



# New perspectives in long-term outcomes in clinical trials of pulmonary arterial hypertension

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**ABSTRACT** The past two decades have seen significant improvements in the management of patients with pulmonary arterial hypertension (PAH). Although outcome has improved, long-term prognosis remains unsatisfactory. The development of new treatment options is clearly important. Equally important is testing new agents in trials designed to provide robust evidence for sustained clinical benefits enabling clinicians to determine the optimal treatment strategy for individual patients. End-points such as the change in 6-min walk distance (6MWD) have been pivotal in the registration trials of currently available PAH-specific therapies. However, as current clinical trials enrol patients with milder disease, many already on background therapy, there is growing evidence that change from baseline in 6MWD is a weak surrogate of outcome in PAH. In addition, while short-term trials allowed for the rapid approval of PAH therapies in the past, there is increasing recognition that clinical trials for new agents must provide evidence of long-term benefits. Clinical trials need to evolve to provide the long-term, clinically relevant data required to appropriately assess new therapies. Event-driven long-term morbidity and mortality trials are currently underway, and will provide robust data on the frequency and timing of events, and are likely to reflect the future of clinical trial design in PAH.



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Long-term, event-driven randomised morbidity and mortality trials provide information on efficacy and safety of PAH agents <http://ow.ly/pGaSg>

## Introduction

While there has been much progress in drug development and the symptomatic management of pulmonary arterial hypertension (PAH) over the past 20 years, long-term prognosis remains unsatisfactory. Data from contemporary registry studies have reported 3-year survival rates of 67% in the French national registry [1] and 57% in the UK national registry [2], with a 7-year survival rate of 49% in the US Registry to Evaluate Early and Long-term PAH Disease Management (REVEAL) [3]. Although an improvement was seen compared with historical data, these cohorts show that, even in countries where expert pulmonary hypertension centres have been established and a wide array of drug treatments are available, mortality remains substantial.

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While national PAH 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 or a single PAH aetiology is therefore unclear. One of the major considerations is whether prevalent (that is, patients with previously diagnosed PAH) or incident (that is, patients with newly diagnosed PAH) are included. The inclusion of prevalent patients in a registry study introduces inherent bias [4]. In PAH, as in any other chronic disease, prevalent cohorts are subject to survivor bias, as patients who die soon after disease onset are unlikely to be included. This means that prevalent cohorts tend to select patients who are therefore likely to have a better prognosis than incident patients. This has been demonstrated in both the French [1] and REVEAL registries [5], where prevalent patients were found to show better survival than incident or newly diagnosed patients. If prevalent “survivors” dominate the patient cohort in the registry, then they will distort the overall survival estimate, particularly in the early months of the study [6]. This disparity has been suggested to be responsible, in part, for lower early mortality figures in the REVEAL registry, which included a high proportion of prevalent patients compared with the French registry, which estimated survival from time of initial diagnosis [6].

In order to accurately assess survival and disease progression in PAH and the impact of medications on these outcomes, data are required from long-term randomised placebo-controlled trials. Data on the number of deaths and number of patients with disease progression are available from short-term randomised placebo-controlled trials of PAH-specific drugs (tables 1 and 2). However, the frequency of these events is low, the inclusion criteria select stable patients and the time scale (<24 weeks) over which patients are observed is short. In addition, about half of these trials have a population sample of <100 patients. Therefore, it is not possible to obtain precise estimates of drug effect on death or disease progression in the PAH population from these studies.

Well-designed sufficiently powered, long-term, randomised controlled trials with appropriate and clinically meaningful end-points are required. Such trials will allow us to gain an understanding of survival and event-free survival in patients with PAH, and to evaluate the efficacy of drugs and treatment strategies on long-term outcomes and prognosis. This article will review the end-points that have been used to date in clinical trials of PAH therapies and provide a perspective on conducting clinical trials of new PAH therapies in the future, using end-points that more directly reflect disease progression and survival.

### Historical clinical end-points in PAH trials

Clinical study end-points should be well defined, reliable and sensitive to the effects of the interventions, readily measureable and interpretable, and clinically meaningful [36, 37]. The strongest end-points are outcomes that are direct measures of clinically meaningful benefits to patients. Historically, clinical trials in PAH have been of a fixed, short-term duration and have generally used the change in 6-min walk distance (6MWD) as a primary end-point (table 1). The 6-min walk test is easy to carry out, does not require specialised equipment, is familiar to physicians as a clinical assessment tool, and is accepted by the regulatory authorities for the registration of PAH drugs. These factors have contributed to its widespread use as a measurement of symptomatic efficacy of PAH drugs in clinical trials. However, in a meta-analysis of 22 trials in PAH, no significant relationship was found between improvements in 6MWD and long-term outcomes including all-cause mortality, hospitalisation for PAH, and/or lung or heart–lung transplantation, or initiation of PAH rescue therapy [38]. Furthermore, a pooled analysis showed only a weak correlation between changes in 6MWD at 3 months and long-term outcomes [39], and so therefore is not a suitable indicator of long-term prognosis with treatment.

Composite end-points have particular attractions in PAH because the statistical power increases with event rate, by combining a number of end-points and allowing for increased detection of therapeutic benefit without having to increase sample size [40]. In addition, the incorporation of non-fatal but important morbidity measures offers a more global assessment of patients and their response to therapy.

Composite end-points of disease progression, such as time to clinical worsening (TTCW), have been employed as a secondary or an exploratory end-point in many PAH trials to assess the effects of drugs on disease progression. The definitions of TTCW have included death, and the morbidity events of hospitalisation and PAH worsening. However, definitions of TTCW have not been uniform across studies (table 2), making meaningful comparisons across trials difficult. As death and hospitalisation are rarely the first event, PAH worsening tends to drive the TTCW effect. As such, this end-point should be clearly defined and robustly assessed. However, historically, PAH worsening has rarely been independently adjudicated, which introduces the potential for bias and for inconsistency between different sites and investigators. For example, among the pivotal trials leading to the submission of therapies for approval to

TABLE 1 Number of deaths in randomised, placebo-controlled trials of pulmonary arterial hypertension-specific therapies

First author [ref.]	Study acronym	Patients n	Study period weeks	Primary end-point	Deaths n	
					Study drug	Comparator
RUBIN [7]		23	8	Haemodynamics <sup>#</sup>	Epoprostenol, n=1	Conventional therapy, n=3
BARST [8]		81	12	Survival and change in $\delta$ MWD <sup>#</sup>	Epoprostenol, n=0	Conventional therapy, n=8
BADESCH [9]		111	12	Change in $\delta$ MWD	Epoprostenol, n=4	Conventional therapy, n=5
SIMONNEAU [10]		470	12	Change in $\delta$ MWD	Treprostinil, n=9	Placebo, n=10
HIREMATH [11]	TRUST	44	12	Change in $\delta$ MWD	Treprostinil, n=3	Placebo, n=5
GALIÉ [12]	ALPHABET	130	12	Change in $\delta$ MWD	Beraprost, n=1	Placebo, n=1
BARST [13]		116	36	Disease progression: death, transplantation, epoprostenol rescue or 25% decrease in peak oxygen consumption	Beraprost, n=1	Placebo, n=2
OLSCHEWSKI [14]	AIR	203	12	Improved by one NYHA FC and 10% increase in $\delta$ MWD	Iloprost, n=1	Placebo, n=4
McLAUGHLIN [15]	STEP	67	12	Change in $\delta$ MWD, NYHA FC, Borg dyspnoea index <sup>#</sup>	Iloprost/bosentan, n=0	Placebo/bosentan, n=0
HOEPER [16]	COMBI	40	12	Change in $\delta$ MWD	Iloprost/bosentan, n=0	Placebo/bosentan, n=0
CHANNICK [17]		32	12	Change in $\delta$ MWD	Bosentan, n=0	Placebo, n=0
RUBIN [18]	BREATHE-1	213	16	Change in $\delta$ MWD	Bosentan, n=4 <sup>†</sup>	Placebo, n=2
GALIÉ [19]	EARLY	185	24	Change in PVR and $\delta$ MWD	Bosentan, n=1	Placebo, n=1
GALIÉ [20]	BREATHE-5	54	16	Change in PVR	Bosentan, n=0	Placebo, n=0
HUMBERT [21]	BREATHE-2	33	16	Change in total pulmonary resistance	Epoprostenol plus bosentan, n=3 <sup>‡</sup>	Epoprostenol plus placebo, n=0
WILKINS [22]	SERAPH	26	16	Changes in right ventricular mass	Bosentan, n=0	Sildenafil, n=1
GALIÉ [23]	ARIES	394	12	Change in $\delta$ MWD	Ambrisentan, n=4	Placebo, n=6
BARST [24]	STRIDE-1	178	12	Change in peak oxygen consumption	Sitaxentan, n=1	Placebo, n=0
BARST [25]	STRIDE-2	247	18	Change in $\delta$ MWD	Sitaxentan, n=0	Placebo, n=2 Bosentan, n=0
SANDOVAL [26]	STRIDE-4	98	18	Change in $\delta$ MWD	Sitaxentan, n=0	Placebo, n=0
SASTRY [27]		22	12	Change in $\delta$ MWD	Sildenafil, n=0	Placebo, n=1
GALIÉ [28]	SUPER-1	278	12	Change in $\delta$ MWD	Sildenafil, n=3	Placebo, n=1
SINGH [29]		20	8	Change in $\delta$ MWD	Sildenafil, n=0	Placebo, n=0
SIMONNEAU [30]	PACES	267	16	Change in $\delta$ MWD	Sildenafil, n=0	Placebo, n=7
GALIÉ [31]	PHIRST	405	16	Change in $\delta$ MWD	Tadalafil, n=2	Placebo, n=1
JING [32]	EVALUATION	66	12 (+12 open label)	Change in $\delta$ MWD	Vardenafil, n=1	Placebo, n=2
LANGLEBEN [33]		71	12	Change in $\delta$ MWD	Terbogrel, n=1	Placebo, n=0
GHOFRANI [34]		59	24	Change in $\delta$ MWD	Imatinib, n=3	Placebo, n=3
HOEPER [35]	IMPRES	202	24	Change in $\delta$ MWD	Imatinib, n=5	Placebo, n=5

$\delta$ MWD: 6-min walk distance; NYHA FC: New York Heart Association functional class; PVR: pulmonary vascular resistance. <sup>#</sup>: primary end-point not specified; <sup>†</sup>: three patients were in the post 12-week treatment period; <sup>‡</sup>: there was one death after withdrawal from study.

the US Food and Drug Administration or European Medicines Agency, only the ARIES study with ambrisentan and IMPRES (Imatinib in Pulmonary arterial hypertension, a Randomized Efficacy Study) had adjudication committees that determined some, although not all, components of TTCW [23, 35]. Even more robust components, such as hospitalisation for PAH, should be independently adjudicated to ensure that hospitalisation events are non-elective and not influenced by non-clinical considerations, such as distance required to travel and availability of hospital beds. It is critical to distinguish between short “ward stays” and genuine hospitalisation and hospitalisation “for PAH” not “with PAH” to limit potential bias. It should be noted that imatinib is not presently approved as a therapy for PAH. Further concerns surrounding TTCW include the short-term fixed duration of the trial, insufficient population sample size, and statistical powering to examine treatment effects, as it has never been used as the primary end-point. This means the results have been based on a limited number of events (table 2) and so robustness is

TABLE 2 Definitions of time to clinical worsening used as secondary end-points in short-term, fixed-duration randomised controlled trials and number of events

First author [ref.]	Study acronym	Patients n	Study period weeks	Definition of time to clinical worsening	Events n	
					Study drug	Comparator
GALIÉ [12]	ALPHABET	130	12	All-cause mortality	Beraprost, n=4	Placebo, n=3
OLSCHEWSKI [14]	AIR	203	12	Hospitalisation for worsening of PH symptoms	Iloprost, n=6	Placebo, n=13
HOEPER [16]	COMBI	40	12	Clinical deterioration Death Need for transplantation	Iloprost/bosentan, n=3	Placebo/bosentan, n=4
CHANNICK [17]		32	12	Death Hospitalisation for right heart failure Deterioration in FC Decrease in $\delta$ MWD by 20% from baseline or <150 m	Bosentan, n=0	Placebo, n=3
RUBIN [18]	BREATHE-1	213	16	Right ventricular heart failure Aggravated pulmonary hypertension Death	Bosentan, n=25	Placebo, n=34
GALIÉ [19]	EARLY	185	24	Lung transplantation Atrial septostomy Hospitalisation for PH Lack of clinical improvement or worsening leading to discontinuation Need for epoprostenol therapy	Bosentan, n=3	Placebo, n=13
GALIÉ [23]	ARIES	394	12	Death Hospitalisation due to PAH Progression of PAH	Ambrisentan, n=12	Placebo, n=20
BARST [24]	STRIDE-1	178	12	Lung transplantation Atrial septostomy Hospitalisation for PH Study withdrawal because of the addition of other PAH medications, or early escape criteria	Sitaxentan, n=1	Placebo, n=3
BARST [25]	STRIDE-2	247	18	Death Atrial septostomy Transplantation Hospitalisation for PAH Initiation of new chronic PAH treatment Combined WHO FC deterioration and 15% decrease in $\delta$ MWD from baseline	Sitaxentan, n=10	Placebo, n=10 Bosentan, n=9
SANDOVAL [26]	STRIDE-4	98	18	Hospitalisation for worsening PAH Death Need for heart–lung or lung transplantation Atrial septostomy Addition of any new type of chronic treatment for PAH A combination of deterioration in WHO FC and 15% decrease in $\delta$ MWD from baseline	Sitaxentan, n=1	Placebo, n=3
GALIÉ [28]	SUPER-1	278	12	Death Transplantation Hospitalisation for PAH Initiation of additional therapies for PAH	Sildenafil, n=10	Placebo, n=7
SIMONNEAU [30]	PACES	267	16	Death Lung transplantation Hospitalisation due to PAH Initiation of bosentan therapy Change in epoprostenol dose of 10% due to clinical deterioration	Sildenafil, n=8	Placebo, n=24
GALIÉ [31]	PHIRST	405	16	Death Lung or heart–lung transplantation Atrial septostomy Hospitalisation due to worsening PAH Initiation of new PAH approved therapy Worsening WHO FC	Tadalafil, n=30	Placebo, n=13
JING [32]	EVALUATION	66	12 (+12 open label)	Death Hospitalisation for PAH progression	Vardenafil, n=1	Placebo, n=4
HOEPER [35]	IMPRES	202	24	Death Hospitalisation for worsening of PAH Worsening of WHO FC by at least one level or a 15% decrease from baseline in $\delta$ MWD	Imatinib, n=37	Placebo, n=32

PH: pulmonary hypertension; FC: functional class;  $\delta$ MWD: 6-min walk distance; PAH: pulmonary arterial hypertension; WHO: World Health Organization.

compromised. Given these limitations, the extrapolation of TTCW data obtained from short-term trials into meaningful outcomes in the long-term should be done with caution. Therefore, although it offers potential advantages over an indirect symptomatic measurement such as changes in 6MWD, TTCW, as used to date, has a number of limitations.

### **Morbidity and mortality in composite end-points in PAH trials**

To further advance the field of PAH and optimise treatment for patients, 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 their effect on prognosis. As death is a relatively rare event, to conduct a mortality study in PAH with enough statistical power to detect a treatment effect, a large number of patients would be required [41]. Given the rare nature of PAH, to coordinate and run a trial with a large patient population requires considerable organisation. In addition, it is generally perceived that at present when multiple therapies are available, conducting a survival trial would be unethical. Increasing the event rate by including clinically relevant morbidity events in the primary end-point (which for PAH may include lung transplantation, atrial septostomy, the requirement for intravenous drugs and PAH worsening) alongside mortality reduces the number of patients required and renders a trial more logistically practicable.

This being said, it still needs to be recognised that large numbers of patients are required for morbidity and mortality studies. Such trials are time-consuming and costly and they reduce the pool of patients available for other clinical studies. For these reasons, careful selection of the drugs to be tested in such a trial design needs to be made. A strong preclinical and clinical rationale for drugs to be tested is required. It is therefore important that candidate drugs are first tested in well-designed phase II clinical trials using appropriate end-points. The conduct of a randomised, placebo-controlled morbidity and mortality study in any fatally progressive disease also requires careful consideration.

An important methodological consideration with long-term randomised trials arises from the changing nature of the disease course and the frequent changes in treatments during follow-up, which both tend to diminish the long-term effects of randomisation. This effect is exacerbated by the inclusion of open-label escape arms that are common so a patient can receive the active drug following withdrawal. In countries where PAH drugs are not available, enrolment into a PAH trial may be the only opportunity a patient has of receiving active treatment. However, such a strategy will impact on the interpretation of the data from both the intent-to-treat and per-protocol analyses of long-term randomised trials, particularly so for a rapidly progressing disease such as PAH. Indeed, the intent-to-treat analysis will only consider the treatment the patients were initially randomised to, not taking into account possible changes over a long follow-up, including the switch of many patients from placebo to the active drug, or changing the dose of the active drug. Such changes are more likely with longer follow-up and will tend to attenuate the measures of effectiveness. However, the per protocol analysis will be based on the compliant patients who continue to do well on treatment, which may overstate the measure of effectiveness.

The Task Force on End Points and Clinical Trial Design, which met at the 4th World Symposium on PH at Dana Point [36], recommended that a composite clinical outcome end-point that includes mortality and morbidity be used as a primary end-point in phase III pivotal trials. The recommended definition for uniform use was based on that used in TTCW with the important difference being robustly defined components and their adjudication by an independent committee. The definition consisted of all-cause mortality, non-elective hospital stay for PAH (with predefined criteria, usually intravenous prostanoid initiation, lung transplantation or atrial septostomy) or disease progression, the latter being defined as a certain decrease in 6MWD and worsening of World Health Organization functional class. In addition, it is important to use all-cause mortality in the primary end-point rather than mortality due to PAH, as this would capture deaths that may be related to the study drug rather than the disease.

The use of morbidity and mortality as the primary end-point by its nature requires that the trial is event driven rather than one that is of a fixed observation time. Event-driven trials enable the true clinical progression of PAH to be assessed over the long term, unlike TTCW in a fixed-duration trial. However, as the number of deaths as a first event in a morbidity and mortality trial is likely to be quite low, a meaningful comparison between the control and active drug on the death component of the primary end-point is not possible. In this context, the measurement of time to the first morbidity or mortality event provides information on whether the intervention is reducing the risk of occurrence of events or deterioration against the control arm. As worsening of PAH is likely to occur prior to death or the need for interventions such as lung transplantation or atrial septostomy, it is likely to be the primary driver in a morbidity and mortality trial. Therefore, it is necessary that not only is worsening of PAH robustly defined but it is also adjudicated. This is especially important in large multicentre, multinational trials to ensure consistency and reliability of the results. The Dana Point Task Force recommended the mandatory adjudication of all events [36].

**PAH trials using composite end-points with morbidity and mortality**

Several trials that adopted the recommendations of the Dana Point Task Force on End Points and Clinical Trial Design for the use of a composite clinical outcome primary end-point in phase III trials, either concluded or are ongoing.

The phase III SERAPHIN (Study with an Endothelin Receptor Antagonist in Pulmonary Arterial Hypertension to Improve Clinical Outcomes) trial of the novel dual endothelin receptor antagonist macitentan has recently been completed [42]. SERAPHIN used a robust definition of morbidity and mortality as a primary end-point to capture clinically relevant events which reflect the true progression of PAH. The end-point incorporated the recommendations of the Dana Point Task Force and further refined them to include a more stringent definition of PAH worsening. In SERAPHIN, PAH worsening was defined as: 1) a decrease in 6MWD by 15% confirmed by a second test conducted on a different day; 2) worsening of PAH symptoms defined as either a worsening of functional class or the appearance or worsening of symptoms of right heart failure; and 3) the need for additional PAH treatments (fig. 1). All events were blindly adjudicated by an independent clinical events committee [42]. The phase III GRIPHON (Prostacyclin Receptor Agonist in Pulmonary Arterial Hypertension) trial is an ongoing multicentre, double-blind placebo-controlled trial evaluating the efficacy and safety of oral selexipag in patients with PAH [43]. The primary end-point used in GRIPHON is in line with the definition of the Dana Point 4th World Symposium of PH [36]. Having been initiated at the end of 2009, the study is expected to run for up to 4.3 years, with an estimated completion date of 2014. Also in progress are two trials examining the effects on long-term outcomes of combining approved PAH drugs. In the COMPASS-2 (Effects of the Combination of Bosentan and Sildenafil *versus* Sildenafil Monotherapy on Pulmonary Arterial Hypertension) study, patients on a stable dose of sildenafil are randomised to either bosentan or placebo and the effects on time to first morbidity or mortality event will be assessed [44]. The study was initiated in April 2004 and is expected to complete in 2014. AMBITION (Study of First-Line Ambrisentan and Tadalafil Combination Therapy in Subjects with Pulmonary Arterial Hypertension) is using time to clinical failure to examine the efficacy of first-line ambrisentan and tadalafil combination therapy *versus* ambrisentan or tadalafil monotherapy in patients with PAH [45]. Total study duration is estimated at 2.75 years, with completion by 2014. Such trials will provide important, clinically relevant data for the assessment of new therapies. Interestingly, it will provide additional data on the rate and timing of morbidity events in the monotherapy plus placebo arms; information that might help predict the length of future trials in PAH. For example, if enough events occur in the first 6 months, or within a year, future trials with such a length could be sufficient to assess the long-term efficacy of novel drugs.

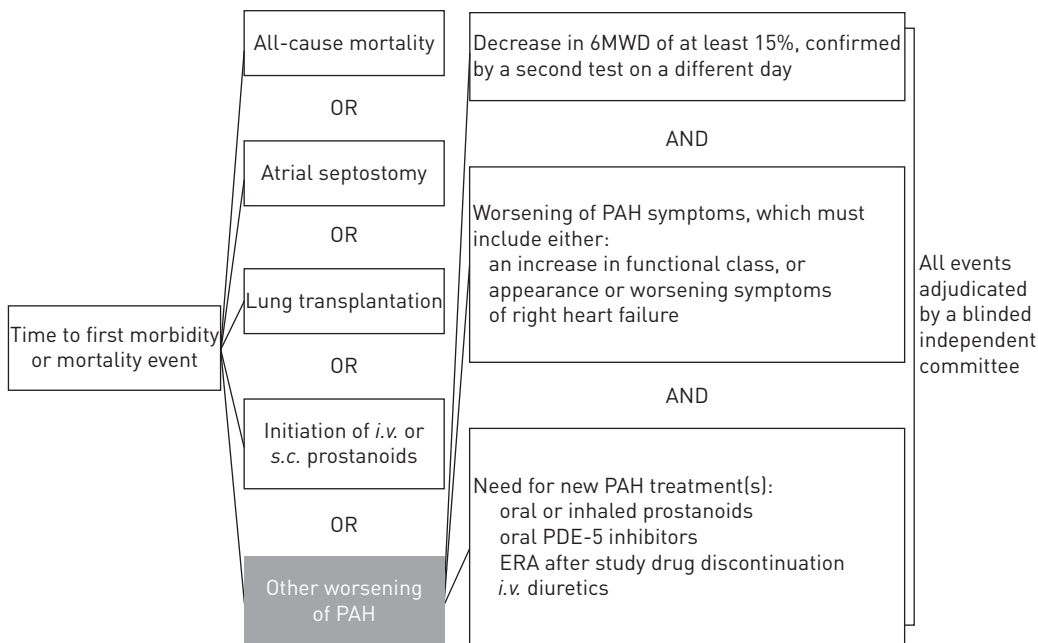


FIGURE 1 Definition of the morbidity and mortality primary end-points used in the SERAPHIN (Study with an Endothelin Receptor Antagonist in Pulmonary Arterial Hypertension to Improve Clinical Outcome) trial. PAH: pulmonary arterial hypertension; 6MWD: 6-min walk distance; PDE-5: phosphodiesterase-5; ERA: endothelin receptor antagonist.



## Conclusion

Data from national PAH registries or single-centre cohort studies provide valuable information on the survival and disease progression of PAH patients in the modern day treatment era. However, prospective, randomised controlled trials with well-defined morbidity and mortality end-points provide more accurate information on the long-term outcomes of PAH treatments or management strategies and might become the methodology used in pivotal phase III trials.

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