Minimizing Burden of Disease-Related Hospitalization Among Pulmonary Arterial Hypertension Patients

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BACKGROUND

- Pulmonary-arterial hypertension (PAH) is a rare, debilitating, and progressive disease that eventually leads to right heart failure and death.
- There is no cure for PAH, but therapies are available to slow disease progression, decrease hospitalizations, improve exercise capacity, functional status, and hemodynamics.
- Hospitalization is often required to manage PAH-related morbidity events, and is recognized as associated with clinical worsening, including increased mortality.
- Macitentan, an endothelin-receptor antagonist (ERA), has demonstrated effectiveness in decreasing PAH-related morbidity (hospitalizations), and is among guideline-recommended therapies. Evidence from the SERAPHIN trial shows that macitentan (10mg) reduced PAH-related hospitalizations for both incident and prevalent patients, even when adjusting for WHO functional class.
- In real world clinical practice, macitentan may be used across a broad range of patients, including previously untreated patients as well as patients on background therapy (with PDE-5is and/or inhaled prostanoids).
- Currently, the differential cost and incremental health impact of PAH management when including macitentan vs not including macitentan is unknown.

OBJECTIVE

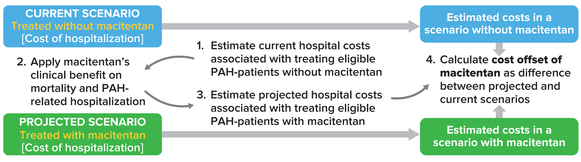
- The purpose of this study is to estimate the burden of hospitalization for patients with PAH from a U.S. payer perspective, and to identify event and cost savings associated with treatment using macitentan versus placebo.

METHODS

Model Approach

- A decision tree model structure was used to estimate PAH-related hospitalizations and costs associated with use of macitentan or placebo in a hypothetical 10 million person population over one to three years from a third party payer perspective.
  - The model estimated the cost offsets associated with macitentan through a comparative cost determination framework (**Figure 1**)
  - The patients with placebo are allowed to have background therapy (with PDE-5is and/or inhaled prostanoids) in the base case
- The base case includes all PAH patients who might be treated with an ERA, as in the SERAPHIN trial; no distinction is made regarding background therapy, functional class, etc.
- The model also examines outcomes associated with macitentan in six patient subgroups, including:
  - Patients with no background therapy;
  - Patients with background therapy;
  - Patients in WHO functional class II (FC II);
  - Patients in WHO functional class III (FC III);
  - Prevalent patients; and
  - Incident patients.

Figure 1: Comparative cost determination framework



Data Sources

- Published data were used to inform the incidence and prevalence of PAH (**Figure 2** provides the patient population cascade), as well as unit costs per hospitalization (**Table 1**).
- Published SERAPHIN trial data (**Table 2**) informed placebo mortality and PAH-related hospitalization rates for placebo and macitentan 10mg (overall population), as well as hazard ratios (HR) for decreasing hospitalization and mortality in discrete trial subgroups: incident (HR: 0.40), prevalent (HR: 0.47), macitentan monotherapy (HR: 0.45), combination therapy (HR: 0.62), and WHO functional classes II and III (HRs: 0.58, 0.49).

Figure 2: Year 1 base case patient population cascade

A hypothetical plan cohort	10,000,000 members	
% Adults (18+)	77.3%[1]	7,730,000 people
PAH prevalence (per million)	93[2]	719 patients
PAH incidence (per million)	2.3[3]	18 patients
Total eligible patients		737 patients

- The base case cohort includes incident (e.g. newly diagnosed in the current year) and prevalent (e.g. previously diagnosed) PAH patients, as both are targeted eligible patients for macitentan.
- Based on the calculated number of eligible patients, the model estimates deaths over the year by incorporating all-cause mortality data from the SERAPHIN trial (i.e. closed cohort model) and assuming that deaths occur halfway through the year on average; this ensures that costs accrue appropriately only for the surviving cohort.

Table 1. Key cost inputs in the model

	Value
Cost per hospitalization case	$53,679[4]
Length of stay (LOS) for placebo	14.20[4]
Length of stay (LOS) for macitentan	6.70[5]

- The hospitalization cost per case is derived from a published US claim database analysis[4] which stratified hospitalization among PAH patients by overall cases, initial hospitalization and subsequent readmissions.
  - For this model, the hospitalization cost across overall admissions is utilized as it permits tractable modeling while reflecting the differential from both types of hospitalizations.
- LOS data for patients with placebo is obtained from Burke 2015[4], in which the value aligns with a principal diagnosis of PH (ICD-9-CM 416.0 or 416.8).
- The default LOS for macitentan patients is calculated by applying a relative reduction in LOS associated with macitentan (52.8%)[5] to the baseline LOS for placebo.

Table 2. Hazard ratios for macitentan treatment, by patient group

Patient group	Mortality or Hospitalization HR
Base case patients[6]	0.64*
Background Tx[7]	0.62
No background Tx[7]	0.45
WHO FCII[8]	0.58
WHO FCIII[8]	0.49
Incident[9]	0.40
Prevalent[9]	0.47

*Notes: * Mortality HR only*

- The model assumes constant annual all-cause mortality (2.6%[6]) and PAH-related hospitalization probability (19.43%[6]) for patients receiving placebo across all subgroups.
- For patients receiving macitentan, hazard ratios by patient group (HR) for the morbidity/mortality combined endpoint are applied to placebo rates to calculate death and PAH-related hospitalization rates associated with macitentan.
  - The model assumes macitentan will have the same relative impact on mortality and on PAH-related hospitalization (morbidity) as on morbidity/mortality combined; hospitalization helped drive the morbidity portion of the combined endpoint
- In the base case, the default hospitalization rate (10.2/100 patient-years) for the macitentan arm is derived directly from Channick 2015[5]; no HR is needed for this population.

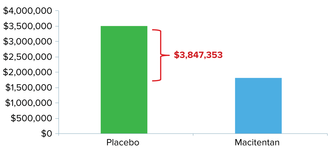
RESULTS

- Base case (**Table 3**):
  - In a hypothetical plan of 10 million covered lives, an estimated 737 PAH cases would be eligible for treatment with macitentan in year 1, growing to 754 and 772 in years 2 and 3, respectively.
  - Of 737 patients, if untreated by macitentan (placebo group ± background therapy in SERAPHIN), the burden of hospitalization would be 143 events within a year at a cost of nearly $8 million. Over 3 years, a sum of 429 hospitalizations would have occurred, at a cost of over $23 million.
  - The addition of macitentan leads to a 50% reduction in hospitalizations (72 fewer) in a year and $3,847,353 in hospital-related savings (**Figure 3**). Average savings per PAH patient associated with hospitalization is $5,223.
  - Across 3 years, total savings due to offset hospitalizations are $11,416,071 when macitentan is added to existing management (patients with or without background therapy).
  - The number needed to treat (NNT) to avert a hospitalization is 10 patients at year 1, and only 4 patients over 3 years
    - Corresponding SERAPHIN trial results indicate that NNT to prevent one morbidity or mortality event is 8 at year 1.

Table 3: Base case results, year 1

Base Case Results	Placebo	Macitentan	Absolute Change	Relative Change
Total patients	737	737	0	0.00%
Total deaths	19	12	-7	-35.70%
Total PAH-related hospitalizations	143	71	-72	-50.08%
Total LOS	2,032	479	-1,553	-76.44%
PAH-hospitalization costs, $	$7,681,902	$3,834,549	-$3,847,353	-50.08%

Figure 3: Base case, total PAH-related hospital costs in year 1

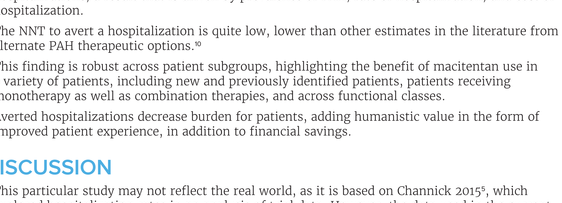


- Subgroup Analyses (**Table 4**):
  - Hospitalization-related savings ranged from 35.5% for patients on background therapy to 57.4% for incident patients (**Figure 4**).
  - Additionally, for patients on macitentan monotherapy, hospitalizations fall by more than 52.3% for total savings of $1,334,364.

Table 4: Subgroup analyses, year 1

Scenario	Total patients	Number of hospitalizations avoided	Hospital-days avoided	Hospitalization-related cost savings
Base case: All SERAPHIN patients	737	72	1,553	$3,847,353
PAH patients w/ background Tx	492	34	944	$1,820,650
PAH patients w/o background Tx	245	25	523	$1,334,364
PAH patients in FC II	386	30	760	$1,585,441
PAH patients in FC III	336	32	701	$1,691,985
PAH incident patients	18	2	39	$106,403
PAH prevalent patients	719	70	1,518	$3,771,230

Figure 4. PAH-related hospitalizations offset with macitentan therapy, by subgroup



CONCLUSIONS

- Macitentan use reduces the cost of care for PAH patients given reductions in disease-related hospitalizations, a result that is driven by prevalence of PAH, rate of hospitalization, and cost of hospitalization.
- The NNT to avert a hospitalization is quite low, lower than other estimates in the literature from alternate PAH therapeutic options.[10]
- This finding is robust across patient subgroups, highlighting the benefit of macitentan use in a variety of patients, including new and previously identified patients, patients receiving monotherapy as well as combination therapies, and across functional classes.
- Averted hospitalizations decrease burden for patients, adding humanistic value in the form of improved patient experience, in addition to financial savings.

DISCUSSION

- This particular study may not reflect the real world, as it is based on Channick 2015[5], which explored hospitalization rates in an analysis of trial data. However, the data used in the current analysis likely translate to conservative hospitalization rates, as a controlled population may more likely adhere to therapy.
  - For instance, Burke 2015[4] reported that 52.9 percent of PAH patients were hospitalized over 1 year; of these 79% are readmitted in a real-world setting. Of the 79%, a number require multiple readmissions (50%, 25%, and 23% are readmitted once, twice, and three or more times, respectively).
- This analysis does not distinguish between an initial hospitalization and readmission, although evidence suggests that readmissions could be more costly.[4] This also suggests that this analysis underestimates true hospital-related savings associated with macitentan treatment.
- Additionally, by focusing on hospitalizations, this analysis does not account for other types of downstream costs for patients who have had a hospitalization, such as the need for readmission, need for rehabilitation services, or the need for additional PAH therapies or referral for transplantation. Therefore, the benefit of offsetting hospitalizations is likewise larger than presented in the current analysis.
- Finally, the model takes a payer perspective rather than health care provider perspective. Given the reduced length of stay for patients receiving macitentan (larger than indicated in this analysis when considering that more patients would be hospitalized in a real-world setting[5]), the benefits to a health system to including macitentan on formulary could be substantial. This is especially true when considering the use of macitentan alone rather than an initial combination therapy, where the costs of the combined drugs may also be substantial.
- Prior models have explored the overall budget impact or cost-utility of different therapeutic options. One study suggests that upfront ERA+PDE-5i combination therapy can lead to savings over time,[10] while additional studies find that ERA or PDE-5i treatment alone can provide good value for money.[11, 12] This study adds to the existing modeling literature by establishing the hospital-related cost-savings occur due to use of macitentan either alone or together with existing background therapies.

AREAS FOR FUTURE RESEARCH

- Following up on this analysis with additional evidence would confirm conclusions as well as identify the magnitude of additional benefit stemming from some of the current analytic limitations. Suggestions for future research include:
  - Identify real world hospitalization rates for initial and subsequent admissions in a generalizable setting, by therapy;
  - Establish the cost of readmission vs initial hospitalization in a real-world setting;
  - Identify and estimate downstream costs related to the need for hospitalization, including readmission, rehabilitation and treatment switching;
  - Alter the analytic perspective to understand the potential financial benefit to a healthcare system of shorter and thus less costly hospital admissions, or more costly but infrequent hospitalizations.

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