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Assessment of the clinical and economic impact of delayed sotatercept initiation as add-on to background therapy in adult patients with symptomatic pulmonary arterial hypertension in Italy

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INTRODUCTION

Pulmonary Arterial Hypertension (PAH) is a rare and progressive disease associated with high morbidity and mortality [1] affecting an estimated 2,100-3,500 individuals in Italy [2]. The phase 3 STELLAR trial evaluated the efficacy of sotatercept added to background therapy (BGT) versus placebo plus BGT, where BGT included combinations of Endothelin Receptor Antagonists (ERA), Phosphodiesterase-5 Inhibitors (PDE-5i), soluble Guanylate Cyclase stimulators (sGC stimulators), prostacyclin analogues (PGI2 analogues), and prostacyclin receptor agonists (PGI2 receptor agonists).

OBJECTIVES

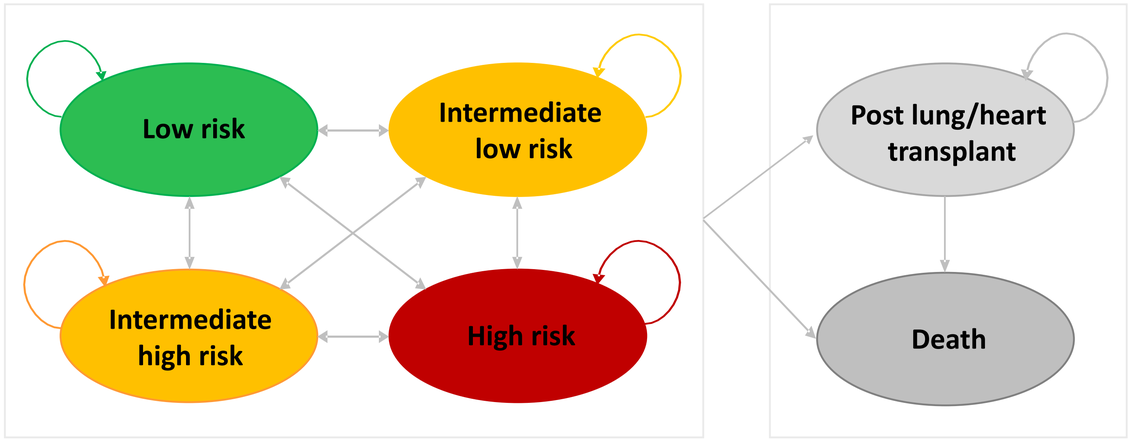
This study aimed to compare life-years (LYs), quality-adjusted life-years (QALYs), disability-adjusted life-years (DALYs), and clinical events, including hospitalizations, transplants, and deaths over a 30-year horizon across three treatment strategies:

- BGT alone;
- immediate initiation of sotatercept as an add-on to BGT;
- delayed initiation of sotatercept, defined as BGT alone for the first 2 years followed by the addition of sotatercept.

METHODS

The analysis was conducted over a 30-year time horizon. The analysis was based on a previously published six-state Markov model [1] to simulate disease progression in a hypothetical cohort of symptomatic PAH patients eligible for treatment with sotatercept in combination with BGT in Italy. The model included four risk strata (low, intermediate-low, intermediate-high and high risk), one related to the post-lung/heart transplant state and one related to death (Figure 1). The cohort included 2,000 patients, estimated by applying the proportion of patients in WHO functional classes II and III (57.2%) [2] to the upper estimate of the prevalent PAH population in Italy (3,500 patients) [3].

Figure 1: Model structure



Transition probabilities and utilities associated with each health state were derived from analyses of STELLAR trial data [4], while risk-stratified mortality, hospitalization and transplant inputs were obtained from COMPERA [5]. Transition probabilities observed between weeks 12 and 24 were assumed to remain constant beyond week 24. Regarding the estimation of DALYs, Years of Life Lost (YLL) due to premature death were estimated by applying age- and sex-specific remaining life expectancy (ISTAT 2024 [6]) to deaths in each cycle. Years Lived with Disability (YLD) were estimated by multiplying the number of patients in each living health state, including the post-transplant state, by the duration spent in that state and the corresponding disability weight. DALYs were calculated as the sum of YLL and YLD. Following the approach adopted by Leary et al. [7] in the Global Burden of Disease (GBD) analysis of PAH, heart failure disability weights from the GBD 2013 study, reported by Salomon et al. (2015) [8], were used as proxies for the disability associated with different levels of PAH severity. Mild, moderate and severe heart failure weights were applied to the low-risk, both intermediate-risk and high-risk strata, respectively, reflecting the association between PAH progression and right heart failure. A separate disability weight from the literature [9] was assumed for the post-transplant state. All outcomes were discounted at 3% annually.

RESULTS

Considering a cohort of 2,000 patients eligible for treatment with sotatercept over a 30-year horizon, the immediate initiation of sotatercept as an add-on to BGT compared with BGT alone was associated with 23,035 additional LYs, 22,290 additional QALYs and 41,161 fewer DALYs (corresponding to 11.5 additional LYs, 11.1 additional QALYs and 20.6 fewer DALYs per patient). When sotatercept initiation was delayed by two years, these benefits were reduced: compared with immediate initiation, delayed initiation was associated with 8,286 fewer LYs, 8,426 fewer QALYs and 15,253 additional DALYs (corresponding to 4.1 fewer LYs, 4.2 fewer QALYs and 7.6 additional DALYs per patient) (Figures 2 and 3).

Figure 2: Cumulative discounted DALYs by treatment strategy

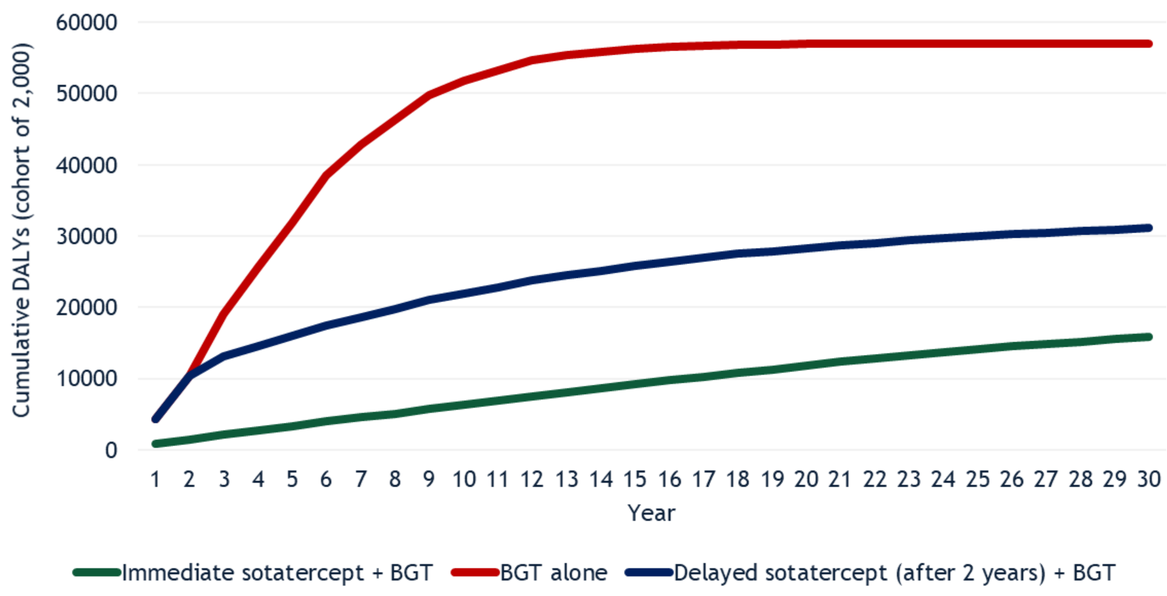
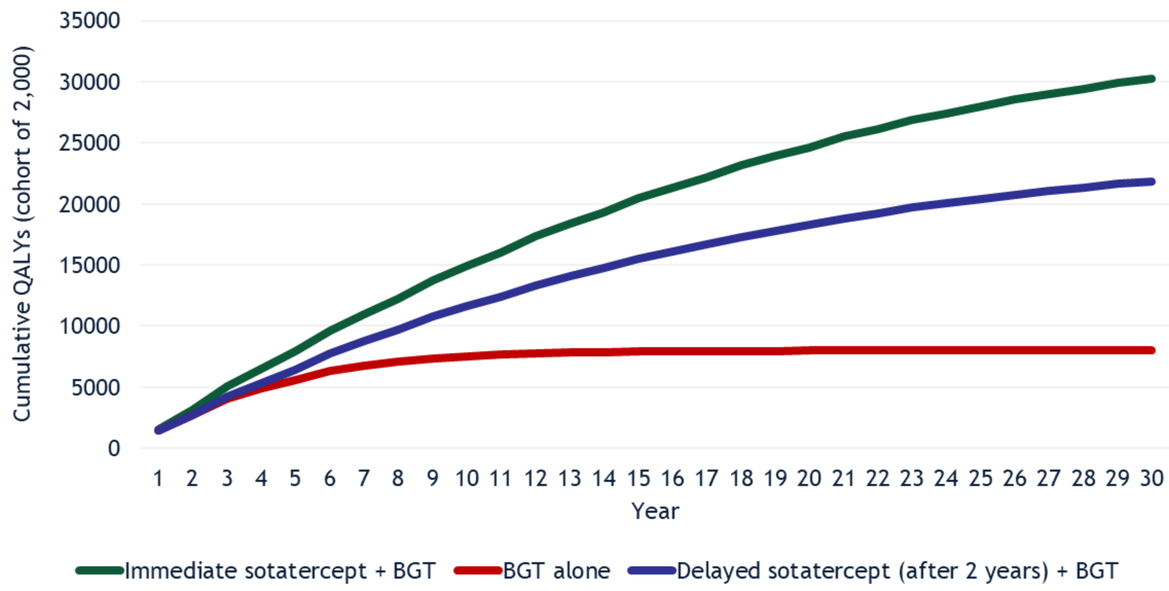
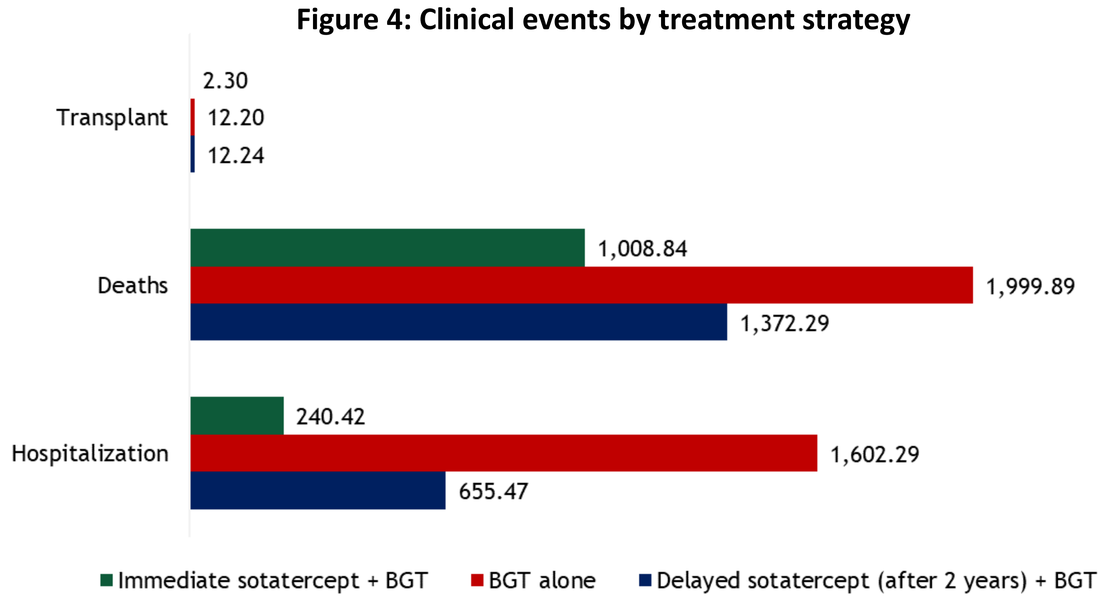


Figure 3: Cumulative discounted QALYs by treatment strategy



Also, in terms of clinical events, a two-year delay in initiation of sotatercept reduced the benefits associated with treatment compared with immediate initiation. Indeed, on a cohort of 2,000 patients, delayed initiation compared with immediate initiation resulted in 415 additional hospitalizations, 10 additional transplants, and 363 additional deaths (Figure 4).

Figure 4: Clinical events by treatment strategy



Compared with BGT alone, the delayed-treatment arm showed a slightly higher number of transplants, mainly because more patients remain alive for longer.

CONCLUSION

Early initiation of sotatercept in combination with BGT in adult patients with symptomatic PAH could reduce the overall burden of the disease. Compared with a two-year delay in initiation and BGT alone, immediate treatment was associated with increased LYs and QALYs and reduced DALYs, hospitalizations and deaths.

These findings should be interpreted in light of the model assumptions: transitions observed during weeks 12–24 were extrapolated beyond week 24, and long-term outcomes were strongly influenced by the assumed mortality benefit of sotatercept (HR: 0.25). Additional limitations include the use of heart failure disability weights as proxies for PAH in absence of specific data, and a background-therapy mix derived from STELLAR even though it was adjusted to exclude treatments not used in Italian clinical practice.

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