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Budget impact analysis for avatrombopag in the treatment of chronic primary immune thrombocytopenia in adult patients refractory to other treatments

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ABSTRACT

Introduction: Primary immune thrombocytopenia is a rare autoimmune disease characterised by a decreased platelet count resulting in an increased risk of bleeding events and even life-threatening haemorrhages. Thrombopoietin receptor agonists (TPO-RAs) are the standard of care second-line therapy for adult patients with chronic immune thrombocytopenia. The first TPO-RAs approved and reimbursed in Italy, eltrombopag and romiplostim, while effective, pose some issues in terms of safety (e.g., hepatotoxicity) or general management (e.g., dietary restrictions). Avatrombopag, an effective and well-tolerated TPO-RA, was recently granted reimbursement.

Methods: A 3-year (2023–2025) budget impact analysis (BIA) was conducted to estimate its impact on the Italian National Health Service (NHS). Two scenarios were compared, of which one represents the current situation, without avatrombopag, and the other provides for an increasing market share of avatrombopag (up to 26.6%).

Results: BIA shows that the increase in the use of avatrombopag correlates with savings for NHS: in the first year, saving would be €1,300,564, increasing to €2,774,210 in the third year, for a total of €6,083,231 over the 3-year period. The sensitivity analysis confirmed these savings in the scenario with avatrombopag.

Conclusions: Based on this BIA, the introduction and reimbursement of avatrombopag is an efficient and advantageous choice for the Italian NHS.

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Avatrombopag; budget impact analysis; cost savings; primary immune thrombocytopenia; Italy

Background and objectives

Immune thrombocytopenia (ITP) is a rare autoimmune disease characterised by a decreased platelet count associated with both accelerated platelet destruction and megakaryopoiesis impairment [1]. It is referred to as 'primary' when it is not associated with other comorbidities or 'secondary' when an underlying medical condition (e.g., autoimmune diseases, viral infections, tumours) can be identified. The primary forms account for approximately 80% of ITPs, and the secondary forms for approximately 20% [2]. In Italy, ITP has an estimated prevalence of 23.6 cases per 100,000 inhabitants [3] and an incidence of 3.3 cases per 100,000 inhabitants [4].

Three phases are in treatment international guidelines based on disease duration: the acute phase, from diagnosis to 3 months post-diagnosis, the persistent phase, from 3 to 12 months after diagnosis, and the chronic phase, where the disease persists beyond 12 months [5–7].

Paediatric ITPs are usually secondary to infectious events and tend to self-limit, with only a minority of cases becoming chronic. Conversely, adult ITPs usually present without apparent triggering events and in most cases they tend to persist until the chronic phase of the disease [8].

ITP, particularly in its chronic form, has a profound impact on patients' quality of life, as a result of both the variable haemorrhagic manifestations and the associated chronic systemic symptoms, with consequent repercussions in various contexts (work, social life, sport, etc.) [9].

The haemorrhagic manifestations most typical of ITP are mucocutaneous bleeding, followed by genitourinary and gastrointestinal bleeding. Major or fatal haemorrhagic manifestations are rare, although the risk can be increased by certain factors such as old age, the presence of multiple comorbidities or concomitant use of antiplatelet or anticoagulant medication [10].

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Although the platelet count cut-offs may not precisely reflect the bleeding risk of the individual patient, the risk of haemorrhage generally increases with a platelet count below 50,000/mm^3 and becomes significant for values under 20–30,000/mm^3. The bleeding risk is highest below 10,000 platelets/mm^3 [10].

In accordance with current international guidelines, the first-line therapies are [6,7]: a) corticosteroids, to which only 25% of patients respond (beyond six weeks of therapy) [5,11–13] and for which long-term treatment is associated with common side effects [6,14,15]; b) IVIg (Intravenous Immunoglobulins) and/or anti-D immunoglobulins (Ig) that can be administered in intravenous infusions, which generate a transient response and are associated with adverse events [5,12,13]. For adult patients with ITP who do not achieve remission or do not respond to first-line therapy with corticosteroids or immunoglobulins, current international guidelines indicate the need for second-line treatment [6]. The main second-line therapies for ITP that are currently approved and reimbursed are thrombopoietin receptor agonists (TPO-RAs), which constitute the standard of care for the majority of patients [7,16,17]. The other second-line drugs that are reimbursed in Italy include fostamatinib, only for patients who are refractory or have contraindications for at least one TPO-RA, and rituximab [18]. Rituximab is used off-label and is reimbursed under Italian Law 648/96 [19].

The first TPO-RAs to be approved and reimbursed in Italy were eltrombopag (ELT) and romiplostim (ROM), drugs that, despite being effective, are associated with some issues [20–22]. ELT, while requires dietary restrictions, is associated with alanine transaminase and bilirubin elevation, for which it has a Boxed Warning regarding a risk of severe and life-threatening hepatotoxicity, and requires caution and close monitoring, especially in patients with liver disease [23]. ROM is associated with the development/progression of the formation of reticulin fibres in the bone marrow and possible bone marrow fibrosis, as well as with injection site reactions being subcutaneously administered [24–26].

The latest TPO-RA reimbursed in Italy, avatrombopag (AVA), can be taken orally without food-type restrictions [27–29]. Treatment with AVA has been shown to result in rapid and long-lasting achievement of a platelet count above 50,000/mm^3 after just eight days of treatment in two out of three patients. This increase occurs gradually from 3–5 days after the start of treatment, and reaches peak effect after 10–13 days [28,30]. Patients treated with AVA generally maintained a platelet count of between 50,000/mm^3 and 150,000/mm^3 for the duration of the pivotal Phase 3 study. AVA is well-tolerated, has demonstrated that it is not associated with significant hepatotoxicity, and is characterised by a low incidence of thromboembolic events [28,30]. Pooling the patients with ITP in 4 clinical studies, thromboembolic events were observed in 9/128 patients [29]; furthermore, AVA has been associated with a reduction in the use of concomitant therapies for the management of ITP [28,30].

Based on these results, AVA was granted reimbursement for the treatment of chronic primary ITP in adult patients who are refractory to other treatments (such as corticosteroids and immunoglobulins) [31]. In order to evaluate the economic/financial impact on the Italian National Health Service (NHS), following the reimbursement of AVA, a budget impact analysis (BIA) over a time horizon of 3 years was carried out.

Materials and methods

The BIA (Figure 1) was conducted in compliance with the Guidelines issued by both the International Society for Health Economics and Outcomes Research (ISPOR) and the Italian Medicines Agency (AIFA) [32,33]. All the hypotheses used in the analysis were validated by two Italian clinical experts and one health economic expert. The analysis was developed from the perspective of the Italian NHS over a time horizon of three years (2023–2025).

The number of patients with chronic primary ITP was estimated based on literature sources, by applying the chronic primary ITP prevalence, incidence and growth rates for the entire adult (≥18 years) Italian population for the period considered [3,4,34]. This population was further analysed in relation to the strategy applied and the corresponding health outcomes to identify the population potentially eligible for treatment with TPO-RAs (target population). It was assumed that 80% of patients with ITP have a primary form and that 71% of the latter require first-line treatment [35,36].

Only a portion of these patients is actually treated with TPO-RAs. In the BIA, these patients were identified as follows:

a. Prevalent patients (which received a diagnosis at least two year before the present study and are currently treated), were considered to already have a chronic form, with 55.2% of them requiring a line of treatment subsequent to the first [35]. Lastly, using market data it was calculated that 38.3% of the subjects identified above are already treated with a TPO-RA [37].

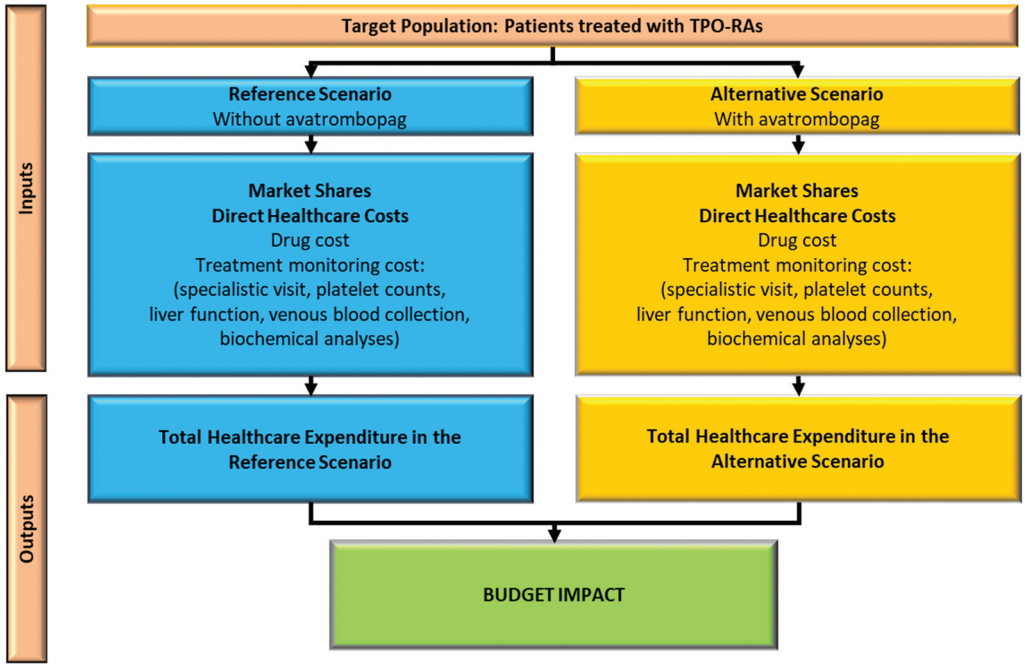

Figure 1. Budget impact model structure.

Note: Legend: TPO-RAs: Thrombopoietin receptor agonists

b. For incident patients (i.e., those diagnosed with the disease in a year the model refers to), it was estimated that 80% of patients evolve towards the chronic form [38] and that 55.2% require a line of treatment subsequent to the first [35]. Lastly, in accordance with the opinion of the clinical experts, it was estimated that in clinical practice approximately 80% of these patients are treated with a TPO-RA.

The epidemiological estimates are shown in Table 1. In the analysis, the population is considered to remain constant and stable over the three years of the time horizon.

Two scenarios are compared in the BIA: a Reference Scenario, without AVA, and an Alternative Scenario, involving the progressive introduction of AVA into the current TPO-RA market, to the detriment of the two reimbursed drugs: ELT and ROM. The values are shown in Table 2.

For the economic quantification, the data obtained from the literature were confirmed and integrated by means of a specific questionnaire administered to the clinical experts to identify the actual patient journey and resource consumption in relation to the therapies used, in terms of average dose of the drug and average annual frequency of specialist consultations and diagnostic tests and procedures.

Consultations and diagnostic, follow-up and laboratory tests were valorised using the outpatient fees currently applicable in Italy [39]. The frequencies and costs associated with monitoring are shown in Table 3. More specifically, in the Base Case an average AVA dose of 17.7 mg/day was used (pooled analysis of data from phase 2/3 trials) [40], whereas for ELT the mean dose of the EXTEND study (51.3 mg/day) was used [41,42]. For ROM, on the other hand, given the extremely variable doses, the analysis used the weighted mean of the packs sold in Italy as a function of the respective market shares [37]: 67.6% for the 250 mcg pack and 32.4% for the 500 mcg pack (329.75 mcg per week). For conservative reasons, 100% compliance was assumed for all the drugs.

The drug therapy costs for AVA, ELT and ROM were estimated considering the ex-factory prices minus the mandatory manufacturer discounts (–5%, –5%) [43]. (Table 4), assuming an absence of drug wastage and an average weight of 70 kg (in accordance with AIFA Guidelines) [33]. The analysis does not consider administration costs, since AVA and ELT are oral drugs, whereas ROM is administered subcutaneously.

In order to assess the robustness of the Base Case results, the authors carried out a deterministic one-way sensitivity analysis, in which the dose used was varied and, more specifically, the doses stated in the technical data sheet were used for AVA (20 mg/day) and ELT (50

Table 1. Target population*†.

	Year 1–3	Reference
Italian population		
Adult population (≥18 years) – A	49,796,335	ISTAT
Prevalent PTS		
Prevalence of chronic ITP – B	23.6/100,000 adults	Feudjo-Tepie 2008
pITP (%) – C	80.0%	Lambert 2017
Adult Prevalent PTS with chronic pITP (n) – D = A*B*C	9,402	Estimate
Prevalent PTS with chronic pITP who have required treatment to stop the bleeding (%) – E	71.0%	Palandri 2016
Prevalent PTS with chronic pITP who have required treatment to stop the bleeding (n) – F = D*E	6,675	Estimate
Prevalent PTS with chronic pITP who have required a treatment after 1st line (%) – G	55.2%	Palandri 2016
Prevalent PTS with chronic pITP who have required a treatment after 1st line (n) – H = F*G	3,685	Estimate
Prevalent PTS with chronic pITP treated with TPO-RAs after 1st line (%) – I	38.3%	IQVIA Market Research
Prevalent PTS with chronic pITP treated with TPO-RAs after 1st line (n) J = H*I	1,411	Estimate
Incident PTS		
Incident of ITP (%) – K	3.3/100,000 adults	Rodeghiero 2020
pITP (%) – L	80%	Lambert 2017
Incident PTS with pITP (n) – M = A*K*L	1,314	Estimate
Incident PTS with pITP who develop a chronic form (%) – N	80.0%	Kistanguri 2013
Incident PTS with pITP who develop a chronic form (n) – O = M*N	1,051	Estimate
Incident PTS with chronic pITP who have required treatment to stop the bleeding (%) – P	71.0%	Palandri 2016
Incident PTS with chronic pITP who have required treatment to stop the bleeding (n) – Q = O*P	746	Estimate
Incident PTS with chronic pITP who have required treatment after 1st line (%) – R	55.2%	Palandri 2016
Incident PTS with chronic pITP who have required treatment after 1st line (n) – S = Q*R	412	Estimate
Incident PTS with chronic pITP treated with TPO-RAs after 1st line (%) – T	80.0%	Expert Opinion
Incident PTS with chronic pITP treated with TPO-RAs after 1st line (n) – U = S*T	330	Estimate
Target population		
Total prevalent and incident PTS with chronic pITP treated with TPO-RAs after 1st line (n) -V = J + U	1,741	Estimate

Legend: ITP: immune thrombocytopenia; pITP: primary immune thrombocytopenia; PTS: patients; n: number; TPO-RAs: Thrombopoietin receptor agonists; Expert Opinion: all the hypotheses used in the analysis were validated by two Italian clinical experts and one health economic expert.
*Number of patients rounded at the first integer. †Percentages rounded to the first decimal number.

Table 2. Estimated patients and market shares broken down by year and therapy: base case and sensitivity analysis *†.

	Year 1–2023	Year 2–2024	Year 3–2025
Reference Scenario			
Avatrombopag – Total	**0 (0.0%)**	**0 (0.0%)**	**0 (0.0%)**
Of which 1st year treatment	*0 (0.0%)*	*0 (0.0%)*	*0 (0.0%)*
Of which ≥ 2nd year treatment	*0 (0.0%)*	*0 (0.0%)*	*0 (0.0%)*
Eltrombopag – Total	**1,137 (65.3%)**	**1,137 (65.3%)**	**1,137 (65.3%)**
Of which 1st year treatment	*216 (12.4%)*	*216 (12.4%)*	*216 (12.4%)*
Of which ≥ 2nd year treatment	*921 (52.9%)*	*921 (52.9%)*	*921 (52.9%)*
Romiplostim – Total	**604 (34.7%)**	**604 (34.7%)**	**604 (34.7%)**
Of which 1st year treatment	*114 (6.5%)*	*114 (6.5%)*	*114 (6.5%)*
Of which ≥ 2nd year treatment	*490 (28.1%)*	*490 (28.1%)*	*490 (28.1%)*
TPO-RAs – Total	**1,741 (100.0%)**	**1,741 (100.0%)**	**1,741 (100.0%)**
Of which 1st year treatment	*330 (19.0%)*	*330 (19.0%)*	*330 (18.9%)*
Of which ≥ 2nd year treatment	*1,411 (81.0%)*	*1,411 (81.0%)*	*1,411 (81.1%)*
Alternative Scenario			
Avatrombopag – Total	**212 (12.2%)**	**326 (18.7%)**	**463 (26.6%%)**
Of which 1st year treatment	*212 (12.2%)*	*114 (6.5%)*	*137 (7.9%)*
Of which ≥ 2nd year treatment	*0 (0.0%)*	*212 (12.2%)*	*326 (18.7%)*
Eltrombopag – Total	**1,024 (58.8%)**	**957 (55.0%)**	**871 (50.0%)**
Of which 1st year treatment	*194 (11.1%)*	*181 (10.4%)*	*165 (9.5%)*
Of which ≥ 2nd year treatment	*830 (47.7%)*	*776 (44.6%)*	*706 (40.5%)*
Romiplostim – Total	**505 (29.0%)**	**458 (26.3%)**	**407 (23.4%)**
Of which 1st year treatment	*96 (5.5%)*	*87 (5.0%)*	*77 (4.4%)*
Of which ≥ 2nd year treatment	*409 (23.5%)*	*371 (21.3%)*	*330 (19.0%)*
TPO-RAs – Total	**1,741 (100.0%)**	**1,741 (100.0%)**	**1,741 (100.0%)**
Of which 1st year treatment	*502 (28.8%)*	*382 (21.9%)*	*379 (21.7%)*
Of which ≥ 2nd year treatment	*1,239 (71.2%)*	*1,359 (78.1%)*	*1,362 (78.3%)*

Legend: TPO-RAs: Thrombopoietin receptor agonists.
*Number of patients rounded at the first integer. †Percentages rounded to the first decimal number.

Table 3. Monitoring costs per patient.

Year	Visit OR exams n	Unit Costs: Specialistic Visit €	Platelet Counts €	Liver Function €	venous blood collection €	Biochemical Analyses (only for the 1st visit) €	Total Monitoring €
Avatrombopag							
Year 1	16	€20.66	€3.17	€0.00	€2.58	€172.70	**€598.71**
Year ≥2	12	€20.66	€3.17	€0.00	€2.58	€0.00	**€316.92**
Eltrombopag							
Year 1	16	€20.66	€3.17	€3.45	€2.58	€172.70	**€650.46**
Year ≥2	12	€20.66	€3.17	€3.45	€2.58	€0.00	**€358.32**
Romiplostim							
Year 1	20	€20.66	€3.17	€0.00	€2.58	€172.70	**€704.35**
Year ≥2	12	€20.66	€3.17	€0.00	€2.58	€0.00	**€316.92**

mg/day), whereas for ROM, in agreement with the clinical experts, an average weekly dose of 5 mcg per kg of body weight (350 mcg per week) was used [23,29]. It was decided to vary only the dose of the drug, since this is the main cost driver.

Results

Target population

The number of adult patients with chronic primary ITP treated with or potentially eligible for treatment with TPO-RAs was estimated to be constant and equal to 1,741 patients in the three years of the analysis. Of these, the number of patients treated with AVA in the Alternative Scenario was 212 in the first year (TPO-RA-naïve) and 463 in the third year (of whom 137 TPO-RA-naïve). The values are shown in Tables 1 and 2.

Patient journey: monitoring consultations and tests

The results of the questionnaire showed that the frequency and type of tests and consultation varied depending on the therapy used:

a. AVA = 16 consultations in the first year and 12 consultations from the second year onwards, for venous blood draws and platelet counts
b. ELT = 16 consultations in the first year and 12 consultations from the second year onwards, for venous blood draws, platelet counts and liver function tests (ALT, AST and total and fractionated bilirubin)
c. ROM = 20 consultations in the first year and 12 consultations from the second year onwards, for venous blood draws and platelet counts

These results, which were used in both the Base Case and the Sensitivity Analysis, showed: a higher number of consultations and tests in the first year (for all treatments) compared to subsequent years; a higher number of consultations and tests in the first year for ROM compared to other therapies; need for a liver function tests for ELT alone vs other therapies (Table 3).

Base case results

In the Base Case, as indicated in Table 4, the per-patient annual drug therapy cost was estimated to be: AVA = € 26558.36; ELT = € 29029.80; ROM = € 37295.25. These costs were constant over the three years of the model.

On the contrary, monitoring costs varied depending on the year of treatment of the patients.

The data show a lower cost for AVA, since for the first year of ROM therapy consultations and tests are more frequent, and for ELT the costs associated with liver function tests must be considered. It therefore follows that the average annual per-patient cost differs depending on the treatment strategy used, linked with the costs for monitoring.

Overall, AVA proves to be the least costly drug for the NHS:

a. AVA = €27,157 (of which € 598.71 for monitoring) for the first year and € 26875 (€ 316.92 for monitoring) for the subsequent years.
b. ELT = € 29680 (€ 650.46) for the first year and € 29338 (€ 358.32) for the subsequent years.
c. ROM = € 38000 (€ 704.35) for the first year and € 37612 (€ 316.92) for the subsequent years.

The overall results of the model are presented as the differential between the reference scenario, which does not provide for the inclusion of AVA as an available treatment option, and the alternative scenario, which

Table 4. Cost per patient/year: base case and sensitivity analysis.

		Drug Cost						
Drug	Year	Pack	Price	Cost €/mg	Dose	Drug cost patient/year €	Monitoring cost	Total Cost
BaseCase Analysis								
Avatrombopag	1	30 tabs x 20 mg	€2.466.53	€4.11	17.70 mg daily	€26,558.36	€598.71	**€27,157.07**
	≥2						€316.92	**€26,875.28**
Eltrombopag	1	28 tabs x 50 mg	€2,170.51	€1.55	51.30 mg daily	€29,029.80	€650.46	**€29,680.26**
	≥2						€358.32	**€29,388.12**
Romiplostim	1	1 vial of 250 mcg	€543.76	€2,175.04	329.75 mcg weekly*	€37,295.25	€704.35	**€37,999.60**
		1 vial of 500 mcg	€1,087.51	€2,175.02				
	≥2	1 vial of 250 mcg	€543.76	€2,175.04			€316.92	**€37,612.17**
		1 vial of 500 mcg	€1,087.51	€2,175.02				
Sensitivity Analysis								
Avatrombopag	1	30 × 20 mg tabs	€2.466.53	€4.11	20.00 mg daily	€30,009.45	€598.71	**€30,608.16**
	≥2						€316.92	**€30,326.37**
Eltrombopag	1	€2,170.51	€1.55	€1.55	50.00 mg daily	€28,294.15	€650.46	**€28,944.61**
	≥2						€358.32	**€28,652.47**
Romiplostim	1	1 vial of 250 mcg	€543.76	€2,175.04	350.00 mcg weekly†	€39,585.73	€704.35	**€40,290.08**
		1 vial of 500 mcg	€1,087.51	€2,175.02				
	≥2	1 vial of 250 mcg	€543.76	€2,175.04			€316.92	**€39,902.65**
		1 vial of 500 mcg	€1,087.51	€2,175.02				

*68.1% of patients treated with 250 mcg weekly and 31.9% treated with 500 mcg weekly. †5 mcg/kg Weekly per an average patient of 70 kg..

provides for an incremental increase of the use of AVA in the same overall number of patients treated over the three years analysed. The drivers considered include the drug therapy costs and the costs of the services generated by the various monitoring regimens considered. These results show, against three-year expenditure with AVA of € 27032,626 (16.6% of total expenditure), cost saving for the NHS of € 1,300,564 in the first year, of € 2,008,457 in the second and of € 2,774,210 in the third, for a total saving over the three-year period of € 6,083,231 (Table 5, Figure 2).

Sensitivity analysis

In this scenario, the doses of therapy were modified in accordance with those stated in the technical data sheet, since the cost of drug therapy was seen to be the most important driver in the total healthcare costs estimate, keeping the monitoring costs stable for conservative reasons.

In the Sensitivity Analysis (Table 4) the estimated per-patient annual cost is:

a. AVA = € 30608 (of which € 598.71 for monitoring) for the first year and € 30326 (€ 316.92 for monitoring) for the subsequent years.
b. ELT = € 28945 (€ 650.46) for the first year and € 28652 (€ 358.32) for the subsequent years.
c. ROM = € 40290 (€ 704.35) for the first year and € 39903 (€ 316.92) for the subsequent years.

In the sensitivity analysis, ELT was the drug with the lowest healthcare costs and was due to the lower dose of ELT (50 mg/day) used in this setting [23].

In the Sensitivity Analysis (Table 6, Figure 3), the overall expenditure for the three-year period (drug therapy and monitoring) is € 170,358,975 in the Reference Scenario vs € 167,129,125 in the Alternative Scenario. The comparison between the scenarios shows that against total expenditure (drug therapy and monitoring) for AVA of € 30487,165 (18.2% of total expenditure) the cost savings would be € 3,229,850. Although it presents hypotheses that are less favourable for AVA, the Sensitivity Analysis confirms the robustness of the model and the estimates.

Discussion

The BIA was developed to estimate the impact on healthcare costs (drug therapy and monitoring) as a function of the reimbursement and increased use of AVA in Italy.

It was developed by adopting a conservative approach to represent the possible cost of the therapies depending on the doses and the monitoring regimen. The data showed that the doses are different to those of the technical data sheets, with a lower consumption of AVA and a lower consumption of ELT [23,29,40–42]. As romiplostim schedule followed a personalized approach on patient's weight basis, consumption data coming from market research and the opinion of Italian clinical experts are considered proxies of the dosage in the clinical practice, in line with AIFA Guidelines for Economic Evaluations [33,37]. The data therefore demonstrate the variability of the results as a function of the doses, illustrating that the cost of therapy is the major driver of this analysis. Although AVA has lower monitoring costs (same-year comparison) than the

Table 5. Budget impact analysis: base case analysis.*

	Year 1–2023	Year 2–2024	Year 3–2025
Reference Scenario			
Avatrombopag – Total	**€0**	**€0**	**€0**
Of which drug therapy	*€0*	*€0*	*€0*
Of which monitoring	*€0*	*€0*	*€0*
Eltrombopag – Total	**€33,477,390**	**€33,477,390**	**€33,477,390**
Of which drug therapy	*€33,006,878*	*€33,006,878*	*€33,006,878*
Of which monitoring	*€470,512*	*€470,512*	*€470,512*
Romiplostim – Total	**€22,761,918**	**€ 22761,918**	**€ 22761,918**
Of which drug therapy	*€22,526,331*	*€22,526,331*	*€22,526,331*
Of which monitoring	*€235,587*	*€235,587*	*€235,587*
TPO-RAs – Total	**€56,239,308**	**€56,239,308**	**€56,239,308**
Of which drug therapy	*€55,533,209*	*€55,533,209*	*€55,533,209*
Of which monitoring	*€706,099*	*€706,099*	*€706,099*
Alternative Scenario			
Avatrombopag – Total	**€5,757,299**	**€8,793,466**	**€12,481,861**
Of which drug therapy	*€5,630,373*	*€8,658,026*	*€12,296,522*
Of which monitoring	*€126,927*	*€135,440*	*€185,339*
Eltrombopag – Total	**€30,150,106**	**€28,177,304**	**€25,645,252**
Of which drug therapy	*€29,726,511*	*€27,781,515*	*€25,284,952*
Of which monitoring	*€423,595*	*€395,790*	*€360,300*
Romiplostim – Total	**€19,031,339**	**€17,260,080**	**€15,337,985**
Of which drug therapy	*€18,834,101*	*€17,081,225*	*€15,179,167*
Of which monitoring	*€197,238*	*€178,856*	*€158,819*
TPO-RAs – Total	**€54,938,744**	**€54,230,851**	**€53,465,098**
Of which drug therapy	*€54,190,985*	*€53,520,765*	*€52,760,641*
Of which monitoring	*€747,759*	*€710,085*	*€704,458*
Δ Alternative Scenario – Reference Scenario			
Total cost per year	**-€1,300,564**	**-€2,008,457**	**-€2,774,210**
Of which drug therapy cost per year	*-€1,342,224*	*-€2,012,444*	*-€2,772,569*
Of which monitoring cost per year	*+€41,660*	*+€3,987*	*-€1,641*
Total cost at 3 years		**-€6,083,231**	

Legend: TPO-RAs: Thrombopoietin receptor agonists.
*Costs rounded at the first integer.

Table 6. Budget impact analysis: sensitivity analysis.*

	Year 1–2023	Year 2–2024	Year 3–2025
Reference Scenario			
Avatrombopag – Total	**€0**	**€0**	**€0**
Of which drug therapy	*€0*	*€0*	*€0*
Of which monitoring	*€0*	*€0*	*€0*
Eltrombopag – Total	**€32,640,959**	**€32,640,959**	**€32,640,959**
Of which drug therapy	*€32,170,447*	*€32,170,447*	*€32,170,447*
Of which monitoring	*€470,512*	*€470,512*	*€470,512*
Romiplostim – Total	**€24,145,366**	**€24,145,366**	**€24,145,366**
Of which drug therapy	*€23,909,780*	*€23,909,780*	*€23,909,780*
Of which monitoring	*€235,587*	*€235,587*	*€235,587*
TPO-RAs – Total	**€56,786,325**	**€56,786,325**	**€56,786,325**
Of which drug therapy	*€56,080,226*	*€56,080,226*	*€56,080,226*
Of which monitoring	*€706,099*	*€706,099*	*€706,099*
Alternative Scenario			
Avatrombopag – Total	**€6,488,930**	**€9,918,521**	**€14,079,715**
Of which drug therapy	*€6,362,003*	*€9,783,081*	*€13,894,375*
Of which monitoring	*€126,927*	*€135,440*	*€185,339*
Eltrombopag – Total	**€29,396,804**	**€27,473,291**	**€25,004,504**
Of which drug therapy	*€28,973,210*	*€27,077,502*	*€24,644,205*
Of which monitoring	*€423,595*	*€395,790*	*€360,300*
Romiplostim – Total	**€20,188,031**	**€18,309,119**	**€16,270,210**
Of which drug therapy	*€19,990,793*	*€18,130,263*	*€16,111,391*
Of which monitoring	*€197,238*	*€178,856*	*€158,819*
TPO-RAs – Total	**€56,073,765**	**€55,700,931**	**€55,354,429**
Of which drug therapy	*€55,326,006*	*€54,990,846*	*€54,649,971*
Of which monitoring	*€747,759*	*€710,085*	*€704,458*
Δ Alternative Scenario – Reference Scenario			
Total cost per year	**-€712,560**	**-€1,085,394**	**-€1,431,896**
Of which drug therapy cost per year	*-€754,221*	*-€1,089,381*	*-€1,430,255*
Of which monitoring cost per year	*+€41,660*	*+€3,987*	*-€1,641*
Total cost at 3 years		**-€3,229,850**	

Legend: TPO-RAs: Thrombopoietin receptor agonists.
*Costs rounded at the first integer.

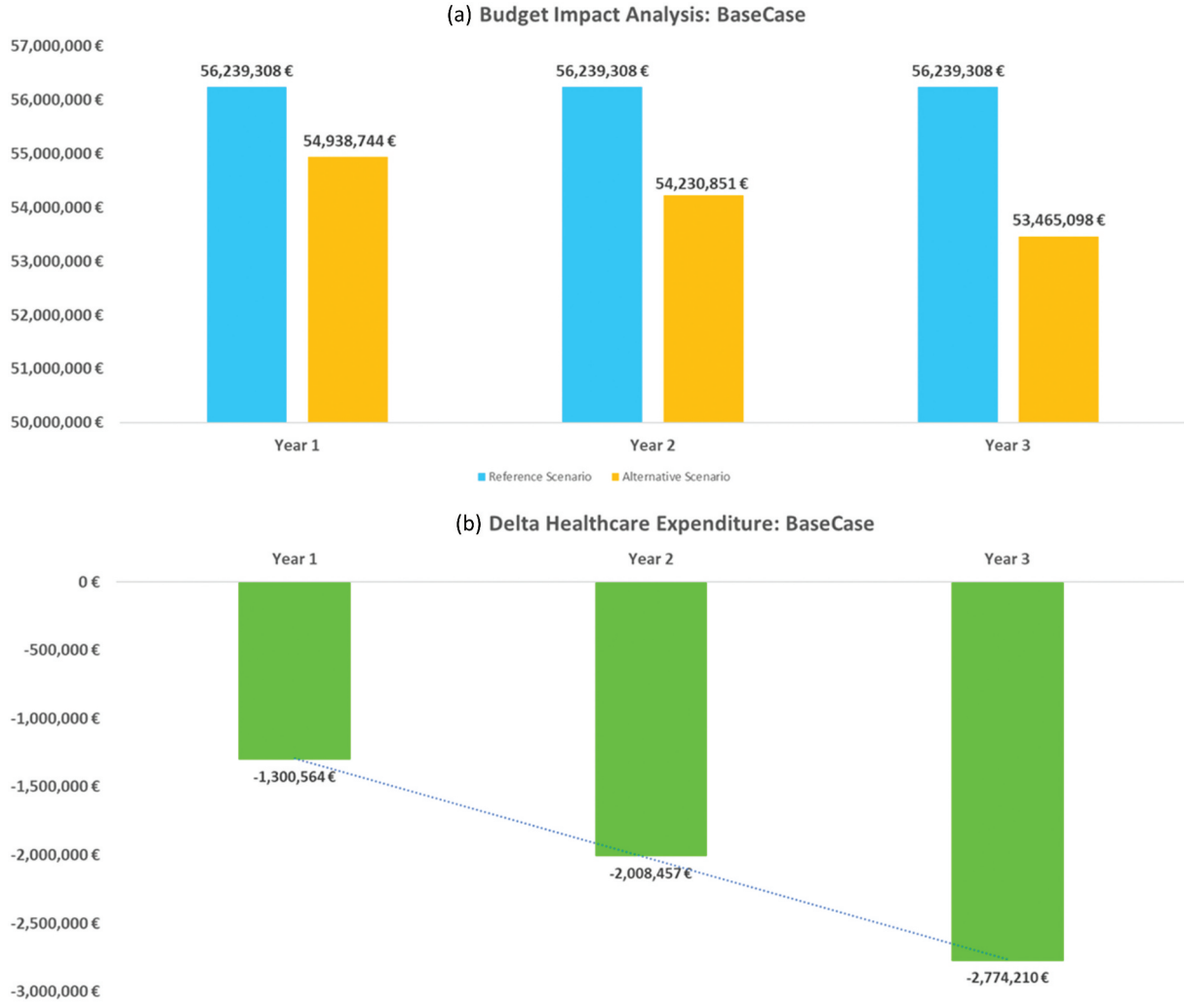

Figure 2. Budget Impact and healthcare expenditure variation per year, linked with avatrombopag reimbursement (Alternative – Reference scenario) per year: base case analysis.

comparators, an assessment of the results shows an increase in expenditure for monitoring between the first and second years as a function of the higher number of patients being treated with a new TPO-RA. This is because all TPO-RAs have higher monitoring costs in the first year of treatment and in the model AVA gains markets shares from both naïve patients and those already treated with the other TPO-RAs. As a matter of fact, for all patients starting therapy with AVA it is assumed that the same first-year tests and consultations will be repeated, regardless of the previous therapies.

To compare the results of the analysis with other international and national papers, an *ad hoc* literature search was carried out, focusing on the studies published over the last 10 years. Unfortunately, there are no other studies that have investigated the economic and financial implications of AVA in this indication, making it impossible to compare our results with other studies. On the other hand, the studies comparing ELT and ROM yielded conflicting results, but tend to favour ELT. The study by Allen et al. analysed the cost of treatment in England and Wales, reaching the conclusion that therapy with ELT is less expensive than that with ROM, with better results in non-splenectomised patients than in splenectomised subjects [44]. The studies by Tremblay et al. and Patwardhan et al., both referring to costs in the United States, reached similar conclusions, with a lower cost for ELT [45,46]. On the contrary, the study by Fust et al., in which the authors developed a cost-effectiveness analysis, calculating the incremental cost effectiveness ratio (ICER) as a function of the incremental number of responder patients, concluded that ROM is more cost-effective than ELT, given its greater effectiveness and lower costs associated. The conclusions can therefore differ depending on the type of analysis presented [47].

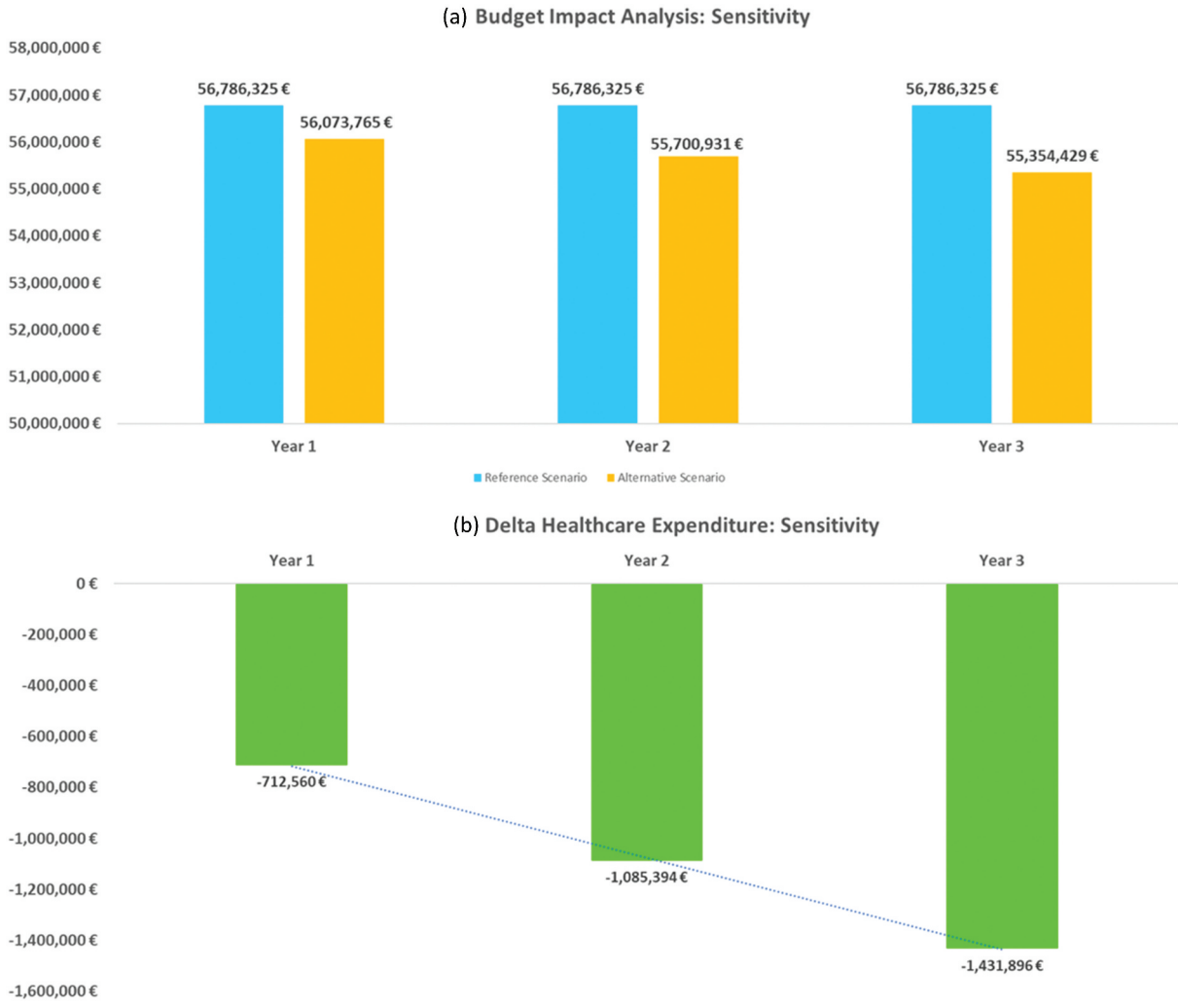

Figure 3. Budget Impact and healthcare expenditure variation per year, linked with avatrombopag reimbursement (Alternative – Reference scenario) per year: sensitivity analysis.

The first limitation of this analysis is the variability of the results depending on the doses used and, therefore, the costs of therapy. It was therefore decided to perform the Sensitivity Analysis, modifying the doses of the therapies. However, it should be pointed out that the Base Case data appear to be particularly robust [37,40,41] and that they should represent real practice better than just using the doses stated on the technical data sheet [23,24,29]. Furthermore, in both analyses, ROM would appear to be the most expensive drug, whereas the introduction of AVA always coincides with a reduction in the overall three-year expenditure for the NHS.

The second limitation of the analysis is the absence of adverse event assessments. They were not included because AVA was studied vs placebo and because in most cases the adverse events were mild or moderate, including: headache (29.8%), bruising (40.4%) and upper respiratory tract infections (23.4%). These frequencies were similar to those observed in the placebo group [27]. Furthermore, it should also be noted that the cost of drug therapy is the major driver of the analysis and that it is unlikely that including the costs related to adverse events would have a considerable impact on the results presented.

Conclusions

Based on this budget impact analysis the introduction and reimbursement of AVA in the treatment of ITP, in adult patients who are refractory to other treatments, is an efficient and advantageous choice for the Italian NHS, with savings in terms of both pharmaceutical expenditure and the expenditure associated with monitoring the therapies. The robustness of the analysis was confirmed also by the sensitivity analysis which has considered very conservative and challenging assumptions for AVA.

Disclosure statement

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