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Initial combination therapy for patients with pulmonary arterial hypertension (PAH): a budget impact analysis from the perspective of the Italian national healthcare system

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ABSTRACT

Background: Initial combination therapy in patients with pulmonary arterial hypertension (PAH) WHO functional class (FC) II or III has demonstrated clinical benefits over initial monotherapy. The objective of this study is to compare the financial impact of initial combination therapy with initial monotherapy for incident patients with PAH in Italy.

Methods: A 3-year budget impact model compared a 'status quo' scenario of initial monotherapy with an endothelin receptor antagonist (ERA), phosphodiesterase 5 inhibitor (PDE5i) or prostanoid, with a 'new' scenario involving initial combination therapy, using Italian national healthcare system (NHS) data for incident patients with PAH WHO FC II or III. The hospitalisation hazard ratio (HHR) from the AMBITION study and expert panel advice on therapy use were employed. Univariate sensitivity analyses were performed.

Results: A difference in costs of €16,070 favouring the 'new' scenario (initial combination therapy) was observed, and attributed to 101 fewer hospitalisations over 3 years. Sensitivity analyses showed that costs were driven by the proportion of patients receiving ERAs versus PDE5i, hospitalisation costs and prostanoid dose.

Conclusion: Initial combination therapy instead of monotherapy could reduce the number and cost of hospitalisations without an increase in the total costs to the Italian NHS.

1. Introduction

Pulmonary arterial hypertension (PAH) is an uncommon disease involving small pulmonary arteries and is characterized by vascular proliferation and remodeling. It results in a progressive increase in pulmonary vascular resistance and, ultimately, in right ventricular failure and death [1]. PAH is a rare condition for which incidence and prevalence are fairly difficult to assess, and there are no data related to Italy. Two European studies each used a reliable method to estimate the incidence and prevalence of PAH, one using the French national registry [2] and another using the linked Scottish Morbidity Record scheme [3]. The estimates of incidence were 2.4 and 7.6 cases/million population/year, respectively, while the estimates of prevalence were 15 and 26 cases/million [2,3].

Therapy with PAH-approved drugs for incident patients diagnosed with World Health Organization functional class (WHO FC) II–III PAH is appropriate for patients who are either not vasoreactive or vasoreactive but do not respond appropriately to calcium channel blockers [4]. After starting monotherapy with endothelin receptor antagonists (ERAs) or phosphodiesterase type 5 inhibitors (PDE5i), it is necessary to monitor treatment response after 3–4 months. In the case of inadequate clinical response, the addition of another PAH-approved drug that targets a separate pathological pathway is recommended [5]. Clinical response is assessed by right heart function, which is measured by a multiparametric assessment that includes clinical evaluation and invasive (right heart catheterization) and noninvasive (echocardiography and laboratory parameters) tests.

Despite the widespread use of this therapeutic approach, there are limited data in the literature, and long-term morbidity and mortality trials of add-on therapy have revealed controversial results. For example, one study showed a beneficial reduction in the time to clinical worsening after adding macitentan to a PDE5i [6], while a more recent study failed to

demonstrate a significant benefit when bosentan was added to stable patients on sildenafil therapy [7].

A recent retrospective chart review of Japanese patients [8] with idiopathic/heritable pulmonary arterial hypertension showed that survival of patients with PAH improved after progress in the use of PAH-targeted drugs, although the results continued to be unsatisfactory, while the Japan Pulmonary Hypertension Registry[9] analyzed treatments and outcomes in patients received PAH-specific therapy showing that initial upfront combination therapy appears to have an advantage in the treatment of PAH. This therapy was associated with improvement in hemodynamic status at first follow-up, similar to the AMBITION trial.

AMBITION (AMBrIsentan and Tadalafil in patients with pulmonary arterial hypertensION; ClinicalTrials.gov identifier: NCT01178073) was the first randomized controlled trial designed to assess the time to clinical failure with first-line (initial) combination therapy of ambrisentan and tadalafil versus monotherapy in treatment naive [10,11].

The study randomized patients with PAH (N = 500; WHO FC II or III) in a 2:1:1 ratio to initial combination therapy with ambrisentan 10 mg plus tadalafil 40 mg, ambrisentan 10 mg, or tadalafil 40 mg. The primary end point was the time to clinical failure, defined as the time from randomization to the first occurrence of death (all cause), hospitalization for worsening PAH (any hospitalization for worsening PAH, lung or heart and lung transplantation, atrial septostomy, or initiation of parenteral prostanoid therapy), disease progression, or unsatisfactory long-term clinical response. Combination therapy significantly reduced the risk of clinical failure by 50% compared with the pooled monotherapy groups (ambrisentan or tadalafil). Initial combination of ambrisentan plus tadalafil also outperformed pooled monotherapy on the primary end point across a variety of subgroups [10]. Statistically significant improvements from baseline at 24 weeks were also observed in the combination therapy group compared with the pooled monotherapy groups for the secondary end points: 6-min walk distance, N-terminal pro-B-type natriuretic peptide levels, and the proportion of patients with satisfactory clinical response, although no significant changes in WHO FC were observed. The adverse events that occurred more frequently in the combination-therapy group than in either monotherapy group included peripheral edema, headache, nasal congestion, and anemia. The rate of adverse events leading to discontinuation of study drug and the rate of serious adverse events (SAEs) were similar in the three study groups [10].

In order to understand the economic impact of this combination therapy and its sustainability, a budget impact analysis (BIA) was conducted. The BIA is a tool to predict the potential financial impact of the adoption and implementation of a new technology or product into a health-care system over a short–medium-term period (generally between 3 and 5 years). The aim of this study was to perform a BIA to compare initial combination therapy options with current monotherapy options in incident patients with PAH as initial strategy. The analysis was conducted using data from the perspective of Italian national health-care service (NHS) (Servizio Sanitario Nazionale [SSN]) and takes into account the direct health-

care costs incurred as a result of PAH disease in a specific population of patients (WHO FC II or III). The time horizon of the analysis was 3 years.

2. Materials and methods

2.1. Model

A budget impact model developed by GlaxoSmithKline was adapted for use with Italian health-care data to assess the economic impact of initial combination therapy versus monotherapy in patients with PAH WHO FC II or III. The model included the following monotherapy options: ERA (ambrisentan or bosentan), PDE5i (sildenafil or tadalafil), and prostanoid (epoprostenol). In addition, the following combination therapies were evaluated: ambrisentan plus tadalafil, ambrisentan plus sildenafil, bosentan plus tadalafil, bosentan plus sildenafil, macitentan plus tadalafil, and macitentan plus sildenafil. The analysis compared a 'status quo' scenario where incident patients received monotherapy as the initial therapy, with a 'new' scenario where an increasing proportion of incident patients would receive combination therapy as initial therapy. The economic impact of this change in terms of therapy and hospitalization costs was assessed over a 3-year period utilizing the hospitalization due to worsening of PAH event rate observed in the AMBITION study [10].

2.2. Population and treatments

Incident patients with PAH WHO FC II or III in Italy were included in the model. Given the lack of Italian incidence data, the incidence of PAH was estimated from the French national registry (2.4 cases/million population/year) [2] and the Scottish registry (7.6 cases/million population/year) [3]. Based on a weighted average of these data, we assumed a baseline incidence of 4.25 cases/million population/year. In addition, the French registry provided data on the proportion of patients in WHO FC II (24%) and III (63%) among the overall PAH population [2]. Considering the total Italian population in 2015, the national institution of statistics ISTAT (Istituto Nazionale di Statistica) projections for the years 2016 and 2017 [12], the incidence rate from the two registries, and the proportion of patients in WHO FC II and III, the eligible incident cases were estimated to be 225 in 2015, 228 in 2016, and 228 in 2017 (Table 1).

In the 'status quo' scenario at baseline, incident patients could receive only monotherapy (a PDE5i, an ERA, or a prostanoid). This assumption was based on the results of a panel of seven Italian experts in the treatment of PAH

Table 1. Estimated number of incident patients with pulmonary arterial hypertension (PAH) World Health Organization functional class (WHO FC) II or III in Italy.

	2015	2016	2017
Total Italian population (*n*)	60,795,612	61,565,556	61,669,462
Incidence of PAH (%)	0.000425	0.000425	0.000425
Proportion of patients with WHO FC II or III PAH (%)	87	87	87
Incident patients with WHO FC II or III PAH (*n*)	**225**	**228**	**228**

Table 2. Assumptions on market share and percentage of patients receiving monotherapy and combination therapy in the 'status quo' and 'new' scenarios.

'Status quo' scenario and 'new' scenario		Source
Market share among monotherapy options	Proportion of patients (%)	
PDE5i monotherapy	34.4 (minimum 20; maximum 50)	Expert panel
ERA monotherapy	60.6 (minimum 47.5; maximum 75)	Expert panel
Prostanoids	5 (minimum 0; maximum 5)	Expert panel
Market share in PDE5i		
Sildenafil	87.7	Expert panel
Tadalafil	13.3	Expert panel
Market share in ERAs		
Bosentan	78.5	Expert panel
Ambrisentan	21.5	Expert panel
Market share in prostanoids		
Treprostinil	70	Assumption
Epoprostenol	30	Assumption
'Status quo' scenario		
Patients starting with combination therapy as initial therapy	0	Expert panel
Patients switching to combination therapy after monotherapy failure	31 (at 6 months), 17 (at 12 months), 7 (at 18 months), 7 (at 24 months), 5 (at 30 months), 5 (at 36 months)	AMBITION study (8)
Market share for combination therapy in the 'status quo' scenario		
Bosentan plus sildenafil	66.25	Expert panel
Ambrisentan plus sildenafil	17.46	Expert panel
Bosentan plus tadalafil	9.82	Expert panel
Ambrisentan plus tadalafil	3.97	Expert panel
Macitentan plus sildenafil	2.00	Expert panel
Macitentan plus tadalafil	0.50	Expert panel
'New' scenario		
Patients starting with combination therapy as initial therapy	52 (at 6 months), 56 (at 12 months), 60 (at 18 months), 64 (at 24 months), 100 (at 30 months), 100 (at 36 months)	Experts' opinion and assumption
Market share for combination therapy in 'new' scenario		
Bosentan plus sildenafil	20.83	Expert panel
Ambrisentan plus tadalafil	79.17	Expert panel

ERA: endothelin receptor antagonist; PDE5i: phosphodiesterase type 5 inhibitor.

(coauthors of this article: CA, RC, MD, SG, MM, PV, and CDV). An average of the values provided by these experts was calculated in order to populate a number of the model parameters. It was estimated, on average, that in the Italian setting approximately 34% of incident patients are treated with PDE5i monotherapy, 60% with ERA monotherapy, and 5% with prostanoids (Table 2). Similarly, the experts provided the proportion of patients receiving specific medications within each drug class (for example, sildenafil or tadalafil as a PDE5i). It was assumed that after 6 months of treatment, only the patients in whom monotherapy did not confer an adequate clinical response would receive another drug therapy in an add-on approach. Similarly, in the 'new' scenario, a percentage of incident patients was assumed to start with each combination therapy based on the information provided by the panel of experts. In the third year, it was assumed that all patients in the 'new' scenario would enter the model receiving combination therapy as the initial option. The market share assumptions for each drug class (averages and assumptions as provided by the expert panel) are shown in Table 2.

2.3. Efficacy data

The analysis focused on the relative difference in hospitalization rate between combination therapy and monotherapy (both as initial therapy). The probability of hospitalization for patients receiving monotherapy was based on data from the AMBITION study at 6, 12, 18, and 24 months and thereafter assumed to be 2% for the following year. The hospitalization hazard ratio (HHR) for worsening PAH for patients starting on initial combination therapy versus monotherapy was also based on AMBITION study data: HHR was calculated at 0.372. No attempt was made to undertake an indirect comparison between combination options, and the HHR from the AMBITION study (for ambrisentan plus tadalafil compared with pooled ambrisentan and tadalafil monotherapy) was applied for any combination options versus monotherapies. The rates of hospitalization for any cause (calculated with the use of information from the SAE and adjudication data sets) did not differ significantly among the groups. The probability of death at 6, 12, 18, and 24 months was also based on the AMBITION study data and assumed to be the same for monotherapy and combination therapy; data for 30 and 36 months were derived from the

Table 3. Efficacy data included in the model.

Time point (months)	Monotherapy failure rate (%)	Hospitalization rate (%)	Death rate (%)
6	31	29.69	5.75
12	17	8.55	13.87
18	7	2.02	21.08
24	7	2.23	27.83
30	5	2	34.83
36	5	2	41.83

Data taken from AMBITION trial [8].

British National Audit of Pulmonary Hypertension (2013) [13]. This study also provided the monotherapy failure rate for each 6-month period. Details of all efficacy data included in the model are presented in Table 3.

2.4. Cost data

The following categories of costs were considered:

- Acquisition costs for PDE5i, ERAs, and prostanoids
- Costs of devices for infusion of prostanoids
- Direct medical costs of visits to professionals (general practitioners and specialists)
- Hospitalization costs.

Annual drug costs were based on the maximum price for the Italian NHS. For prostanoids, the costs of the devices used for infusions were added to the final drug costs. In the case of a patient in WHO FC III or IV with worsening disease, the choice of epoprostenol has been assumed because epoprostenol is considered as the gold-standard drug [14]; conversely, in the case that treprostinil is employed instead of epoprostenol, this should be taken into account in the cost estimate, where the cost related to the higher dosage of treprostinil (and therefore increased amount of drug required) should be weighted.

The costs of health-care specialist visits were estimated on the basis of the experts' opinions, with the aim of being representative of Italian real-world clinical practice and to reflect the 'new' scenario considering the European Society of Cardiology/European Respiratory Society Guidelines on PAH [5]. Unit costs for professional visits were taken from official national tariffs [13]. Hospitalization costs included a hospital stay for PAH (Diagnosis-Related Group [DRG 127]; cardiac insufficiency), right heart catheterization, echocardiogram (1.5 per patient; experts' opinion), and intensive care unit (ICU) stay (for 10% of patients; experts' opinion). Unit costs for hospitalizations were also taken from official national tariffs [15], except for ICU costs, which were taken from a previously published study [16]. Details of all costs included in the analysis and their sources are given in Table 4.

3. Results

3.1. Base case results

Evaluation of the costs of the two scenarios revealed that the cost of initial combination therapy is slightly lower than that of monotherapy, since the higher cost associated with drug treatment is balanced mainly by a reduction in hospitalization

Table 4. Cost items included in the model.

Drug acquisition cost	Annual cost (€)	Source
Sildenafil	4968	Price for NHS
Tadalafil	6088	Price for NHS
Bosentan	28,735	Price for NHS
Ambrisentan	27,075	Price for NHS
Macitentan	28,705	Price for NHS
Epoprostenol	247,609.20	Flolan® (0.5 + 1.5 mg) 45 ng/kg/min
Administration devices for prostanoids	15,514.60	Manufacturer

Other costs		Source
Specialist visits (cost per visit, €)	20.66	Gazzetta Ufficiale (2013 [15])
No. of specialist visits	6.5	Experts' opinion
Cost per hospitalization, €	4979	This includes hospitalization due to cardiac insufficiency (DRG 127), the cost of catheterization, the cost of ECG (1.5 per patient), and the cost of ICU (for 10% of patients) [15]

DRG: Diagnosis-Related Group; ECG: echocardiogram; ICU: intensive care unit; NHS: national health-care system.

costs. Over a 3-year period, the overall cost of therapy in the 'status quo' scenario is €34,558,222, while the cost in the 'new' scenario is lower (€34,542,152; Figure 1).

The use of initial combination therapies reduced the number of hospitalizations, thereby reducing the overall costs by approximately €0.5 million over 3 years (€767,348 vs. €1,282,659; Figure 2).

In particular, when comparing the number of hospitalized patients in the 'status quo' scenario with the number in the 'new' scenario, there would be a decrease from 71 to 52 in the first year, from 86 to 62 in the second year, and from 92 to 34
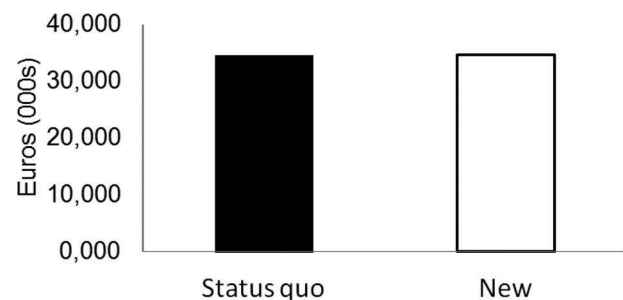

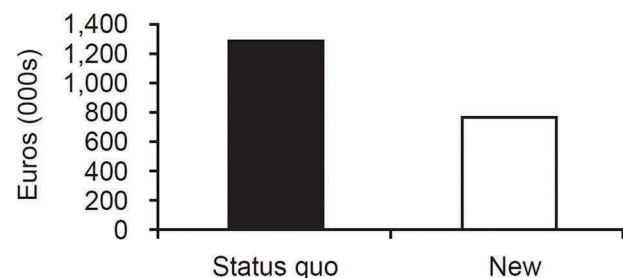**Figure 1.** Total cost in € over 3 years. 'Status quo': €34,558,222; 'new' scenario: €34,542,152.

Figure 2. Total hospital cost over 3 years. 'Status quo': € 1,282,659; 'new' scenario: € 767,348.

in the third year (when all patients in the 'new' scenario would receive combination treatment as initial therapy). This equates to a total of 101 hospitalizations avoided over 3 years.

3.2. Sensitivity analyses

Given the uncertainty associated with some of the data used in this model, univariate sensitivity analyses were conducted on selected key parameters. Specifically, the following alternative scenarios were examined:

- Change in the proportion of patients receiving initial combination therapy in the 'new' scenario (up to 100%; highest possible assumption)
- Change in the number of patients that initiate therapy with either ERAs or PDE5i
- Change in the cost of hospitalization
- Change in HHR for initial combination therapy versus monotherapy
- Change in the doses of epoprostenol (Flolan®)

In the situation where it was assumed that all patients in the 'new' scenario receive combination therapy as initial therapy (while no changes were made for the 'status quo' situation), there was an increase in the cost of the therapy for the 'new' scenario, but there was a simultaneous decrease due to reduced hospitalizations. Over the 3-year time period of the analysis, the cost of the 'new' scenario was €33,730,594 versus €33,003,677 in the 'status quo' scenario, whereas hospitalization costs were €477,157 versus €1,282,680, respectively. The total cost of the 'new' scenario was €34,479,629 versus €34,558,222 for the 'status quo' scenario. The reduction in the number of hospitalizations over 3 years was 157 (92 versus 249 in the 'new' and 'status quo' scenarios, respectively).

Results of the evaluated models were highly sensitive to the changes in the percentage of patients who received ERAs versus PDE5i in the 'status quo' scenario at baseline. We varied these percentages considering the maximum and minimum values suggested by the expert panel, namely 47.5% ERAs, 47.5% PDE5i (A) or 75% ERAs, 20% PDE5i (B) (prostanoids were considered fixed at 5% as recommended by the experts). Based on the first option (A), the 'new' scenario led to overall increased costs of approximately €1.4 million, while for option B, the 'new' scenario was cheaper than the 'status quo', leading to savings of more than €1.5 million. The reason for these differing financial impacts is the much higher cost of ERAs compared with PDE5i; patients taking ERA monotherapy at baseline already incur costs between €27k and €29k per year and the addition of a PDE5i to the existing treatment in these patients does not substantially increase drug costs but reduces both the number of hospitalizations and associated costs. Conversely, the addition of an ERA to a PDE5i is relatively expensive, and the reduction in hospitalizations does not compensate for this increase in treatment costs (Table 5).

The cost of hospitalization also has an impact on the results of this model. Clearly, as the cost per hospitalized patient increases, savings with the 'new' scenario increase, as fewer

Table 5. Results of sensitivity analysis (patients that start with endothelin receptor antagonist [ERA] or phosphodiesterase type 5 inhibitor [PDE5i]).

Case	% of Patients with ERA	% of Patients with PDE5i	Δ New situation vs. status quo[a]
Base case	34.4	60.6	−€16,070
Option A	47.5	47.5	€1,387,608
Option B	75	20	−€1,552,312

[a]Status quo = €34,558,222.

Table 6. Results of sensitivity analyses.

	Status quo (€)	New scenario (€)	Difference (€)
Base case	34,558,222	34,542,152	**−16,070**
100% patients receiving initial combination therapy in the 'new' scenario	34,558,222	34,479,629	**−78,593**
75% ERAs and 20% PDE5i at baseline in the 'status quo' scenario	36,771,691	35,219,380	**−1,552,312**
47.5% ERAs and 47.5% PDE5i at baseline in the 'status quo' scenario	32,535,754	33,923,362	**1,387,608**
Hospitalization cost doubled	35,840,881	35,309,500	**−531,381**
HHR 0.217	34,558,222	34,414,965	**−143,257**
HHR 0.639	33,558,222	34,761,241	**203,019**
Epoprostenol (40 ng/kg/min)	33,646,771	34,263,583	**616,812**
Epoprostenol (50 ng/kg/min)	35,469,675	34,820,721	**−648,954**

ERA: endothelin receptor antagonist; HHR: hospitalization hazard ratio; PDE5i: phosphodiesterase type 5 inhibitor.

patients are hospitalized compared with the 'status quo' scenario. In the base case, the cost of hospitalization was calculated according to the DRG 127 (cardiac insufficiency) tariff, which may underestimate the overall cost of hospitalization of patients with PAH. If the cost of the hospitalization was doubled, the difference between the two scenarios for all patients would increase substantially, to €531,831 over 3 years. Also, changing the HHR for combination versus monotherapy according to the 95% confidence interval found in the AMBITION trial (0.217–0.639; HHR, 0.372) would mean that the increase in total costs for the 'new' scenario option *for all patients* would vary between €427,406 and €773,682.

Finally, assuming that a patient of 70 kg receives greater or smaller doses of epoprostenol (Flolan®) [17–19] with respect to the base case (40 or 50 ng/kg/min), this would lead to a difference in costs over 3 years for the 'new' scenario versus the 'status quo' for all patients of €616,812 for the higher dose and of −€648, 954 for the lower dose. Results of the sensitivity analyses are detailed in Table 6.

4. Discussion

This analysis has shown that using initial combination therapy of ambrisentan and tadalafil for an increasing percentage of incident patients instead of monotherapy (either with ERAs or with PDE5i) would lead to a slight decrease in the total costs to the Italian NHS (a decrease of €16,070) and would lead to a substantial reduction in hospitalizations (101 out of 249 cases avoided, −40.5%). These results are based on the assumption that the HHR determined in the AMBITION study [10] can be applied to all combination options versus monotherapy. The AMBITION study was not set up to evaluate the risk predictor,

so it is not possible to address this point and there are no other studies using upfront combination therapy.

The results are sensitive to changes in the proportion of patients starting with ERAs versus PDE5i as initial monotherapy at baseline in the 'status quo' scenario. For example, varying the proportion of patients starting with ERAs according to the minimum and maximum values suggested by the clinical experts who participated in this study led to differences in costs in favor or against the 'new' scenario ranging from −€1.5 to €1.4 million. Similarly, the cost of hospitalization has an impact on the results of the model. In the base case, the cost of a hospitalization due to PAH was set at €4979 on the basis of DRG tariffs and other assumptions. However, the experts suggested that this value might not represent the real cost of patients hospitalized with PAH, which may be much higher than this.

Some important limitations of this analysis should be acknowledged. First, there was no attempt to compare combinations of therapies (ambrisentan plus tadalafil/sildenafil, bosentan plus tadalafil/sildenafil, or macitentan plus tadalafil/sildenafil) because of the lack of head-to-head studies and the difficulty in comparing studies that used different outcome measures. Therefore, the clinical benefits in terms of reduction of hospitalizations for ambrisentan plus tadalafil versus either ambrisentan or tadalafil alone were assumed to be the same for the other combination options compared with other monotherapy options. However, in the base case, it was assumed that 70% of patients would receive ambrisentan plus tadalafil as the initial combination option, and for these patients, the data are supported by the AMBITION study findings, the only randomized clinical trial that evaluated the upfront therapy with ambrisentan plus tadalafil versus the ambrisentan and tadalafil monotherapy [10]. The use of a single clinical trial for most clinical inputs might be also seen as a potential issue of the analysis. When further data become available regarding the other combinations, this analysis should be performed using the specific values for those combinations. A second limitation of the present study is that it did not reflect the real data of PAH-active drugs usage but the 'expert opinion'. Nevertheless, the BIA may be calculated on a hypothetic model. Another limitation of the analysis is the lack of Italian data on the incidence of PAH. It was necessary to rely on two European registries [2,3] and apply an average of those to the Italian population. However, the number of incident patients arising from this calculation was deemed valid by the expert panel. Similarly, owing to the lack of published data, most estimates of the percentage of incident patients receiving each treatment were based on the experts' opinions, which are likely to be representative of Italian real-world clinical practice. Unit costs were obtained from standard Italian tariffs, but the hospitalization cost for PAH remains uncertain and may have been underestimated in the base case. Furthermore, the model did not evaluate the costs of adverse events due to PAH therapies, including those that resulted in hospitalization, which could minimize the cost difference between the two scenarios. SAE rates, which include hospitalizations for adverse events (AEs), were similar between the combination group (36%), the ambrisentan group (36%), and tadalafil (41%) group. The most common SAEs were worsening pulmonary hypertension (4% combination; 9% ambrisentan; and 7% tadalafil) and pneumonia (4% combination; 6% ambrisentan; and 3% tadalafil). It should be

highlighted that the observed difference in hospitalization between the combination therapy group and the pooled monotherapy group (4% vs. 12%) is related to the hospitalization for worsening PAH. The proportion of patients with any 'hospitalization for worsening PAH' is 8% and 18% [8]. In a *post hoc* analysis, all-cause hospitalization (hospitalization due to worsening PAH or SAE hospitalization) was experienced by 37% of combination patients and 43% of monotherapy patients [10].

Data on market share were not taken from real data on consumption but came from an experts' panel which covers a large sample of patients currently treated for PAH in Italy. We think this might be more representative of the Italian current practice and potential future changes.

Finally, the model did not include the cost of right heart catheterization for those patients who switch from monotherapy to combination therapy, as recommended by new guidelines [5] and as is already being carried out in specialist PAH centers in Italy. Had these costs been included, the differences in total costs between the two scenarios would be increased as more patients switch from monotherapy to combination therapy in the 'status quo' scenario compared with the 'new' scenario.

5. Conclusion

According to the results of this budget impact model, the use of combination therapy instead of monotherapy as initial therapy for incident patients with WHO FC II and III PAH is likely to substantially reduce the costs of hospitalizations without an increase in the total costs to the Italian NHS (SSN).

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Declaration of interest

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