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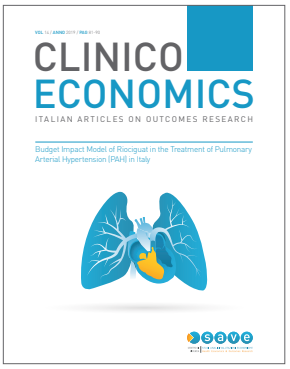

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Budget Impact Model of Riociguat in the Treatment of Pulmonary Arterial Hypertension (PAH) in Italy

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ABSTRACT EN

INTRODUCTION

Pulmonary arterial hypertension (PAH) is a serious, progressive, rare disease. It is dangerous for the heart and lungs and involves increased blood pressure within the pulmonary arterioles, which can cause heart failure and death. Riociguat is a new oral drug of the class of soluble guanylate cyclase stimulators and the only drug so far showing a significant clinical benefit both in PAH and in chronic thromboembolic pulmonary hypertension CTEPH (inoperable CTEPH and persistent/recurrent CTEPH after pulmonary endarterectomy). The goal of our analysis was to develop a budget impact model based on real-world data, in order to assess the economic impact of the introduction of riociguat in the PAH management from the perspective of the Italian national health service (Servizio Sanitario Nazionale, SSN), using a value-based approach.

METHODS

The model was developed based on administrative data collected from December 2014 to March 2018 and compared the direct (healthcare) costs of two strategies: "NO riociguat" (scenario 1) and "WITH

ABSTRACT ITA

INTRODUZIONE

L'ipertensione arteriosa polmonare (PAH) è una malattia grave, progressiva e rara. È pericolosa per cuore e polmoni e comporta un aumento della pressione sanguigna all'interno delle arteriole polmonari, che può causare insufficienza cardiaca e morte. Riociguat è un nuovo farmaco orale della classe di stimolatori di ciclica guanylate solubili e l'unico farmaco finora che mostra un significativo beneficio clinico sia nella PAH che nell'ipertensione polmonare tromboembolica cronica CTEPH (CTEPH inoperabile e CTEPH persistente/ricorrente dopo endarterectomia polmonare). L'obiettivo della nostra analisi è stato quello di sviluppare un modello di impatto sul budget basato su dati reali, al fine di valutare l'impatto economico dell'introduzione del riociguat nella gestione l'ipertensione arteriosa polmonare dal punto di vista del servizio sanitario nazionale italiano (Servizio Sanitario Nazionale, SSN), utilizzando un approccio basato sul valore.

METODI

Il modello è stato sviluppato sulla base dei dati amministrativi raccolti da dicembre 2014 a marzo 2018 e ha confrontato i costi diretti (sanitari) di due strate-

riociguat" (scenario 2). The analysis was carried out from the perspective of the Italian SSN and covered a time horizon of 3 years and 4 months. The direct costs were obtained from national price lists and validated by an expert group. Scenario 1 is the current scenario based on data from the available administrative databases (real clinical practice). Scenario 2 assumes that patients treated with the ERA + PDE-5i drug combination who fail to reach an adequate therapeutic response are given riociguat instead of PDE-5i, before switching to a parenteral or inhaled prostanoid (PCA). It is common clinical practice to reassess patients after about 180 days in order to decide if a therapy change is needed. In the light of the RESPITE study results, 30% of the patients are expected to continue with riociguat, while 70% will add a PCA after this time.

RESULTS

In the real-life cohort (N=177), total drug costs were € 16.1 million in scenario 1, and € 14.1 million in scenario 2. The treatment costs for patients on ERA + PDE-5i + PCA (N=35) were € 7.2 million in scenario 1 and € 5.2 million in scenario 2, with an overall savings of € 2 million (-28%).

DISCUSSION

Riociguat can improve functional class and delay clinical worsening to more serious stages of PAH. Moreover, our analysis showed that its use may defer the start of the next line of treatment (parenteral prostanoids) in patients whose PAH is not adequately controlled with traditional regimens. Therapy with riociguat seems able to bring about a decrease in Italian pharmaceutical and healthcare expenditure. Our analysis demonstrated an overall savings of 2 million € on the treated population.

gie: "SENZA riociguat" (scenario 1) e "CON riociguat" (scenario 2). L'analisi è stata effettuata dal punto di vista del SSN italiano e ha coperto un orizzonte temporale di 3 anni e 4 mesi. I costi diretti sono stati ottenuti da gazzetta ufficiale nazionale e convalidati da un gruppo di esperti. Lo scenario 1 è lo scenario corrente basato sui dati dei database amministrativi disponibili (pratica clinica reale). Lo scenario 2 presuppone che ai pazienti trattati con una combinazione di farmaci ERA - PDE-5i che non riescono a raggiungere un'adeguata risposta terapeutica venga dato riociguat invece di PDE-5i, prima di passare a un prostanoide parenterale o inalato (PCA). È pratica clinica comune rivalutare i pazienti dopo circa 180 giorni al fine di decidere se è necessario un cambiamento di terapia. Alla luce dei risultati dello studio RESPITE, il 30% dei pazienti dovrebbe continuare con il riociguat, mentre il 70% aggiungerà un PCA dopo questo tempo.

RISULTATI

Nella coorte reale (N.177), i costi totali dei farmaci sono stati pari a 16,1 milioni di euro nello scenario 1 e a 14,1 milioni di euro nello scenario 2. I costi di trattamento per i pazienti affetti da ERA - PDE-5i -PCA (N.35) sono stati pari a 7,2 milioni di euro nello scenario 1 e 5,2 milioni di euro nello scenario 2, con un risparmio complessivo di 2 milioni di euro (-28%).

DISCUSSIONE

Riociguat può migliorare la classe funzionale e ritardare il peggioramento clinico a stadi più gravi di PAH. Inoltre, la nostra analisi ha mostrato che il suo utilizzo può differire l'inizio della prossima linea di trattamento (prostanoidi parenterali) in pazienti la cui PAH non è adeguatamente controllata con i regimi tradizionali. La terapia con riociguat sembra in grado di portare ad una diminuzione della spesa farmaceutica e sanitaria italiana. La nostra analisi ha dimostrato un risparmio complessivo di 2 milioni di euro sulla popolazione trattata.

KEYWORDS: Riociguat, pulmonary arterial hypertension, budget impact, soluble guanylate cyclase stimulators, real-world evidence, value-based approach.

INTRODUCTION

Pulmonary arterial hypertension (PAH) is a rare, progressive, disabling condition. It is characterized by obstructive lesions in the pulmonary arterioles that cause a progressive increase in vascular resistance and pulmonary pressure, leading to serious dysfunction of the right ventricle.

The prevalence of PAH in Europe is 15 to 50 cases per million population,[1,2,3] and the median survival has increased from 2.4 to 7 years in the last 20 years.[4] PAH can have different forms. It can manifest itself without associated conditions, in which case it is called idiopathic pulmonary hypertension, or it can be associated with other diseases such as congenital heart diseases, immune diseases, HIV infection, or portal hypertension. Since the symptoms are non-specific,[5] it is difficult to diagnose PAH in its initial stages.

Until recently, the therapeutic resources were scarce and lung transplants were needed in the most advanced cases.[6] At present, various drugs are available with demonstrated effectiveness in improving patients' clinical conditions and reducing morbidity. The approved drugs fall into 4 categories: endothelin receptor antagonists (ERA), phosphodiesterase type 5 inhibitors (PDE-5i), soluble guanylate cyclase (sGC) stimulators, and prostacyclin analogs (PCA) (in the prostanoid class).

The management strategies outlined in the ESC/ERS 2015[6] European guidelines (GL) recommend treating patients with PAH according to their clinical conditions, starting with up-front monotherapy or combination therapy, and adding a new drug after about 4 to 6 months in cases of inadequate clinical results based on clinical or imaging criteria. Considering the difficult management of parenteral and inhaled prostanoids, the great majority of patients receive an oral combination therapy (ERA+PDE-5i) a few months after being diagnosed. In patients who do not reach the clinical goals, a prostanoid should be added to the regimen. This scenario may change with the advent of riociguat. Riociguat is a new oral sGC stimulator, the only in its class to have shown a significant clinical benefit in the two types of pulmonary hypertension for which treatment is currently available: PAH and chronic thromboembolic pulmonary hypertension (CTEPH).[7] In PAH patients, riociguat has proved effective both as monotherapy and in combination with an ERA, resulting in functional class improvement and reduced or delayed clinical worsening. This in turn allowed deferring the start of the next line of treatment which, although more effective, is also more expensive. The use of riociguat could therefore lead to economic savings and to improved quality of life for patients.[8] The goal of our analysis was to develop a budget impact model [9] based on real-world data in order to assess, by means of a value-based approach, the economic impact of the new therapeutic option riociguat in PAH management, from the perspective of the Italian national health service (Servizio Sanitario Nazionale, SSN).

MATERIALS AND METHODS

We used Microsoft Excel® to develop the model for calculating the budget impact. In order to provide a realistic assessment, we used data from the administrative database of the Pulmonary Hypertension Center at Policlinico Umberto I in Rome over a period of 3 years and 4 months (from December 2014 to March 2018, date when the last data extraction was performed before proceeding with the analysis), the model allowed us to evaluate direct healthcare costs in terms of resources associated with the drug treatment in patients with PAH. Furthermore, the model and all the assumptions behind it, were validated through a panel of experts at national level.

ANALYZED POPULATION

Our population included 177 patients treated at the Pulmonary Hypertension Center at Policlinico Umberto I in Rome. All patient data were retrieved from the hospital database. Data extraction showed that during the observation period, patients were treated for PAH with

specific drugs as monotherapy or combination therapy. The drugs belonged to the four therapeutic classes (ERA, PDE-5i, PCA and sGC stimulators) and are listed in **Table 1**.

Based on the drugs taken either as monotherapy or combination therapy, patients were divided into 11 macro-categories:

- ERA
- PDE-5i
- prostanoid
- riociguat
- ERA + PDE-5i
- ERA + PDE-5i + prostanoid
- ERA + PDE-5i + riociguat
- ERA + prostanoid
- ERA + riociguat
- PDE-5i + prostanoid
- prostanoid + riociguat

In the macro-categories including several drugs, they have been either administered in combination or as successive monotherapies during the observation period. **Table 2** shows the distribution of patients among the treatment categories.

Information on the kind of therapy administered (drug and strength) and the duration (start and end date) was gathered for each patient. The actual number of days of drug treatment was determined for each patient by processing the data in the database. **Table 3** shows the mean number of treatment days per patient for each of the therapeutic macro-categories.

TABLE 2
Analyzed patients

Therapeutic category	Patients (N)
ERA	38
PDE-5i	36
Prostanoid	4
Riociguat	10
ERA + PDE-5i	25
ERA + PDE-5i + prostanoid	35
ERA + PDE-5i + riociguat	1
ERA + prostanoid	7
ERA + riociguat	7
PDE-5i + prostanoid	13
Prostanoid + riociguat	1
TOTAL	**177**

COST ANALYSIS

The analysis was carried out from the perspective of the Italian healthcare system and therefore comprised only direct healthcare costs. The drugs and their strengths included in the budget impact analysis were exactly those registered in the database for each pa-

TABLE 1
Analyzed drugs

Therapeutic class	Drug	Brand name
ERA	Ambrisentan	Volibris®
	Bosentan	generic
	Macitentan	Opsumit®
PDE-5i	Sildenafil	Revatio®
		generic
	Tadalafil	Adcirca®
		generic
Prostanoid	Epoprostenol*	Flolan®
	Iloprost**	Ventavis®
	Treprostinil*	Remodulin®
Soluble guanylate cyclase stimulator	Riociguat	Adempas®

Note: * IV administration; ** inhaled.

TABLE 3
Days of treatment

Therapeutic category	Days of treatment
ERA	640
PDE-5i	643
Prostanoid	601
Riociguat	591
ERA + PDE-5i	667
ERA + PDE-5i + prostanoid	474
ERA + PDE-5i + riociguat	591
ERA + prostanoid	750
ERA + riociguat	685
PDE-5i + prostanoid	471
Prostanoid + riociguat	365

tient. The total number of medication unit doses in each package and their dosage for PAH treatment were obtained from the summaries of product characteristics (SPC) for each drug administered to patients according to the administrative database. The dosage data also allowed us to determine the total number of medication unit doses administered daily to each patient. For each drug, ex-factory prices were considered net of temporary statutory reductions (-5%) pursuant to the AIFA (Italian Medicines Agency) decision of 3 July 2006, and of a further 5% reduction pursuant to the AIFA decision of 27 September 2006. To obtain the total daily cost of drug therapies, we multiplied the unit doses/day for each drug by the cost per unit, as calculated according to ex-factory prices (source updated April 2019, software: Tunnel® by the Farmadati Italia© database) (**Table 4**).

STATISTICAL AND SENSITIVITY ANALYSIS

The budget impact model allows to create hypothetical expenditure projections by comparing the direct (healthcare) costs of scenario 1, "NO riociguat" and scenario 2, "WITH riociguat". Scenario 1 represents the current situation as registered in the database. Scenario 2 includes changes in the type of treatments administered to patients receiving the drug combination ERA + PDE-5i + PCA (N=35). In this scenario, it is assumed that patients are treated with riociguat alone or, if so prescribed, in combination with ERA, for 180 days (a hypothetical treatment with PDE-5i and/or PCA in the same period of time would be therefore discontinued). In fact it is common clinical practice to reassess patients after about 180 days in order to decide if a therapy change is needed. In the light of the RESPITE study results, 30% of the patients are expected to continue with riociguat, while 70% will add a PCA after this time.[10] After this period, in the light of the results relating to clinical worsening, 30% of these patients (N=11) continue the riociguat therapy, in combination with ERA if so prescribed, whereas the administration of PDE-5i is not resumed because the PDE-5i + riociguat combination is contraindicated. The remaining 70% of patients (N=24) go back to being treated with PCA, in combination with ERA and PDE-5i, if so prescribed (**Table 5**). The implemented spreadsheet can randomly extract these patients (N=11, 30% of patients; N=24, 70% of patients) by means of simple random sampling without repetition. This prevents potential selection biases: each individual belonging to a therapeutic category has the same probability of becoming part of the sample, which makes it possible to obtain reliable expenditure projections.

To assess the robustness of the model, we carried out a probabilistic sensitivity analysis, simulating 100 random extractions of the 30% of patients belonging to the ERA + PDE-5i + PCA therapeutic category who, after 180 days of therapy, continue treatment with riociguat (with or without ERA), and of the remaining 70% who go back to being treated with PCA (with or without ERA and PDE-5i). In the sensitivity analysis, extraction was also carried out by means of simple random sampling without repetition, as in the base case.

RESULTS

The estimated total expenditure was obtained by adding up the direct healthcare costs of drug treatment of patients in each of the two scenarios, "NO riociguat" and "WITH riociguat". First, the total cost of treatment for each patient was determined by multiplying the daily

TABLE 4
Drug cost

Therapeutic category	Drug	Brand name	Strength	Units per package	Units/day	Ex-factory price	Cost per unit	Cost/day
ERA	ambrisentan	Volibris®	5 mg	30 tab	1.00	€ 2,290.55	€ 76.35	€ 76.35
			10 mg	30 tab	1.00	€ 2,290.55	€ 76.35	€ 76.35
	bosentan	generic	62.5 mg	56 tab	2.00	€ 226.61	€ 4.05	€ 8.09
			125 mg	56 tab	2.00	€ 226.61	€ 4.05	€ 8.09
	macitentan	Opsumit®	10 mg	30 tab	1.00	€ 2,572.13	€ 85.74	€ 85.74
PDE-5i	sildenafil	Revatio®	20 mg	90 tab	3.00	€ 513.90	€ 5.71	€ 17.13
		generic	20 mg	90 tab	3.00	€ 361.79	€ 4.02	€ 12.06
	tadalafil	Adcirca®	20 mg	56 tab	2.00	€ 592.84	€ 10.59	€ 21.17
		generic	20 mg	56 tab	2.00	€ 391.26	€ 6.99	€ 13.97
Prostanoid	epoprostenol*	Flolan®	1.5 mg	2 vials	2.59	€ 156.05	€ 104.03	€ 269.65
	iloprost	Ventavis®	10 mcg/mL	120 doses (30 2-mL vials)	8.00	€ 812.25	€ 6.77	€ 54.15
			20 mcg/mL	120 doses (30 2-mL vials)	8.00	€ 812.25	€ 6.77	€ 54.15
	treprostinil*	Remodulin®	2.5 mg/mL	1 20-mL vial	2.25**	€ 6,994.38	€ 139.89	€ 314.24
			5 mg/mL	1 20-mL vial	2.25**	€ 13,988.75	€ 139.89	€ 314.24
			10 mg/mL	1 20-mL vial	2.25**	€ 27,977.50	€ 139.89	€ 314.24
	treprostinil*	Remodulin®	2.5 mg/mL	1 20-mL vial	3.11**	€ 6,994.38	€ 139.89	€ 435.11
			5 mg/mL	1 20-mL vial	3.11**	€ 13,988.75	€ 139.89	€ 435.11
			10 mg/mL	1 20-mL vial	3.11**	€ 27,977.50	€ 139.89	€ 435.11
sGC	riociguat	Adempas®	0.5 mg	42 tab	3.00	€ 1,259.71	€ 29.99	€ 89.98
			1 mg	84 tab	3.00	€ 2,519.42	€ 29.99	€ 89.98
			1.5 mg	84 tab	3.00	€ 2,519.42	€ 29.99	€ 89.98
			2 mg	84 tab	3.00	€ 2,519.42	€ 29.99	€ 89.98
			2.5 mg	84 tab	3.00	€ 2,519.42	€ 29.99	€ 89.98

Note: * we considered the pharmaceutical forms used for the chronic treatment of patients; ** treprostinil posology varies depending on the time in treatment (up to 24 months: 2.25 units/day; after 24 months: 3.11 units/day).

TABLE 5
Variations in the model scenarios

Therapeutic category: ERA + PDE-5i + prostanoid
Scenario 1
ERA + PDE-5i + prostanoid
Scenario 2
for 180 days: 100% of patients: (ERA) + riociguat
after 180 days: 30% of patients: (ERA) + riociguat 70% of patients: ERA + PDE-5i + prostanoid

cost of the used drugs by the relative value of the days of therapy with those drugs. Then the total costs for each single therapeutic category were calculated by adding up the costs attributed to each patient in a specific therapeutic category. Lastly, the cumulative costs of all therapies in the two scenarios were determined by adding up those expenses. As shown in **Table 6**, the total cost for the drug treatments of the whole group of patients was € 16.175,735 in scenario 1 ("NO" riociguat) and € 14.135,664 in scenario 2 ("WITH" riociguat).

In more detail, the costs of treatment for the category of patients taking the ERA + PDE-5i + prostanoid combination were € 7.278,634 in scenario 1, and € 5.238,563 in scenario 2. This amount is the mean value given by 10 random extractions of patients. In order to obtain the total cost of therapy in the "WITH riociguat" scenario for all 35 patients, any expenses due to ERA were includ-

TABLE 6
Total costs

Therapeutic category	Patients (N)	Scenario 1 Total cost	Scenario 2 Total cost
ERA	38	€ 1,171,589	€ 1,171,589
PDE-5i	36	€ 314,364	€ 314,364
Prostanoid	4	€ 702,244	€ 702,244
Riociguat	10	€ 585,135	€ 585,135
ERA + PDE-5i	25	€ 1,252,863	€ 1,252,863
ERA + PDE-5i + prostanoid	35	**€ 7,278,634**	**€ 5,238,563**
ERA + PDE-5i + riociguat	1	€ 170,342	€ 170,342
ERA + prostanoid	7	€ 1,840,561	€ 1,840,561
ERA + riociguat	7	€ 951,845	€ 951,845
PDE-5i + prostanoid	13	€ 1,760,616	€ 1,760,616
Prostanoid + riociguat	1	€ 147,541	€ 147,541
TOTAL	**177**	**€ 16,175,735**	**€ 14,135,664**

ed in the first 180 days, and expenses related to PDE-5i were set to zero, because simultaneous administration of PDE-5i and riociguat is contraindicated; the daily cost of each type of prostanoid taken by patients in scenario 1 was substituted with the daily cost of riociguat, i.e., €89.98. For the treatment days after the first 180, the above-mentioned values were maintained for 30% of patients (N=11), while the costs related to ERA, PDE-5i and PCA were considered for the remaining 70% of the patients (N=24) who took these drugs according to the administrative database. The analysis demonstrated that in subjects with a clinical profile indicating the need for treatment optimization, the use of riociguat could bring about a significant clinical benefit that might delay the transition to the next line of treatment, resulting in a cost reduction of € 2.040,071. Such a savings corresponded to 28% of the pharmaceutical expenditure if we considered only the ERA + PDE-5i + prostanoid therapeutic category, and to 13% if we considered the total expenditure for the whole cohort of analyzed patients. (**Table 7**) It is important to underline that is a remarkable result obtained from the use of riociguat in only 35 of the 177 total patients.

RESULTS OF THE SENSITIVITY ANALYSIS

The sensitivity analysis carried out to test the robustness of the model is a probabilistic analysis. Of the 100 extractions, we considered the outcomes of 95% (N=95 extractions); we eliminated the outliers (first and last 5 values), i.e., the numerically distant values from the remaining collected data. (**Figure 1**) The total cost of drug treatment had a minimum value of € 4,822,371 and a maximum value of € 5,726,545. (**Table 8**) This shows that the outcome obtained in the base-case, € 5.238,563, is statistically included within the range determined by the probabilistic sensitivity analysis.

The sensitivity analysis results are graphically presented in the histogram in **Figure 2**, showing the frequency with which, the cost values recur within the set of total

TABLE 7
Savings

	Patients (N)	Total cost therapeutic category ERA + PDE-5i + prostanoid		Patients (N)	Total cost	
Scenario 1 ("NO" riociguat)	35	€ 7,278,634		177	€ 16,175,735	
Scenario 2 ("WITH" riociguat)	35	€ 5,238,563		177	€ 14,135,664	
Savings		**€ 2,040,071**	**-28%**		**€ 2,040,071**	**-13%**

FIGURE 1
Results of the sensitivity analysis

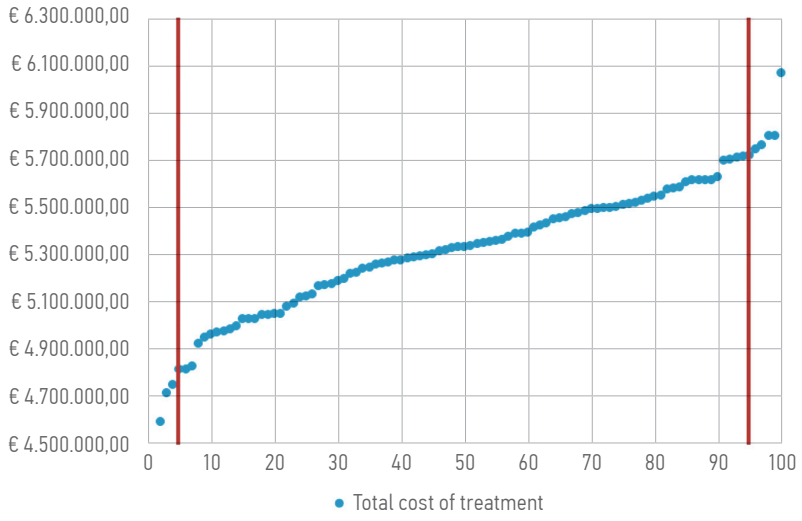


TABLE 8
Results of the sensitivity analysis

95% extractions	Min. cost	Max. cost
N=95	€ 4,822,371	€ 5,726,545

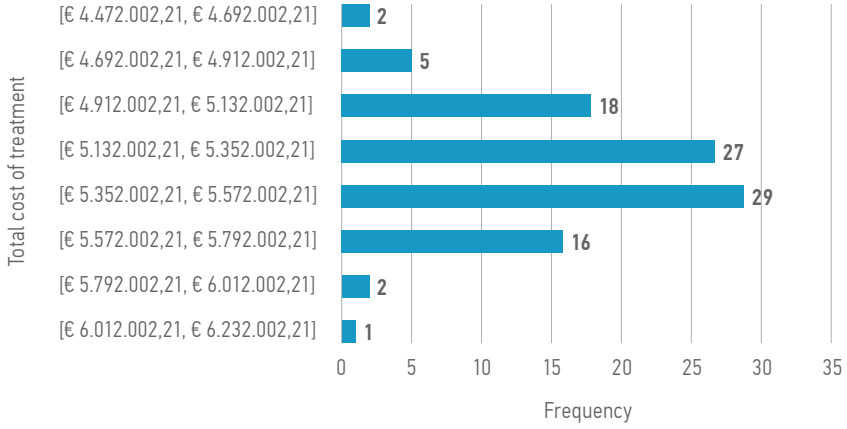
treatment costs. The range of values appearing most often (29 times) includes total treatment costs between € 5,352,002.21 and € 5,572,002.21, which is very close to the base-case result (€ 5,238,563).

DISCUSSION AND CONCLUSIONS

PAH is a rare disease with high morbidity and mortality rates. If left untreated, patients progress to worsening of the disease and to higher WHO functional classes (3 and 4), culminating in terminal right ventricular failure and death. Mean survival in untreated PAH patients is 2.8 years.[11] Riociguat, an sGC stimulator, has been shown to be effective both in PAH and in CTEPH (inoperable and persistent/recurrent after pulmonary endarterectomy).[7] As demonstrated by the PATENT 1 [12] and PATENT 2 [13] clinical studies, the use of riociguat allows to obtain significant improvement in these patients in terms of exercise capacity, both in the short and long term (2 years of treatment); quality of life; increased overall survival and clinical-worsening-free survival; and, in some cases, improvement of functional class.

The present analysis has some limitations. Firstly, it is susceptible to an intrinsic bias because the correctness of the collected data in the administrative data-

FIGURE 2
Sensitivity analysis. Frequency of occurrence of cost values in the sets of total costs for treatment



base cannot be ascertained. Secondly, it only considers costs related to drug treatments and does not include costs associated with diagnostics, visits by health practitioners, or hospitalizations. Finally, the analysis concerned a single-center study with specific management modalities. It would be interesting to extend it to other clinical situations with different organizational settings, in order to understand if our results are validated in other healthcare settings.

However, our study has an added value: it is the first economic analysis carried out in this therapeutic area on the basis of real-world data, with a value-based approach. Our study presents a picture of the use of current therapies in a real-world setting. The obtained results prove that riociguat is a cost-saving alternative for the Italian national health service, allowing to reduce or defer clinical worsening of the disease to more serious stages and in some cases allowing to delay the transition to the next lines of treatment, which are often more expensive. This creates an overall savings of € 2,040,071 within a period of 3 years and 4 months. A remarkable result due to the fact that it is given by the use of riociguat in only 35 of the 177 total patients considered in the analysis as the target population. Our budget impact analysis has shown that the use of riociguat before prostanoid drugs (parenteral or inhaled) is a sustainable alternative and can improve patients' quality of life and postpone the transition to the next line of treatment.[8] The robustness of the case-base results was confirmed by the probabilistic sensitivity analysis. In the light of the real-world data of this study, we conclude that the use of riociguat can result in a direct cost reduction at a national level from a healthcare system perspective, with a view to ensuring sustainability in the medium-long term. The estimates must, however, be considered as conservative, given that they do not include other direct healthcare costs (hospitalization, visits, etc.) nor the indirect costs burden.

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REFERENCES

1. National Pulmonary Hypertension Audit – 2012. Mar 2013. Available at: http://www.hscic.gov.uk. Accessed: Dec 2017.
2. Humbert M et al., *Pulmonary arterial hypertension in France: results from a national registry.* Am J Respir Crit Care Med 2006;173(9):1023–30.
3. Peacock AJ et al., *An epidemiological study of pulmonary arterial hypertension.* Eur Respir J 2007; 30(1):104–9.
4. Benza RL et al., *The REVEAL registry risk score calculator in patients newly diagnosed with pulmonary arterial hypertension.* Chest 2012;141(2):354–62.
5. Hoeper et al., *Definition, classification, and epidemiology of pulmonary arterial hypertension.* Semin Respir Crit Care Med. 2009 Aug;30(4):369-75. doi: 10.1055/s-0029-1233306. Epub 2009 Jul 24.
6. Galiè et al., 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS), with the support of the International Society for Heart and Lung Transplantation (ISHLT).
7. Summary of Product Characteristics of Adempas® - Riociguat. https://ec.europa.eu/health/documents/community-register/2017/20170502137814/anx_137814_en.pdf.
8. Delcroix et al., *Pulmonary arterial hypertension: the burden of disease and impact on quality of life.* European Respiratory Review Dec 2015, 24 (138) 621-629; DOI: 10.1183/16000617.0063-2015.
9. Sullivan et al., *Principles of good practice for budget impact analysis II: Report of the ISPOR Task Force on Good Research Practices – Budget Impact Analysis.* Value Health 2014:17:5-14.
10. Hoeper MM et al., *RESPITE: switching to riociguat in pulmonary arterial hypertension patients with inadequate response to phosphodiesterase-5 inhibitors.* Eur Respir J 2017; 50 (3). pii: 1602425. doi: 10.1183/13993003.02425-2016.
11. Humbert et al., *Survival in incident and prevalent cohorts of patients with pulmonary arterial hypertension.* Eur Respir J. 2010 Sep;36(3):549-55. doi: 10.1183/09031936.00057010. Epub 2010 Jun 18.
12. NCT00810693. A Study to Evaluate Efficacy and Safety of Oral BAY63-2521 in Patients with Pulmonary Arterial Hypertension (PAH) (PATENT-1). https://clinicaltrials.gov/ct2/show/NCT00810693.
13. NCT00863681. BAY63-2521: Long-term Extension Study in Patients With Pulmonary Arterial Hypertension (PATENT-2). https://clinicaltrials.gov/ct2/show/NCT00863681.

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