.17
ICER	–	Dominant	Dominant

The figures used in the model include all relevant decimal places. The figures shown in this table are rounded and as a result, any calculations made solely using the rounded figures may not provide an accurate result

^a Other costs are active treatment costs: drug, physician and other utilization costs, and account for the length of time on therapy

ICER incremental cost-effectiveness ratio, LY life-year, QALY quality-adjusted life-year, SoC standard of care, Dominant indicates more effective at lower cost

3.3 Deterministic and Probabilistic Sensitivity Analyses

Figure 3 shows the results of the deterministic sensitivity analysis, presented as the incremental net benefit considering a willingness-to-pay threshold of €30,000 per QALY. The variables with the largest effect on the model were similar when comparing romiplostim with either eltrombopag or SoC. These were use of romiplostim, and

the cost and use of IVIg. It should be noted that these findings are driven by the chosen ranges used in sensitivity analyses. No variables had an impact on the cost-effectiveness results at a threshold of €30,000 per QALY.

PSA showed that, in the majority of cases, treatment with romiplostim was more cost effective than treatment with either eltrombopag or SoC (Fig. 4). Romiplostim dominated both eltrombopag and SoC in over 66 % of cases, with a mean incremental net benefit of €35,823

Table 5 Sensitivity analyses

Treatment arm	Costs (€)	QALYs	Incremental costs (€)	Incremental QALYs	ICER
Short-term treatment duration with TPOra (1 year)					
SoC	621,376	10.91	–	–	
Romiplostim	622,272	11.13	895	0.22	€4,155
Eltrombopag	622,607	11.03	335	–0.10	Dominated
Use of TPOra after rituximab treatment					
Romiplostim	594,354	12.05	–	–	–
Eltrombopag	610,633	11.31	16,279	–0.74	Dominated
SoC	621,376	10.91	10,743	–0.40	Dominated
Use of unadjusted response rate for eltrombopag					
Romiplostim	598,704	12.08	–	–	–
Eltrombopag	604,209	11.55	5,506	–0.54	Dominated
SoC	621,376	10.91	17,167	–0.63	Dominated
Use of EQ-5D utility values					
Romiplostim	598,704	11.29	–	–	–
Eltrombopag	611,962	10.61	13,258	–0.68	Dominated
SoC	621,376	10.24	9,415	–0.37	Dominated

The figures used in the model include all relevant decimal places. The figures shown in this table are rounded and as a result, any calculations made solely using the rounded figures may not provide an accurate result

ICER incremental cost-effectiveness ratio, QALY quality-adjusted life-year, SoC standard of care, TPOra thrombopoietin receptor agonist, Dominated indicates less effective at higher cost

Fig. 3 Deterministic sensitivity analysis: **a** romiplostim vs. eltrombopag, **b** romiplostim vs. standard of care (incremental net benefit is based on the incremental QALYs multiplied by the willingness-to-pay

threshold, minus incremental costs. The central vertical line represents the base-case net benefit). *CI* confidence interval, *IV* intravenous, *IVIg* intravenous immunoglobulin, *OP* outpatient

versus eltrombopag and €56,869 versus SoC at a €30,000 per QALY threshold (Figure 2A, Online Resource 1). There was a 90 % probability that romiplostim was cost effective versus eltrombopag and a 96 % probability versus SoC at a threshold of €30,000 per QALY (Figure 2A, Online Resource 1).

4 Discussion

In phase III randomized, placebo-controlled clinical trials, the majority of patients treated with romiplostim achieved a platelet count of $\geq 50 \times 10^9/L$, while bleeding events and the need for concurrent ITP therapies, including

Fig. 4 Cost-effectiveness acceptability frontier for romiplostim, eltrombopag and standard of care. *QALY* quality-adjusted life-year

corticosteroids and rescue treatments, were reduced [13, 21, 28–30]. Long-term extension studies demonstrated that platelet responses were sustained during prolonged treatment periods of up to 5 years [15, 31, 32], with use of glucocorticoids continuing to decrease [29]. The efficacy of romiplostim was also demonstrated in a European observational study [26].

The model presented here showed that romiplostim treatment was dominant, demonstrating better efficacy and cost savings than both eltrombopag and SoC. Savings were achieved through the higher response rates associated with romiplostim, which led to a reduction in bleeding-related episodes, including the use of rescue therapies. Romiplostim remained dominant throughout a variety of potential scenarios, including short-term (1 year) treatment with TPORa, placement after rituximab, use of unadjusted response rates for eltrombopag and the use of an alternative source for utility values. The model was most sensitive to assumptions surrounding the use of romiplostim, IVIg and steroids, and the duration of response to romiplostim. Nevertheless, romiplostim remained cost effective for all model parameters. PSA showed that romiplostim was likely to be cost effective in over 90 % of cases versus eltrombopag and 96 % versus SoC at a willingness-to-pay threshold of €30,000 per QALY.

The results of this cost-effectiveness analysis were dependent on Irish treatment practice and the healthcare system. Although the driver of the cost-effectiveness results was the efficacy of romiplostim, transferability of the results to other countries is subject to local costing and healthcare systems. Romiplostim has been shown to be cost effective compared with SoC and rituximab in other countries. In Canada, a net cost impact model showed that romiplostim is less expensive to prepare and administer than IVIg and is associated with lower indirect costs from a Canadian healthcare perspective [33]. Romiplostim was also associated with lower cost per response over 6 months

when compared with rituximab from the French national health system perspective [34] and when compared with SoC in Spain [35].

Although the results of our analysis were robust to multiple sensitivity analyses, several limitations need to be recognized. Direct comparison could not be made between romiplostim and eltrombopag due to a lack of head-to-head clinical trial data. Hence, estimates of comparative efficacy between the treatments were made using the indirect comparison recommended by Cooper et al. [18]. Uncertainty in this indirect comparison was assessed both in PSA and through scenario analysis. When the unadjusted response rates were used for both TPORa, romiplostim still provided better efficacy over eltrombopag, and remained cost saving. Additionally, clinical trial data for romiplostim and eltrombopag were comparatively better quality, and more recent, than the data for the other treatments (notably rituximab). Moreover, in some cases, published data for treatment pathways in Ireland were not available. Where this was the case, clinician validation by two Irish clinicians was used. Data from the USA have been used in estimating the mortality associated with ITP, as information was not available for Ireland or the UK. However, the impact of this parameter is limited, as one-way sensitivity analysis showed that it was not a key model driver.

The model was built from the perspective of the national healthcare payer in Ireland. The exclusion of a wider societal perspective could have underestimated overall costs associated with treatment. For romiplostim, because of more frequent nurse appointments associated with subcutaneous administration, indirect costs could include costs for time taken off work, transport and other out-of-pocket costs. However, the magnitude of these additional costs is uncertain, especially as a large proportion of romiplostim patients are able to administer romiplostim at home [15]. A lifetime time horizon was deemed to be the most appropriate, since adult ITP tends to be a chronic disease; the

4-week cycle was used to match the evaluation schedule used in the long-term romiplostim extension study [15].

The base-case analyses assumed that TPORa were placed before rituximab in the treatment pathway and used according to their approved indication in Europe, i.e. adult patients with chronic ITP failing splenectomy or as second-line therapy in patients who have contraindications to surgery [10, 11]. We assumed that patients would receive, successively, azathioprine, mycophenolate mofetil and cyclosporine, after TPORa and rituximab. We did not include splenectomy in the model since it was assumed that all patients who were candidates for this procedure would already have been splenectomized.

It is important to note that the model was based on conservative assumptions. We assumed that only one course of rituximab was given, whereas the literature suggests that repeated courses may be needed to sustain response [2, 36]. The lack of inclusion of adverse events also represents a conservative assumption when comparing romiplostim with SoC. Available data indicate that romiplostim has a good safety profile [37], particularly in comparison with currently available treatments that are based on immunosuppression, which may predispose patients to serious infections, a major cause of death in ITP patients [38]. However, the exclusion of adverse effects associated with romiplostim and other treatments may underestimate the overall treatment costs reported in this analysis.

5 Conclusions

In summary, the addition of romiplostim to the chronic ITP treatment pathway, compared with eltrombopag or SoC including rituximab, is likely to be cost effective in Ireland. This was shown despite the generally conservative assumptions applied in the model.

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Author contributions DL, AH, PT and LK evaluated the literature. DL, AH, LK, RD and NB were involved in the model design. DL, AH and NB built the model and conducted the model analyses. PT provided input on Irish clinical practice. DL, LK, NB and PT interpreted the data. DL, PT, LK and AH drafted the manuscript. All authors reviewed and approved the final submitted version of the manuscript. DL is the guarantor for the overall content.

Conflicts of interest LK is an employee, and RD a former employee, of Amgen, and both hold stock options in the company. DL, AH and NB are employees of BresMed Health Solutions Ltd, a consulting company contracted by Amgen to develop the cost-effectiveness model. PT has no conflicts of interest to declare.

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