

# EVENT-DRIVEN STUDIES AND SERIOUS CHRONIC DISEASES: ADDRESSING PLACEBO, DRUG EFFICACY, AND TREATMENT FAILURE IN PULMONARY ARTERY HYPERTENSION

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## ABSTRACT

Clinical development of novel therapies for pulmonary artery hypertension (PAH) requires trials of larger patient cohorts, who are studied for longer periods and with more robust and meaningful efficacy endpoints, using event-driven studies. When employing an event-driven methodology in orphan conditions such as PAH, it is important to consider study endpoints, the use of placebo, and the approach used for treatment. The most relevant clinical endpoints in rare conditions, such as death, can be a rare event in the trial duration. The use of composite or surrogate endpoints based on biomarkers can provide a wealth of information regarding benefits observed in randomised controlled trials (RCTs). Biomarkers that predict morbidity and mortality at an early stage are required. The use of placebo in event-driven studies of PAH is a growing issue, as the development of novel treatments over past years means that future therapies possibly cannot be compared against placebo. Crossover study designs, randomised discontinuation trials, registry trials, and re-randomisation may instead be utilised in RCTs of PAH. Owing to the heterogeneity of responses to PAH treatment, differing strategic approaches should be assessed in RCTs including combination therapy and sequential therapy.

**Keywords:** Event-driven study, pulmonary artery hypertension, study endpoints, biomarkers, composite endpoint, surrogate endpoint, combination therapy, sequential therapy.

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## INTRODUCTION

Chronic disease affects almost every aspect of a patient's life; ranging from physical and mental health, to their ability to function day-to-day both as an individual, and on a societal level. Studies of chronic diseases must be sufficiently powered to assess the effects of treatment on all clinically-relevant aspects of the disease, while including appropriate endpoints to directly measure how the patient feels, functions, or survives.<sup>1</sup>

In some serious, rare conditions this is compounded by a small patient population and a general lack of consensus on the best endpoints. For example, pulmonary artery hypertension (PAH) is a progressive orphan disease occurring in 15 people per million adults per year.<sup>2</sup> As a result, randomised clinical studies (RCTs) of PAH have traditionally been of short duration, comprised small populations of affected patients, and limited in evaluating the scope and duration of treatment effects. Clinical development of novel therapies for PAH in the future will require trials of larger patient

cohorts who are studied for longer periods, and with more robust and meaningful efficacy endpoints.<sup>1</sup> One approach is to use registry-based or open-label studies to generate patient-level data. But, while national registries and open-label studies give an indication of population survival, there are limitations that need to be considered when extrapolating to the individual patient. As they include unselected, 'real-world' patients, registries comprise mixed patient populations with different comorbidities and co-medications. The applicability of data from mixed patient populations to the individual is therefore unclear.<sup>3</sup>

There is currently interest in the use of event-driven, or outcome-driven, studies for investigating patient-level responses in serious, rare diseases. Event-driven studies are less dependent than traditional RCTs on achieving pre-specified sample size, instead being powered to detect the occurrence or frequency of predefined events. Traditional sample size criteria are often employed to assess the number of events required to fulfil the hypothesis-testing approach. Such an approach enables the true clinical progression of serious, rare conditions to be assessed over time.<sup>1</sup> In all RCTs, the calculation of sample size is based on the anticipated number of events – estimated using previously published data – and the number of subjects enrolled is estimated in order to obtain the required number of events with adequate follow-up, including losses to follow-up or drop-out.<sup>4</sup>

When employing an event-driven methodology in orphan conditions such as PAH, it is important to consider study endpoints, the use of placebo, and the approach used for treatment.

## ENDPOINTS AND METHODOLOGY OF EVENT-DRIVEN STUDIES

A study endpoint may be defined as the occurrence of a clinical sign, symptom, or change in parameters that is predefined as a target outcome of the study. A primary endpoint is the outcome that defines the success or failure of the treatment under investigation. Secondary endpoints, in contrast, are investigated but meeting these endpoints is not critical to the success or failure of the study. In order to provide an understanding of survival and event-free survival in patients with serious, rare diseases, as well as to evaluate the efficacy of drugs and treatment strategies on long-term outcomes and prognosis, event-

driven studies require appropriate endpoints.<sup>5</sup> In general, endpoints should be well defined, reliable, sensitive to the effects of the interventions, readily measurable and interpretable, and clinically meaningful. The strongest endpoints are outcomes that are direct measures of clinically meaningful benefits to patients.<sup>1,5</sup>

The most relevant clinical endpoints can be relatively rare. In PAH there is a need to evaluate the efficacy of drugs and treatment strategies on long-term morbidity and mortality outcomes in order to truly determine the effect of treatment on prognosis. But, as death, for example, is a relatively rare event, to conduct a mortality study in serious, rare diseases with enough statistical power to detect a treatment effect, a large number of patients would be required. In addition, it is generally perceived that when multiple therapies are available, conducting a survival trial would be unethical. The use of composite endpoints as a primary outcome requires that the trial is event-driven, or outcome-driven, rather than being of a fixed observation time.<sup>5</sup>

Event-driven studies tend to focus on longer duration primary outcomes – such as time to treatment discontinuation, all-cause mortality, and time to death or hospitalisation<sup>6-9</sup> – which may not be appropriate effectiveness measures for acute illnesses, where healing may occur within a short time, or in intermediate illnesses in which symptoms come and go.<sup>6</sup> In order to gain more information regarding the patient's condition, more descriptive secondary outcomes may also be employed, such as disease-specific changes (e.g. oedema, body weight, dyspnoea) or rates of adverse events during the treatment phase.<sup>6-9</sup>

The use of surrogate endpoints can provide a wealth of information regarding the mechanism of action of benefits observed in RCTs. For example, in studies of systemic hypertension, blood pressure reduction is a frequently used endpoint because it has been shown to be a surrogate for survival.<sup>10</sup> In PAH, changes in pulmonary haemodynamic parameters during the typical period of a RCT (i.e. at 16 weeks) is useful to determine long-term prognosis.<sup>11</sup> Such endpoints may be particularly useful in RCTs, and the clinical management, of orphan diseases such as PAH. Indirect surrogate endpoints that are commonly used in PAH include the 6 minute walking distance (6MWD), cardiopulmonary haemodynamics, and biomarkers.<sup>12</sup> It is worth

noting that some indirect surrogate endpoints are dependent on patient motivation or clinical judgement. To eliminate this, there may be a preference for surrogate markers that measure biological processes: namely biomarkers.<sup>5</sup>

In RCTs and the clinical management of PAH, there is a need for biomarkers that identify the disease and are able to predict morbidity and mortality at an early stage.<sup>13</sup> Levels of brain natriuretic peptide (BNP) and the N-terminal fragment of pro-BNP have been identified as biomarkers for mortality risk stratification, but there is no established threshold for good or poor prognosis.<sup>12</sup> Also, despite the observation that patients who respond to treatment with short-acting vasodilators are likely to respond to treatment with calcium channel blockers, treatment responses in PAH are generally unpredictable and additional biomarkers are required to assess this.<sup>12</sup> Biomarkers can also be used to assess the effects of treatment and any change in a biomarker as a result of an intervention is considered direct evidence of biological activity. It is important to bear in mind, however, that such evidence can be unreliable. This is particularly the case if biomarkers are strongly correlated with clinical efficacy measures in natural history observations, yet are not in the causal pathway of the disease process.<sup>5</sup>

Completed and ongoing studies in PAH have utilised composite endpoints to enable a stringent assessment of the effects of treatment on clinically-relevant outcomes. The Phase III SERAPHIN study,<sup>14</sup> for example, assessed the efficacy of macitentan using a primary endpoint that was a composite of death, atrial septostomy, lung transplantation, initiation of treatment with intravenous or subcutaneous prostanoids, and worsening of PAH. SERAPHIN also utilised a rigorous definition of PAH worsening to define morbidity and mortality. In this study, PAH worsening was defined as a decrease in 6MWD by 15%, confirmed by a second test, worsening of PAH symptoms, and the need for additional PAH treatments. The mean duration of study treatment was up to 103.9 weeks.<sup>14</sup> Based on data from SERAPHIN, macitentan is recommended to delay the time to clinical worsening in treatment-naïve PAH patients and in patients with symptomatic PAH despite treatment with a phosphodiesterase Type 5 inhibitor.<sup>12</sup>

The Phase III GRIPHON study<sup>15</sup> is an ongoing investigation of selexipag versus placebo in patients

with PAH. The primary endpoint is the time to first morbidity or mortality event, over a period of up to 4.3 years; which is defined as death or hospitalisation for worsening of PAH, resulting in need for lung transplantation or balloon atrial septostomy, initiation of parenteral prostanoid therapy or chronic oxygen therapy, or disease progression.<sup>15</sup> The AMBITION study<sup>16</sup> is an ongoing Phase III assessment of first-line ambrisentan combined with tadalafil versus monotherapy with ambrisentan or tadalafil for PAH. The primary endpoint is time to clinical failure, with an estimated study duration of 3.5 years. Secondary endpoints include change from baseline in 6MWD, change from baseline in N-terminal pro-BNP, and proportion of patients with unsatisfactory clinical response.<sup>16</sup>

Therefore, event-driven studies – such as SERAPHIN,<sup>14</sup> GRIPHON,<sup>15</sup> and AMBITION<sup>16</sup> – are not only key in driving the future of therapy in PAH, these trials also have an integral role in defining the endpoints and characteristics of future studies. SERAPHIN,<sup>14</sup> for example, demonstrates that large-scale, long-term studies on morbidity and mortality in PAH are feasible. GRIPHON<sup>15</sup> and AMBITION<sup>16</sup> should provide data regarding appropriate primary and secondary outcomes and the timing of these outcomes, thus guiding the selection of endpoints and the duration of future studies.

## ISSUES IN PLACEBO-CONTROLLED EVENT-DRIVEN STUDIES (PCEDS)

PCEDS typically take the form of two distinct methodologies. In the first, the placebo or active treatment under investigation is added to the standard of care (SOC) in a single-blinded manner. In the second, only the placebo or active drug are randomised, with no SOC included; the patients included in the study receive either no therapy or the test drug. The majority of PCEDS include the addition of the active drug or placebo to a SOC.<sup>7,8</sup> As the SOC is recommended by clinical bodies, based on the most up-to-date efficacy and tolerability data, patients in the placebo arm should, in effect, be receiving treatment with the most effective agent or combination of agents.

PCEDS studies cannot be ethically performed in illnesses where a SOC or multiple therapies exist. As per the Declaration of Helsinki: “Every patient—including those of a control group, if any—should be assured of the best proven diagnostic

and therapeutic methods.<sup>17</sup> It is also the case that in clinical practice, a patient diagnosed with PAH would always receive active treatment. Hence, when an active treatment exists, the control arm should not receive placebo without SOC as this is unethical and methodologically incorrect. This is the case in PAH, where the development of novel treatments over past years means that future therapies cannot be compared against placebo.<sup>1</sup> Yet there is a clear need for the development and investigation of novel efficacious treatments for PAH. Novel clinical trial designs are therefore required.

Crossover designs may be considered for PAH studies, in which subjects complete one course of therapy and are then switched to a different therapy. A crossover design is effective in assessing short-term differences in outcomes between two treatment approaches, though it utilises a short washout period and assumes negligible carry-over effects of treatment. In PAH, any washout period raises the concern of rebound of clinical symptoms.<sup>18</sup> Other novel approaches to study design have also been developed. Factorial trials, for example, allow the testing of more than one novel element in a single trial design.<sup>19</sup> In a factorial trial, participants are allocated to receive neither intervention, one or the other, or both interventions. By including all participants in both analyses, such a design enables consideration of the separate effects of each intervention, as well as the benefits of combining the interventions. However the power of factorial trials may be limited and large populations required to achieve adequate power.<sup>19</sup>

Randomised discontinuation trials (RDTs) are a second novel study design. RDTs are two-phase studies, in which all participants are treated open-label with the investigational drug in Phase I. Those who respond to treatment enter Phase II and are randomised to placebo or to continue treatment. This approach eliminates non-compliers and adverse reactions.<sup>20</sup> In one analysis, the RDT methodology was found to have a very strong effect on trial efficiency and required a sample size 20–50% that of a traditional RCT.<sup>20</sup> There is concern that removal of the active drug in Phase II of RDTs may be detrimental to participants. Also, the selected population may not be representative of the larger affected population.<sup>1</sup>

In order to strike a balance between effective treatment and data generation, a re-randomisation approach has also been developed. Such an

approach ensures that patients are continually receiving an active treatment and can be followed for the entire study duration. Such a methodology was employed in the Clinical Anti-psychotic Trials of Intervention Effectiveness studies<sup>6</sup> in schizophrenic patients. In this methodology, patients were randomised to one of several medications; upon treatment failure or discontinuation, patients were re-randomised to another double-blind treatment. This treatment was discontinued at the discretion of the investigators and the subject entered into a non-randomised open-label phase. In order to further mimic usual patient care, inclusion and exclusion criteria were open, and physicians could change the dosage of the double-blind treatment whenever warranted.<sup>6</sup>

## STRATEGIES FOR THE MANAGEMENT OF SERIOUS, RARE DISEASES INCLUDING PAH

Patients diagnosed with PAH share numerous disease-specific clinical characteristics. There are, however, numerous underlying disease processes and risk factors that can cause PAH. Particularly in the case of idiopathic PAH, disease may be caused by numerous pathological processes. Thus, RCTs generally recruit patients with PAH caused by numerous factors, which results in the heterogeneity of responses to treatment.<sup>12</sup> It is, therefore, essential that differing strategic approaches to treatment are assessed in RCTs.

### Combination Therapy

Through event-driven studies – as described above – two strategies have emerged as being effective for the management of serious, rare diseases: combination therapy and sequential therapy. In the combination approach, one drug is administered and a second drug is added to the regimen if the patient begins to deteriorate, does not reach treatment goals, or does not improve at all. This differs from adjuvant therapy, where an additional drug(s) is added at a fixed point in the treatment pathway, such as in cancer therapy.<sup>21</sup>

Combination therapy is limited by the requirement for the demonstration of synergy and favourable pharmacodynamic characteristics between two or more agents.<sup>21</sup> In many cases, the proposed benefits of combination therapy are based on *in vitro* tests demonstrating ‘synergy’. However, the demonstration of synergy varies across studies and results differ

with the methodology used. Importantly, *in vitro* phenomena should translate into clinical benefit for patients, as demonstrated in prospective RCTs.<sup>21</sup> Unfortunately, numerous obstacles have prevented the development of properly controlled trials of combination therapy, including the cost of multiple drug regimens and the difficulty in achieving collaboration between different manufactures on studies that examine the efficacy of one agent versus a combination of other agents.<sup>22</sup>

In PAH, treatment with combination therapy with two or more agents is common, owing to the numerous pulmonary vascular abnormalities that have been identified as being pathogenic. A growing number of RCTs have subsequently demonstrated the efficacy of adding a second medication to stable background monotherapy, as compared with the addition of placebo.<sup>12</sup> In patients with PAH who remain symptomatic despite initial therapy, it is recommended that physicians add a second agent to the patient's background therapy.<sup>23</sup> The aim of combination therapy should be to improve surrogate outcome measures – such as 6MWD, cardiopulmonary haemodynamics, and biomarkers – and delay the time to clinical worsening.<sup>12</sup> But, as different patients are likely to have different pathogenic mechanisms as the cause of their disease, the first medication will only identify patients who are responsive to that therapy.<sup>22</sup>

### Sequential Therapy

The second strategy for treating serious, rare diseases is to switch the patient onto another drug at the point of treatment failure and discontinue the original agent. Such an approach is commonly used during treatment with antibiotics where, if an antibiotic is prescribed to eradicate an infection and the ensuing response is judged to be unsatisfactory, the physician switches to another antibiotic in the hope of achieving a better outcome. Such 'sequential' administration of treatments also occurs in clinical psychiatry. Sequential therapy may involve switches to different types of drugs, as is often the case in drug-refractory depression.<sup>24</sup>

### New Approaches in the Therapy of Serious, Rare Diseases

Sequential therapy offers patients more than just another treatment option in the case of resistance. In cancer therapy, the concept of sequential therapy is being utilised in a 're-challenge' approach. Re-challenge is used later in the treatment pathway of an agent in which resistance has previously developed.<sup>25</sup> A second treatment modality, termed 'cyclic treatment', stems from re-challenge.<sup>26</sup> In this system, a number of drugs are selected, based on their characteristics and the patient's clinical needs, and are used sequentially. Once all the drugs have been used, re-challenge with each of the drugs is undertaken.<sup>26</sup> Such a methodology may prove successful in other serious, rare diseases and may be incorporated into event-driven studies.

Observations from event-driven studies – in particular using re-randomisation-type methodologies – should be used to guide drug switching strategies and develop an adaptive treatment strategy (ATS). An ATS is a set of rules for adapting a treatment plan to the changing state of an individual patient, taking into account both the history of previous treatments and the response to those treatments.<sup>27</sup> For example, the clinical management of HIV infection may begin with a particular combination of anti-viral medications and then, as the patient's viral load and CD4 count change over time, the combination may be changed or other treatments may be instituted.<sup>27</sup> ATSs may be an essential component of PAH management, where individualised approaches to treatment are required, owing to the heterogeneity of responses across PAH patients.<sup>12</sup> Also necessary is the identification of biomarkers and genes that can predict treatment responses, and thereby facilitate an approach to therapy that is tailored to individual patients.

As medicine improves its abilities to stave off mortality, the result is a growing list of previously acute conditions that have become chronic.<sup>27</sup> This necessitates the introduction of new RCT methodologies and treatment approaches to study the management of serious, rare diseases, and identify novel biomarkers to predict treatment responses and prognosis.

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