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## The evolving landscape of pulmonary arterial hypertension clinical trials

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## 1 **Summary**

2 Despite being a rare disease, the number of available therapeutic options for treating pulmonary arterial  
3 hypertension (PAH) has increased since the late 1990s with multiple drugs developed and demonstrated  
4 to be effective in phase 3 randomized controlled trials. Despite meaningful progress, the prognosis of  
5 PAH remains poor. Existing therapies target pulmonary endothelial dysfunction with vasodilation and  
6 anti-proliferative effects. Novel therapies that target the proliferative vascular remodeling and influence  
7 important outcomes, are urgently needed. There is need for additional innovations in clinical trial design  
8 so that all emerging candidate therapies can be rigorously studied. PAH trial design has shifted from  
9 short-term submaximal exercise capacity as a primary endpoint to larger clinical event-driven trial  
10 outcomes. Event-driven PAH trials may face feasibility and efficiency issues in the future with increasing  
11 samples sizes and longer follow-up durations needed, which would be problematic in such a rare disease.  
12 Enrichment strategies, innovative and alternative trial designs, and novel trial endpoints are potential  
13 solutions that could improve the efficiency of future PAH trials while maintaining rigor and clinically  
14 meaningful level of evidence.

## 1 **Introduction**

2 Pulmonary arterial hypertension (PAH) is a rare disease characterized by pathologic remodeling in the  
3 small pulmonary arteries, which leads to elevated pulmonary arterial pressure and increased right  
4 ventricular afterload(1). The currently available therapies target pulmonary endothelial dysfunction, the  
5 imbalance between vasodilation and vasoconstriction, and have anti-proliferative effects via one of three  
6 pathways: the nitric oxide-cyclic guanosine monophosphate pathway (targeted by phosphodiesterase type-  
7 5 inhibitors and soluble guanylate cyclase stimulators), the endothelin-1 pathway (targeted by endothelin  
8 receptor antagonists), and the prostacyclin pathway (targeted by prostacyclin analogues and prostacyclin  
9 receptor agonists). Effective therapies that can reverse proliferative vascular remodeling and modify the  
10 disease course of PAH are desperately needed, as the existing therapies do not accomplish this goal.

11 With the development of the current therapeutics, combination therapy strategies, and improved general  
12 medical care, outcomes for patients with PAH have improved since the 1980s. However, despite these  
13 important advances, PAH remains a progressive, life-threatening disease, with many patients succumbing  
14 to right heart failure or other complications of the disease. Survival for patients after a new diagnosis of  
15 PAH has plateaued(2,3) and remains unacceptably poor with a median survival after diagnosis of  
16 approximately 5 years(4).

17 The design of randomized controlled trials (RCTs) in PAH has evolved with a shift from 6-minute walk  
18 distance (6MWD) as the primary outcome to an increasing number of large, event-driven phase 3  
19 trials(5). There are also several novel pharmacologic and non-pharmacologic therapies under  
20 development, which are being evaluated across all phases of RCTs. Given the rare nature of PAH and  
21 limited number of patients available for clinical trial enrollment, there is opportunity to innovate RCT  
22 design and efficiency so that all novel options in the therapeutic pipeline can be rigorously evaluated. The  
23 objective of this review is to summarize the progress in PAH clinical trials and identify future  
24 opportunities for innovative trial designs and novel clinical endpoints in phase 2 and phase 3 RCTs.

25

## 1 Search strategy and selection criteria

2 This review reflects the discussions of a multidisciplinary panel of PAH clinical trialists, clinical experts,  
3 pharmaceutical manufacturers, patients, and representatives from regulatory agencies met during the  
4 virtual Cardiovascular Clinical Trials Global Forum (<https://www.globalcvctforum.com/>) in December  
5 2021 (**Web Appendix**). This content was supplemented by searching PubMed  
6 (<https://pubmed.ncbi.nlm.nih.gov/>) and ClinicalTrials.gov using terms “pulmonary arterial hypertension”,  
7 “pulmonary hypertension”, “randomized controlled trial”, “clinical trial”, “enrichment”, “adaptive trial”,  
8 “platform trial”, “pragmatic trial”, “risk assessment”, “actigraphy”, “patient reported outcome”, without  
9 language or date filters. We also searched the websites of the U.S. Food and Drug Administration (FDA)  
10 and European Medicines Agency (EMA) for regulatory documents using the terms “pulmonary arterial  
11 hypertension” and “pulmonary hypertension”.

12

## 13 **Part 1. Progress in trial design**

### 14 Traditional design of phase 3 PAH therapy trials

15 Through the 1990s-early 2000s, clinical trial design for PAH trials relied largely on randomized, double-  
16 blind, monotherapy, placebo-controlled, superiority trials (5–7). These trials were powered on the primary  
17 outcome of 6MWD, led to the approval of several therapies based on efficacy for improving 6MWD over  
18 relatively short-term (often 3-4 months, but ranging 2-6 months) periods with sample sizes ranging from  
19 ~ 100 to 500 patients(8). Secondary outcomes typically included hemodynamics and a composite of time  
20 to clinical worsening. Most studies in the early 2000s did not permit enrollment of patients who were  
21 receiving other background PAH therapies, so the placebo groups were usually receiving no specific PAH  
22 treatment. As PAH therapies were shown to be effective, trials in the later 2000s and 2010s began to  
23 include patients on background treatment, marking a shift to trials of ‘add-on’ sequential combination(9–  
24 16), and even initial combination of two therapies versus monotherapy(17). Overall, this approach was

1 extremely successful, resulting in multiple unique drugs being developed (administered by four different  
2 routes: oral, inhaled, subcutaneously, and intravenously), and a landmark improvement in functional  
3 capacity for patients with PAH. Still, there remained uncertainty about the durability of response and  
4 there was a lack of definitive data for reducing hospitalization and mortality outcomes. In the interim,  
5 several meta-analyses supported mortality improvements(6,8,18), and trial design in the 2010s progressed  
6 to include a primary endpoint of time to first event of clinical failure/worsening, which required larger  
7 (~300-1100) and longer drug exposure (>1 year) studies (**Figure 1**).(9–11,13–17,19–26) Innovative  
8 designs and alternative novel endpoints have potential advantages, which permit similarly robust trials but  
9 with greater efficiency or with smaller sample sizes (**Table 1**).

10

#### 11 A critical appraisal of classical endpoints in past and recent PAH phase 3 trials

12 The main necessary characteristic of a primary endpoint for a registration trial is to be a clinically  
13 meaningful outcome. Specifically, regulatory agencies such as the U.S. FDA and EMA in Europe require  
14 that a clinical trial endpoint reflects how a patient feels, functions, or survives(27,28). Between 1996 and  
15 2013, the change in 6MWD, a measure of function and exercise tolerance, was chosen as the primary  
16 endpoint in eight pivotal trials(29,30). The first six pivotal trials included only treatment-naïve  
17 patients(20,22–24,29). In these short-term duration trials (12 to 17 weeks), the placebo-subtracted  
18 treatment effect was 16 m to 60 m, the clinical relevance of which is questionable. The 6MWD endpoint  
19 had the advantage of being simple, inexpensive, reproducible and was a valid reflection of exercise  
20 capacity. However, change in 6MWD also had some drawbacks, particularly in patients with less  
21 advanced disease and in those on background PAH therapies(10,26). In these patients, the change in  
22 6MWD was smaller with a ceiling effect seen in patients with milder disease. Finally, data from  
23 observational studies and randomized trials in PAH suggested that short-term changes in 6MWD were not  
24 associated with better outcomes(18,31–34), whereas achievement of an absolute threshold value in  
25 6MWD (> 400 to 440 m) was strongly associated with survival(32,34,35).



1 The primary endpoints in PAH trials, starting in 2013, changed to composite endpoints of time to first  
2 event of clinical failure (including death, hospitalization for PAH worsening, disease progression, need  
3 for parenteral prostanoid, lung transplantation or unsatisfactory long-term clinical response). Four trials  
4 have been completed with such an endpoint(14–17), however, the primary endpoint definition varied  
5 between these studies (**Table 2**). Not surprisingly, this approach necessitated the inclusion of larger  
6 patient populations and a longer study period (up to three years) compared to historical trials. In all those  
7 studies, the primary composite endpoint was driven by differences in hospitalization due to PAH  
8 worsening and/or disease progression and not by mortality(14–17). A partial explanation for this  
9 observation is that only the first event of clinical failure was considered and the occurrence of sudden  
10 death without antecedent clinical deterioration is uncommon in PAH trials(14,15,36). Additionally, the  
11 proportion of functional class IV patients, who have a higher risk of death, was quite small (0-2%) in  
12 RCTs. Finally, clinical stability for at least three months (no change in therapy and no recent  
13 hospitalization) was one of the major inclusion criteria in most RCTs. This selects for patients with a  
14 lower likelihood of death because of their recent stability compared to patients with recent deterioration.  
15 Nevertheless, a landmark analysis of the SERAPHIN (Study with an Endothelin Receptor Antagonist in  
16 Pulmonary Arterial Hypertension to Improve Clinical Outcome) and GRIPHON (Prostacyclin (PGI<sub>2</sub>)  
17 Receptor Agonist In Pulmonary Arterial Hypertension) trials showed that clinical worsening events  
18 occurring in the first 3, 6 or 12 months of those trials increased the risk of subsequent mortality(36). In  
19 contrast, a recent meta-analysis of 35 trials found only modest correlation between the effects of PAH  
20 therapies on clinical worsening events and effects on mortality, suggesting that clinical worsening may  
21 not be a surrogate for mortality at the trial-level(37). There was also variability in importance of each  
22 component to patients, indicated that the components of clinical worsening endpoints are not  
23 interchangeable. Finally, clinical failure composite primary endpoints require long-term duration trials  
24 and large sample sizes. Additionally, the composite endpoints used to date in PAH trials do not  
25 provide information on the highly relevant endpoint of clinical improvement.

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## Comparator and background therapy issues

With evolving treatment paradigms over the past ten years, future PAH trials may face efficiency challenges. The efficiency of a trial is a balance between research value (internal and external validity, potential health impact) and costs (risks and burdens to participants, number of participants, financial). The efficiency of RCTs must be acceptable to be ethically viable. Background therapy with one or more approved PAH drugs is now the standard of care in most settings. This poses potential efficiency problems since it becomes more difficult to demonstrate efficacy of a new treatment on top of background PAH therapies. For example, in the event-driven GRIPHON trial, which compared selexipag versus placebo, an interim analysis noted more patients on background therapy than expected. As such, the number of primary endpoint events needed increased from 202 to 331 and the required sample size nearly doubled from 670 to 1150. With the expectation of increasing background therapy use and lower baseline event rates in the control arms in future trials, larger and longer trials will be necessary. It is likely not feasible to conduct and complete multiple event-driven trials simultaneously if each requires 2000-3000 patients, given the rarity of PAH(15). Another issue arises from standardization of usual care (i.e., background therapy), which may increase internal validity (whether results reflect the truth in the trial population) but decreases external validity (generalizability to clinical practice), since most real-world patients will not be using the exact same background regimen that was used in the trial.

Add-on therapy trials have been more common in PAH in recent years. The add-on strategy retains any possible benefit with additional/synergistic effect of the newly added therapy. Replacement trials test whether switching one medication to another is advantageous in terms of further improvements in efficacy or maintaining effects with decreased burden on the patient in terms of side effects, or cost savings. The open-label REPLACE (Riociguat replacing PDE5i therapy evaluated against continued PDE5i therapy) trial recently demonstrated that in patients with an inadequate response on a phosphodiesterase type-5 inhibitor, switching to the soluble guanylate stimulator riociguat improved the

1 primary outcome of clinical improvement at week 24 (odds ratio 2.78 (95% CI 1.53–5.06), compared to  
2 continuation of the phosphodiesterase type-5 inhibitor(38). As a pragmatic, unblinded study, participant  
3 knowledge of treatment group could have biased their reporting of functional capacity or performance on  
4 the 6MWD (two of the three components of the primary endpoint). Even so, only a minority of patients  
5 achieved clinical improvement (41% with riociguat versus 20% with continuation of the  
6 phosphodiesterase type-5 inhibitor).

7

### 8 Improving trial efficiency with target patient populations: phenotyping and risk enrichment

9 Enrichment strategies have the potential to decrease trial sample size by selecting patients phenotypically  
10 and/or mechanistically more likely to respond to the investigational drug (predictive enrichment) and/or at  
11 higher risk of progressing to the trial endpoint (prognostic enrichment). Given its promise, both the U.S.  
12 Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have encouraged  
13 consideration of enrichment in phase 3 trials, though it should be noted that such strategies can affect  
14 generalizability and applicability of trial results. ‘Enrichment’ strategies, at least in terms of prognostic  
15 enrichment by disease severity, are not entirely new to PAH trials as they have historically used a range  
16 of clinical data (e.g., World Health Association/New York Heart Association (WHO/NYHA) functional  
17 class, 6MWD, subtype of PAH) to target higher-risk cohorts of PAH patients. Adaptive strategies for  
18 future PAH trials might include: 1) the use of validated risk scores as inclusion/exclusion criteria, 2)  
19 adaptive enrichment using biomarkers, and 3) adaptive randomized discontinuation (**Figure 2**)(5,39–41).

20 One potential enrichment strategy is the use of PAH risk scores such as the Registry to Evaluate Early and  
21 Long-Term PAH Disease Management (REVEAL) 2.0 score or the Swedish Pulmonary Arterial  
22 Hypertension Registry (SPAHR)/ Comparative, Prospective Registry of Newly Initiated Therapies for  
23 Pulmonary Hypertension (COMPERA) approach, which are well-validated and clinically useful in  
24 PAH(42–45). Retrospective trial analyses have suggested the potential to integrate risk scores into PAH  
25 clinical trials to identify/screen for a particular risk population and enable time, sample size, and cost

1 savings(46). The ongoing ZENITH (A Study of Sotatercept in Participants With PAH WHO FC III or FC  
2 IV at High Risk of Mortality) trial restricts enrollment to high-risk patients defined as WHO/NYHA class  
3 III or IV and have a REVEAL Lite 2 risk score  $\geq 10$  in the eligibility criteria (ClinicalTrials.gov  
4 NCT04896008). Since high-risk PAH patients have higher baseline rates of clinical worsening events, the  
5 targeted trial sample size in ZENITH will be 166 patients, substantially smaller than other PAH trials with  
6 clinical worsening primary endpoints.

7 With adaptive enrichment, a pre-specified interim analysis is performed, and results utilized to enrich the  
8 target enrollment population in a pre-specified manner, often with ongoing enrollment throughout the  
9 process. This may require unblinding of the study arms for results analysis, usually by data and safety  
10 monitoring boards, although adjudication and then continued study completion by the steering  
11 committees and investigators can remain blinded. This may also be done in a blinded fashion by looking  
12 at the event rates in sub-populations and selecting to enroll more of certain sub-populations. Adaptive  
13 enrichment can facilitate several goals including prognostic enrichment (i.e., a higher risk population  
14 likely to have more events), predictive enrichment (i.e., patients with a greater likelihood to respond  
15 mechanistically to the intervention), and assessing futility (for overall study, for specific dose arm, or for  
16 sample size adjustment). While adaptive enrichment has not yet been performed in PAH trials, it has been  
17 used in oncology trials(47,48). The ongoing PVDOMICS study, which will apply deep phenotyping  
18 approaches in a large PAH population(49), may identify novel biomarkers (e.g. genetic or epigenetic  
19 markers, metabolomic profiles) as identify candidate prognostic or predictive enrichment variables in  
20 future trials.

21 Though not an enrichment strategy, adaptive randomized discontinuation studies utilize a single-blinded  
22 period to assess for drug tolerance, intervention response, and disease progression in individual  
23 participants, aiming to minimizing exposure to groups that do not respond or experience progression(7).  
24 Disease progression according to pre-defined criteria during this period results in withdrawal from the  
25 study if patients were in the intervention arm or conversion to active therapy if patient were on placebo.

1 This requires several pre-requisites: 1) intervention is not curative, 2) efficacy endpoints detect clinically  
2 meaningful responses, and 3) investigational drug discontinuation is safe. The last criterion may remain a  
3 concern in PAH, even though most PAH trial patients are receiving multi-agent background medications.  
4 Randomized discontinuation should have some potential benefit to the patient such as improved  
5 convenience or tolerance of the investigational treatment. An example of this design in PAH was  
6 performed by Rubenfire and colleagues who randomized 22 stable patients receiving intravenous  
7 epoprostenol to transition to subcutaneous treprostinil or placebo, with an allocation ratio of 2:1 in favor  
8 of subcutaneous treprostinil(50). Patients who deteriorated after transition from epoprostenol were rapidly  
9 re-initiated to intravenous epoprostenol. Patients in the placebo arm were less frequently able to transition  
10 from epoprostenol and seven of eight patients (88%) deteriorated compared to only 1 patient (7%) in the  
11 treprostinil group. This illustrates that randomized withdrawal trials should not be performed on PAH  
12 patients on monotherapy as their potential to deteriorate is high. This design may potentially be  
13 acceptable in stable patients on background therapy, though such a trial requires clinical expertise in PAH  
14 to ensure patient safety with vigilant observation and strict criteria for resuming therapy.

15

#### 16 Adaptive trial designs and Bayesian approaches

17 Innovative trial designs incorporating adaptive and Bayesian methods may improve efficiency and lower  
18 costs for future PAH RCTs. As opposed to traditional RCTs with a consistent randomization plan  
19 throughout the course of a trial, adaptive trials permit modifications of the design and statistical  
20 procedures based on observations that accumulate during the trial at pre-specified interim analyses at set  
21 intervals(51).

22 Adaptive trials are increasingly used in all phases of clinical research(51). There are several applications  
23 of adaptive methods to clinical trial design including adaptive dose-finding (e.g. dropping doses that seem  
24 non-informative), adaptive hypotheses (e.g. a shift from single to multiple hypotheses), adaptive group  
25 sequential (e.g. a variation of classical group sequential study but with adaptive sample size re-estimation,

1 or pre-specified options of adding or deleting treatment arms, changing doses, or changing study  
2 endpoints), adaptive randomization (e.g. where patients have varying probability of allocation to a  
3 treatment arm based on previous analyses), biomarker-adaptive design (e.g. where allocation or design  
4 adapts based on the response of biomarkers) and seamless phase 2/3 designs(52). Seamless designs  
5 combine two separate phase 2 and phase 3 trials which are operationally seamless. Adaptive seamless  
6 phase 2/3 trials therefore use data from phase 2 to inform the phase 3 study (**Figure 3**).

7 The goals of using adaptive seamless phase 2/3 trials are to reduce cost and duration of separate phase 2  
8 and 3 trials, which is particularly important in a rare disease such as PAH, with a limited number of  
9 patients available for trials. Other potential advantages of adaptive designs are to reduce the number of  
10 patients needed in the phase 3 study, improved selection of target doses and participants for the phase 3  
11 trial, identification of covariates between short-term endpoints in phase 2 and long-term clinical outcomes  
12 in phase 3. An ongoing seamless phase 2/3 trial is evaluating an inhaled soluble guanylate cyclase  
13 stimulator (MK-5475) in PAH, using a phase 2 study to select the best safety profile and efficacy for  
14 reducing pulmonary vascular resistance, progressing into a phase 3 confirmatory cohort evaluating the  
15 effect on 6MWD (ClinicalTrials.gov NCT04732221). Similarly, the IMPAHCT (Inhaled iMatinib  
16 Pulmonary Arterial Hypertension Clinical Trial) study is a randomized, double-blind study with a phase  
17 2b, an intermediate phase, and a phase 3: continuous recruitment is utilized, and an operationally seamless  
18 adaptive design allows for optimal dose selection (ClinicalTrials.gov NCT05036135). In phase 2b a low,  
19 medium, and high dose inhaled imatinib will be compared to placebo and whichever dose has the optimal  
20 efficacy and safety properties for the phase 2b outcomes will be selected for phase 3.

21 Adaptive trials may employ traditional frequentist statistical approaches or may use Bayesian approaches  
22 using data from patients enrolled before and after adaptation. Philosophically, Bayesian approaches differ  
23 from the frequentist statistical approach in trials, which must reject a null hypothesis that two treatments  
24 are equivalent, to establish efficacy and/or safety. The Bayesian approach determines a probability of  
25 estimates of the unknown treatment effect based on the observed data(53). Bayesian trials may provide

1 fewer clear-cut decisions since there is a subjective aspect to what probability threshold would change  
2 clinical practice (e.g. a 10% improvement vs 20% improvement in an outcome). The Bayesian approach  
3 incorporates prior beliefs and experience about treatment effect from before the trial, provide a formal  
4 method for updating information about the treatment effect as new data are observed during the trial (thus  
5 being well suited to multiple interim analyses), and then combines prior knowledge and accumulated data  
6 to calculate a posterior probability of the treatment effect. This posterior probability then can inform our  
7 decision to use (or not use) a treatment.

8 A criticism of Bayesian trial analyses is that they are ‘too’ subjective, being based on opinions or beliefs  
9 formed before study conduction. However, proponents argue that knowledge is incremental and  
10 cumulative, and that both frequentist and Bayesian approaches incorporate prior knowledge, rather than  
11 ignore it. Furthermore, it is possible to use non-informative priors in Bayesian analyses, which are neutral  
12 and not subjectively elicited, tending to arrive at similar results as a conventional frequentist analysis.  
13 Bayesian approaches may also improve efficiency of clinical trials. For example, the OSCAR (Oscillation  
14 in Acute Respiratory Distress Syndrome) trial compared high-frequency oscillatory ventilation to usual  
15 ventilation strategy in patients with acute respiratory distress syndrome(54). The trial was analyzed using  
16 a conventional frequentist approach, finding no difference between high-frequency oscillatory ventilation  
17 and usual ventilation on mortality (41.7% vs. 41.4%,  $p=0.85$ ). A re-design of the OSCAR trial using  
18 Bayesian methods and assumptions with a virtual re-execution suggested that a Bayesian design would  
19 have obtained the same conclusion considerably sooner (40 weeks) and with fewer patients enrolled(55).  
20 Bayesian analysis of RCTs may also deliver entirely different conclusions from a trial compared to  
21 frequentist analyses(56). For example, in the EOLIA (Extracorporeal Membrane Oxygenation (ECMO) to  
22 Rescue Lung Injury in Severe Acute Respiratory Distress Syndrome) trial there was not a statistically  
23 significant effect of ECMO on mortality ( $p=0.09$ ) despite the point estimate for absolute reduction in  
24 mortality of 11%(57). Using a Bayesian analysis of the EOLIA data with informative priors, the posterior  
25 probability of a mortality benefit with ECMO (relative risk [RR] < 1) was 96% and the posterior

1 probability of a RR of  $< 0.8$  was 60%. With data-derived prior distributions the posterior probability of a  
2 RR  $< 1$  was 99% and the posterior probability for a RR  $< 0.8$  was 83%. Thus, Bayesian analyses may  
3 provide posterior probabilities that still support the utility of certain therapies in certain clinical situations,  
4 even when the canonical ‘p-value’ threshold of 0.05 is not met in a RCT. Regulatory agencies expect to  
5 evaluate the body of evidence as a whole, whether the prior information has been formally incorporated  
6 into a Bayesian analysis or not. A trial generating a p-value of 0.09 in favour of a treatment should not  
7 simply be thought of as a ‘negative’ trial but as an addition to the overall evidence available against the  
8 null hypothesis. Bayesian statistics are not a panacea and also rely on specific assumptions, require  
9 substantial modelling to implement, and require agreement beforehand as to what constitutes a reasonable  
10 prior and treatment effect. In essence, these decisions may be as subjective as the selection of a suitable p-  
11 value and treatment effect size in a frequentist analysis.

12

### 13 Proposal for an adaptive platform trial for right ventricular failure in PAH

14 Adaptive platform trials use a ‘master protocol’ and adaptive trial features (e.g. adaptive enrichment,  
15 adaptive randomization) to evaluate several therapies simultaneously, with the flexibility to add or  
16 remove arms based on pre-defined rules and new information as it accumulates during the trial(58).  
17 Platform trials have been remarkably successful in answering therapeutic questions quickly and  
18 efficiently during the COVID-19 pandemic in the SOLIDARITY(59,60) and REMAP-CAP  
19 programs(61,62). We propose that an adaptive platform trial could be ideally suited to evaluate multiple  
20 candidate therapies that target mechanisms of right ventricular failure in patients with PAH (63). A  
21 flexible multi-arm multi-stage platform design could incorporate the seamless phase 2/3 feature with pre-  
22 specified stopping boundaries at interim analyses; this would to allow early removal of therapies likely to  
23 be futile and only promising therapies would proceed to phase 3 (see **Figure 3**)(64). Traditional and novel  
24 endpoints discussed later in this review could be incorporated in phases 2 and 3. The platform trial  
25 approach permits the addition of new therapies as they arise while reducing the required total sample size



1 (and consequently, costs) required to evaluate each investigational therapy in separate trials. The PAH  
2 adaptive platform infrastructure could also be more broadly extended to a ‘basket’ platform to include  
3 populations with right ventricular failure due to other conditions such as pulmonary hypertension  
4 associated with lung disease or congenital heart disease (**Figure 4**). Control of the type 1 error (false  
5 positive) rate, ensuring adequate sample sizes at interim analyses, and adequate justification of this  
6 approach would be essential from the regulatory perspective(65,66). A PAH platform trial would require  
7 monumental collaboration and cooperation between multiple pharmaceutical companies, investigators,  
8 patients, regulators, and funding bodies, but could revolutionize our approach to evaluating therapeutics  
9 that target right ventricular failure.

10

11

## 12 Pragmatic trials and real-world data

13 Evidence from RCTs is not sufficient to completely guide choice of treatment for real-world patients, who  
14 may be more diverse or have more comorbidities than patients represented in RCTs. Pragmatic trials and  
15 real-world data provide complementary evidence about effectiveness and safety in clinical practice, which  
16 is important to clinicians and to payers (67). They can be useful to guide health policy decisions or  
17 adoption of new therapies in real-world clinical practice.

18 Pragmatic trials, like traditional RCTs, require a careful choice of clinical setting, a relevant study  
19 population, mode of intervention, comparator population, and appropriate outcomes(67). In contrast to  
20 standard RCTs that aim to determine the efficacy of an intervention under ideal circumstances and often  
21 take place in tertiary academic centers, pragmatic trials aim to evaluate effectiveness of an intervention in  
22 real-world populations and settings. Pragmatic trials should be similar to usual care in terms of the  
23 eligibility of trial investigators and participants, flexibility of delivering the intervention, the nature of  
24 follow-up(67). Patient-centric outcomes, such as quality of life, may be particularly relevant in pragmatic

1 trials where some RCT endpoints, such as invasively measured hemodynamics, may be less frequently  
2 available. Data collection and data monitoring should have minimal impact on delivery of usual care in  
3 the clinical setting. In PAH, recent RCTs have excluded patients with a variety of comorbidities and risk  
4 factors for left heart or lung disease, yet these patients are common in clinical practice and are frequently  
5 treated with PAH therapies(68,69). Pragmatic trials could provide complementary evidence for the use of  
6 PAH drugs in these patients with minimization of exclusion criteria but would still need to ensure  
7 rigorous and accurate diagnosis of PAH (e.g. requiring a right heart catheterization to establish the  
8 diagnosis). Pragmatic trial designs are being used currently in the SPHERe (Supervised Pulmonary  
9 Hypertension Exercise Rehabilitation) trial(70) and in a study comparing monotherapy versus dual  
10 therapy in pediatric PAH (NCT04039464).

11 Pragmatic trials face several challenges including the monitoring and reporting of safety events, which  
12 may in turn alter usual care. Since pragmatic trials are usually not blinded, reporting of adverse events  
13 and reasons for discontinuation may be biased. Other challenges include obtaining detailed informed  
14 consent in clinical practice settings, lack of incentives or support to centers for enrolment or data  
15 collection, and the inefficiencies introduced by participating in trials. PAH treatment availability,  
16 reimbursement, and clinical practice patterns may vary considerably between countries, which could  
17 influence enrollment and generalizability of pragmatic trials in PAH. Solutions include creating organized  
18 research centers to support and execute pragmatic trials across several clinics and use of existing data  
19 infrastructure to facilitate data collection. For example, linkage to electronic health records could  
20 overcome some of the problems in pragmatic trials with adverse event reporting and may accurately  
21 identify serious adverse events, as demonstrated in the West of Scotland Coronary Prevention Study  
22 (WOSCOPS)(71,72). However, electronic health record systems may not be available in some low-to-  
23 middle-income countries or in non-academic centers in other settings, potentially limiting real-world  
24 centers from participating. A pragmatic PAH trial could also be embedded within an existing disease  
25 registry for data collection, such as the Pulmonary Hypertension Association Registry in the United

1 States, which already uses electronic case report forms and includes patient-reported measures such as  
2 quality of life(73).

3

#### 4 Health economics and cost-effectiveness

5 The cost of new PAH therapies will need to be justified to payers. Economic evaluations can be run in  
6 parallel with RCTs to estimate the value of resources used in each trial arm(74). The payers' perspectives  
7 and requirements across multiple countries and settings should be elicited and integrated prior to phase 3  
8 design to ensure that successfully approved drugs will be widely reimbursed to benefit the greatest  
9 number of patients. For an economic evaluation, a universal metric of health is needed to compare across  
10 and within diseases, such as quality of life measured using the standardized international questionnaire,  
11 EQ-5D (3L or 5L)(75). Such analyses can compare the incremental benefit of adding a new PAH therapy  
12 or can compare the relative difference between PAH treatments(76). Differing follow-up periods and  
13 missing data present a challenge in economic evaluations. Furthermore, censoring during a trial, due to  
14 patient dropout, loss to follow-up, or death, is problematic for these analyses as they result in missing data  
15 which is often missing not at random(77). Different methods of imputation to death with such missing  
16 data can lead to substantially different estimates for the incremental cost effectiveness(78,79).

17

## 18 **Part 2 - Redefining clinically meaningful endpoints**

### 19 Proposals for innovating composite endpoints

20 While the event-driven trials provide a higher level of evidence and represent a major advance in PAH  
21 trial design, there are several potential solutions that may overcome the limitations of previously used  
22 composite endpoints. Most PAH trials have not captured or reported subsequent or recurrent events after  
23 the first clinical failure event (other than death). Thus, future trials could consider recurrent events  
24 analyses, capturing and reporting the total number of morbidity events even after the first clinical failure

1 event, since recurrent deteriorations are highly relevant to patients, physicians, and payers. Another  
2 potential approach to consider for composite endpoints in future PAH trials is the win ratio(80), which  
3 was used in the CHART-1 (The Congestive Heart Failure Cardiopoietic Regenerative Therapy) trial that  
4 evaluated cardiopoietic stem cells for heart failure patients with reduced left ventricular ejection fraction  
5 ( $\leq 35\%$ )(81). The key principle of the win ratio is that pair-wise comparisons are made between all  
6 patients in the treatment group and all patients in the comparator group(80). Within each pair, the  
7 components of the composite outcome are compared sequentially in an order that reflects the hierarchy of  
8 importance for the individual components. For example, in a hypothetical PAH trial with a time to first  
9 clinical failure composite endpoint, the relative importance in descending order of severity could be  
10 considered as death, lung transplantation, hospitalization for worsening PAH, improvement in risk status,  
11 followed by improvement in functional capacity or a PRO reflecting quality of life (**Figure 5**). With the  
12 win ratio method different types of endpoints including non-time-to-event outcomes such as quality of life  
13 and clinical improvement components can easily be included. If the patient in the comparator group of the  
14 pair dies and the patient in the treatment group does not, it is called a win for the treatment group. If both  
15 die, it can be designated as a tie, or the one who dies later is designated as the win. If neither patient dies,  
16 we proceed to the next outcome of lung transplantation, and proceed in this way for each component of  
17 the composite. The ratio of wins between the treatment and comparator group is the effect of the  
18 intervention, or the probability of a 'win' with treatment. While this approach has been used in several  
19 trials, it remains less familiar to most clinicians and trialists and has not yet been used in a PAH clinical  
20 trial.

#### 21 Hemodynamic remote monitoring endpoints

22 Studies have shown that selected hemodynamic variables such as right atrial pressure, cardiac index, and  
23 stroke volume index (defined as cardiac index/heart rate) are predictive of outcome in PAH(82–84). As  
24 hemodynamic decompensation occurs earlier than right ventricular failure, early and remote detection of  
25 hemodynamic worsening could be helpful for the management of patients with PAH(85). Right heart

1 catheterization remains the gold standard for the evaluation of right ventricular function in PAH(86–88).  
2 However, it is an invasive method that must be performed in supine position at rest and therefore it  
3 provides only a single time point assessment. Furthermore, short-term assessment of changes in  
4 hemodynamic variables only explains a small proportion of the overall treatment effect on clinical  
5 outcomes(89), and as such are not surrogates for clinical outcomes. To provide additional information on  
6 hemodynamic changes at different times, continuous hemodynamics tools have been developed in both  
7 left heart failure and PAH.

8 The CardioMEMS™ is a small, wireless monitoring sensor implanted in the pulmonary artery to monitor  
9 pulmonary arterial pressure and heart rate. An early study showed that patients with left heart failure  
10 monitored and managed using this device had significantly fewer hospitalizations due to heart failure as  
11 compared to the control group(90). CardioMEMS™ seems to be safe and reliable in patients with left  
12 heart failure(91,92). It has been studied in a small cohort of 26 patients with severe PAH(93), and two  
13 other studies are ongoing employing CardioMEMS™ to titrate treatment to goal mean pulmonary artery  
14 pressure (ARTISIAN Trial, ClinicalTrials.gov NCT05203510 and CS1-003 Trial, ClinicalTrials.gov  
15 NCT05224531). The main limitation of using the current CardioMEMS™ system as a trial endpoint is  
16 that it evaluates only pulmonary artery pressure, which does not reflect the severity of PAH, and misses  
17 measures of cardiac output and stroke volume index that are more important prognostic factors. However,  
18 a next generation CardioMEMS™ system is under development which may be able to estimate cardiac  
19 output (ClinicalTrials.gov NCT05428384), potentially overcoming this limitation.

20

#### 21 Proposal of novel endpoints based on actigraphy

22 Unlike the 6MWD, which is a snapshot of submaximal exercise capacity at one moment in time,  
23 actigraphy captures activity levels in daily life averaged over time. Actigraphy devices have been used  
24 widely in studies of healthy individuals and various cardiopulmonary diseases but have limited evaluation  
25 in PAH trials. Step counts measured by accelerometry devices correlate with markers of disease severity

1 and are associated with clinical outcomes in adult and pediatric PAH patients(94–97). Daily step counts  
2 and activity intensity (sedentary, moderate, vigorous) were associated with several domains on the Short  
3 Form-36 quality of life instrument, in stable PAH patients(98). The TRACE (Effect of Selexipag on Daily  
4 Life Physical Activity of Patients With Pulmonary Arterial Hypertension) trial measured step counts with  
5 actigraphy as an endpoint and demonstrated the feasibility of actigraphy within the context of a PAH trial,  
6 but found with no significant difference observed between add-on selexipag and placebo on daily step  
7 counts or non-sedentary activity(99). Another recent feasibility RCT also found that actigraphy-measured  
8 step counts were responsive to a mobile health intervention, demonstrating that such endpoints can be  
9 sensitive to interventions in patients with PAH(100).

10 Potential challenges to using actigraphy can be extrapolated from recent experience in heart failure trials.  
11 Changes in activity levels may be discordant from other measures of exercise capacity such as the 6MWD  
12 and may not necessarily mirror changes in other clinical outcomes(101). In the AWAKE-HF study, there  
13 was no improvement in mean activity counts with sacubitril/valsartan vs enalapril even though long-term  
14 clinical outcomes were significantly improved with sacubitril/valsartan(102). There are also potential  
15 challenges to actigraphy-based endpoints from the regulatory perspective. Scoring of activity intensity  
16 uses algorithms (most of which are proprietary) that may differ between devices, which may give a  
17 different result for the same activity. It is also unclear how to best handle missing data for actigraphy  
18 outcomes in clinical trials. Lastly, the minimal clinically important difference for within-patient change in  
19 actigraphy measures are not defined. Thus, before actigraphy outcomes are widely integrated in PAH  
20 trials, future studies are needed to determine which actigraphy-based measures to use in PAH patients,  
21 how they related to other established clinical outcomes, what is the minimal clinically meaningful  
22 difference for change in actigraphy-based measures in PAH patients, and how to interpret discordant  
23 results with changes in 6MWD or other commonly used measures of function. Many of these questions  
24 may be answered in the recently launched ACTiPH study (Physical Activity in Pulmonary Arterial  
25 Hypertension, National Institutes of Health, project number 1R01HL159997-01).

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## Proposal of novel endpoints based on multiparametric assessment risk stratification

As discussed above, the endpoints used in previous PAH trials, such as 6MWD and time to clinical worsening, have some important limitations. Multicomponent improvement endpoints are one potential solution that were used as the primary endpoint in the recent REPLACE study of switching a phosphodiesterase type-5 inhibitor to riociguat(38) and as an exploratory endpoint in the PULSAR (A Study of Sotatercept for the Treatment of Pulmonary Arterial Hypertension) trial of sotatercept as add-on therapy(103). However, multicomponent risk-based endpoints are not currently accepted as a primary endpoint in any ongoing study. Despite the established predictive value in numerous registry studies, the role of risk stratification tools in clinical trial endpoints remains unclear and these endpoints have not yet been accepted by regulatory authorities. If one uses multicomponent improvement endpoints, all components must be relevant to patients and each need to be predictive of clinically relevant outcomes.

A retrospective study from the COMPERA registry compared the value of the change in different variables from baseline to follow-up to predict survival in treatment naïve PAH patients(104). Sole improvements in 6MWD or N-terminal pro-brain natriuretic peptide (NT-proBNP), respectively, did not have any predictive value for future outcomes, whereas improvement in multicomponent endpoints and improvement in risk status carried prognostic information. The French non-invasive model (including congruent improvement of functional class, 6MWD and NT-proBNP level)(105) was the most discriminant model to predict survival.

In addition to reflecting patient symptoms, function, or survival, a primary endpoint should be validated (ideally prospectively) and should be highly discriminatory. Risk scores as a primary endpoint could satisfy all these requirements. Ideally, a new therapy would change a score and the change in score would predict the change in outcome. Several different risk scores have been proposed from Europe and the USA (**Table 3**)(4,42–45,84,105–109). The U.S. REVEAL 2·0 score categorizes patients into eight levels of risk(42), with its simplified version (REVEAL Lite 2)(108), the SPAHR and the COMPERA method

1 using three strata(44,45). Additionally, the French approach can identify patients at low risk of  
2 mortality(84,105). More recently, a four-strata approach based on widely available non-invasive variables  
3 has been proposed by the COMPERA registry investigators and validated in the French Registry(4,109).  
4 Risk scores predict both 1- and 5- year survival and, for some scores, clinical worsening and  
5 hospitalizations(42,110). Risk scores also correlate with quality of life(110). Many risk scores have been  
6 validated retrospectively across global registries(4,43,107,111) and in post-hoc analyses of clinical  
7 trials(112–114). Exploratory analyses using risk stratification have been performed in randomized control  
8 trials such as GRIPHON, PATENT-1 (Pulmonary Arterial Hypertension Soluble Guanylate Cyclase–  
9 Stimulator Trial 1) and AMBITION (Ambrisentan and Tadalafil in Patients with Pulmonary Arterial  
10 Hypertension) to determine subgroups of patients in whom treatment effects were more pronounced. It is  
11 important to highlight that in the registry studies and post-hoc analyses of clinical trial populations, the  
12 predictive abilities of the available risk scores are better when applied at the time of reassessment than at  
13 baseline. Finally, the COVID-19 pandemic illuminated the utility of exclusively non-invasive risk  
14 assessments and that such risk scores can adequately discern if a patient is at low risk(105,108).

15 Surrogate endpoints have been used in place of clinical outcomes in some circumstances, such as with  
16 blood pressure as the primary outcome in systemic hypertension trials. To be an acceptable surrogate for  
17 mortality, treatment induced changes in risk scores must reliably and strongly predict benefit on mortality,  
18 based on evidence from clinical trials and epidemiologic studies(27,115,116). There are currently no  
19 accepted surrogate endpoints for mortality or any other clinical outcomes PAH trials. An acceptable  
20 surrogate would be useful in a rare disease like PAH where important clinical outcomes (death,  
21 transplantation, hospitalization) occur at a low frequency or in the distant future. While risk scores are  
22 associated with mortality in observational studies, and could offer advantages and efficiencies as trial  
23 endpoints, correlation alone does not establish these as acceptable surrogates for clinical outcomes. As  
24 discussed, previously used clinical worsening endpoints are not strongly correlated with mortality at the  
25 trial level(37). To establish risk scores as surrogates for mortality, or other clinical outcomes such as



1 hospitalization for worsening PAH, we propose that they be incorporated as in all ongoing and future  
2 trials in a standardized manner to allow comparisons across multiple trials. Next, the association between  
3 changes in risk and changes in clinical outcomes should be assessed across multiple trials in a future  
4 meta-analysis, ideally by pooling individual participant-level data. Additionally, it should be clearly  
5 established that changes in risk scores reflect an outcome that is important to patients(110,117).

6

### 7 Incorporating the patient perspective in clinical trials: design and patient-reported outcomes

8 Recently, patients with PAH and their caregivers have been engaged in setting future research  
9 priorities(118) and a recent “Call to Action” by the Pulmonary Hypertension Association (PHA) Europe  
10 framed the importance of empowerment of patient and advocacy organizations, including in clinical  
11 research and innovation(119,120). Future PAH clinical trials should mandate incorporating PAH patient  
12 representatives on steering committees and carefully consider patient perspectives in trial design, conduct,  
13 and how results will be communicated to patients after the trial is completed. The 6th World Symposium  
14 on Pulmonary Hypertension also recommended including patient partners as consultants in the RCT  
15 design process to ensure the importance of overall well-being as a central component. It was  
16 recommended that patient-reported outcomes (PROs) should be regarded with equal importance as other  
17 endpoints such as 6MWD and morbidity events(121). A (PRO) is any report of a patient’s health  
18 condition that comes directly from them without the interpretation of their response by a clinician or other  
19 person, or any outcome evaluated by the patient based on their own perception of a disease and its  
20 treatment(122,123).

21 The impact of PAH on quality of life is profound, with more than 85% of patients reporting significant  
22 impairment in their emotional wellbeing(124). Improvement in quality of life can be equally important to  
23 patients with PAH as is increased life expectancy, though this may depend on what stage the patient is in  
24 during their illness(124). The traditional endpoints in PAH trials measure pathophysiologic features of the  
25 disease but do not capture the patient experience. The impact of new treatments on symptoms and quality

1 of life, as well as burdens of treatment, are relevant to patients and regulatory agencies(125). There are  
2 several validated questionnaires that could be used as PROs in PAH trials, including generic instruments,  
3 such as the Short Form-36, and disease-specific instruments such as the CAMPHOR (Cambridge  
4 Pulmonary Hypertension Outcome Review), PAH-SYMPACT (PAH Symptoms and Impact) and  
5 EmPHasis-10 (e**Table** in Web Appendix)(126–132). The PAH-SYMPACT is a multidimensional tool  
6 that considers symptoms and impact, whereas EmPHasis-10 is a unidimensional questionnaire relative to  
7 quality of life. There is some overlap between these questionnaires but there are also unique questions on  
8 each tool. Therefore, it is critical to select the right tool to ask the most relevant questions to PAH patients  
9 for a given trial. Importantly, no tool captures the full spectrum of symptoms, quality of life and  
10 emotional well-being across the broad range of ages, genders, and cultures as is seen in PAH.

11 There are several important challenges and limitations to incorporating PROs in RCTs. It is important to  
12 choose a questionnaire that has been developed in line with regulatory guidance(122). Currently, the  
13 PAH-SYMPACT is the only PAH PRO developed in accordance with FDA guidance for PROs(127). The  
14 CAMPHOR instrument requires a fee for use, limiting its use in research and clinical practice. There are  
15 also practical and economic limitations including the risk of questionnaire “fatigue” in participants, need  
16 for linguistic validation and cultural adaptation to varied populations, and the financial cost associated  
17 with certain questionnaires and the validation methodology. The PAH patient and clinical trialist  
18 communities should work together to determine which trial endpoints are most meaningful to patients,  
19 which PROs should be used, where PROs stand in relation to other endpoints, and whether PROs could  
20 be acceptable as primary endpoints and/or as components in composite primary endpoints.

#### 21 What drugs are currently in phase 2 and 3 clinical trials?

22 Several medications with novel mechanisms of action or unique delivery routes are transitioning into  
23 phase 3 investigation (**Figure 6** and **Table 4**)(133). Specifically, through efforts to optimize drug  
24 delivery, dry powder inhalation has emerged as an appealing route of administration that has been and  
25 continues to be investigated in phase 3 trials (i.e. treprostinil, phosphodiesterase type-5 inhibitors, and

1 soluble guanylate cyclase stimulators), primarily with the goal of improving patient  
2 convenience(134,135). Investigational approaches on existing pathways include ralinepag, a novel  
3 prostacyclin receptor agonist currently in phase 3 trials(136), inhaled vardenafil, a phosphodiesterase  
4 type-5 inhibitor, which is under study in a phase 2 trial (ClinicalTrials.gov NCT04266197), and MK-4575,  
5 an inhaled soluble guanylate cyclase stimulator that is in a phase 2/3 trial (ClinicalTrials.gov  
6 NCT04732221).

7 There are three investigational agents targeting novel mechanisms that aim to rebalance the proliferative  
8 and anti-proliferative pathways in PAH pathobiology that are currently in phase 2 and 3 trials: sotatercept,  
9 a transforming growth factor-beta superfamily modulator that acts to re-balance the growth-promoting  
10 activin and growth-inhibiting bone morphogenic protein pathways(103), seralutinib, an inhaled inhibitor  
11 of platelet derived growth factor receptor (PDGF-R), colony stimulating factor 1 receptor (CSF1R), and  
12 stem cell factor receptor (c-KIT)(137), and inhaled imatinib (AV-101), a multi-target tyrosine kinase  
13 inhibitor. Imatinib is a well-established tyrosine kinase inhibitor with hematologic oncology applications  
14 and possible beneficial effects in PAH but due to trial design and concomitant medication interactions  
15 was unsuccessful when administered orally(138). Other novel pharmacologic approaches under  
16 investigation include rodatristat ethyl, an oral prodrug of a tryptophan hydroxylase inhibitor that blocks  
17 the serotonin pathway(133) and apabetalone, which is an oral inhibitor of the transcriptional and  
18 epigenetic regulator bromodomain-containing protein 4 (BRD4). Apabetalone improved pulmonary  
19 vascular disease and right ventricular function in animals(139) and will soon begin a phase 2 study after a  
20 recent pilot study demonstrated feasibility in patients with PAH(140). While several promising new  
21 potential therapies are currently under investigation, sotatercept is the only agent targeting a novel  
22 pathway that has so far met the primary endpoint in a phase 2 trial.

23

24 **Conclusion**

1 There has been astounding progress in therapies for PAH over the past 30 years. However, future PAH  
2 trials face important challenges as patients are increasingly on one, two or three PAH drugs, making it  
3 more difficult for new therapies to demonstrate effectiveness. In rare diseases like PAH there is a limited  
4 number of patients who are available and who are eligible for clinical trial participation. The need for  
5 more trials of novel therapies must be balanced with the need for increasingly large sample sizes for  
6 conventional event-driven trials. Innovative trial designs and novel patient-relevant endpoints could help  
7 solve these problems, allow more efficient trials, and permit rigorous testing of new therapies and novel  
8 pathways.

1 **Declaration of Interests**

2 JW has received research grants paid to his institution from Janssen, Actelion, Merck, and Bayer;  
3 consulting fees paid personally from Janssen; honoraria for lectures from Janssen; payment for expert  
4 testimony from Sprigings Intellectual Property Law; travel support from Janssen; and payment for  
5 participation in advisory boards from Janssen and Acceleron; all outside the submitted work.

6 AB has received grants paid to her institution from Acceleron, Janssen and MSD; honoraria for lectures  
7 from Janssen, MSD, and AOP; and travel support from Janssen, outside the submitted work.

8 AP has received a training grant from the National Heart, Lung, and Blood Institute paid to his institution;  
9 discloses stock or stock options in Bristol Myers Squibb, outside the submitted work.

10 DM has received research grants paid to his institution from Acceleron, Janssen, and Merck; consulting  
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12 KP has received research grants from British heart Foundation and SPARKS society in 1995-98 for  
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14 MAP declared no conflicts of interest.

15 FZ has received consulting fees from Amgen, Applied Therapeutics, Bayer, Boehringer Ingelheim,  
16 Cellprothera, CVRx, Janssen, Merck, Novartis, AstraZeneca, Cardior, Novo Nordisk, Servier, Vifor  
17 Fresenius; honoraria for lectures from Boehringer Ingelheim, Bayer, Vifor Fresenius; payment for expert  
18 testimony from Hogan Lovells; advisory board payment from Acceleron; leadership role with  
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21 MGM has received grants paid to her institution from Altavant; Aerovate, Acceleron, Merck, Bayer and  
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23 Therapeutics; honoraria for CME from Medscape; advisory board payments from Janssen, Aerovate, and  
24 Gilead; leadership roles on the board of directors for the International Society of Heart & Lung

1 Transplantation, Scientific Leadership Committee of the Pulmonary Hypertension Association and  
2 Scientific Advisory Board of United Therapeutics; outside the submitted work.

3 VM has received grants paid to his institution from Acceleron, Janssen, Sonovie, and United  
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6 Directors at Clene; outside the submitted work.

7 GS has received consulting fees from MSD, Bayer, Actelion, and Janssen; payment for lectures from  
8 MSD, Bayer, Actelion and Janssen; advisory board payments from Acceleron; outside the submitted  
9 work.

10 MH has received grants paid to his institution from Acceleron, AOP Orphan, Janssen, Merck, and Shou  
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13 board payments from Acceleron, Altavant, Janssen, Merck, and United Therapeutics; outside the  
14 submitted work.

15

**Note**

This is the submitted version of the article. Editorial modifications have been made:

- Figures 1a and 1b are e-Figure 1 in the published version
- Figure 3 is e-Figure 2 in the published version
- Figure 4 is e-Figure 3 in the published version
- Figure 2 is figure 1 in the published version
- Figure 5 is figure 2 in the published version
- Figure 6 is figure 3 in the published version
- Table 4 is Table 1 in the published version
- Table 1 has been omitted
- Table 2 is e-Table 1 in the supplemental material
- Table 3 is e-Table 2 in the supplemental material
- e-Table 3 has been added in the supplemental material

**1 Contributors Statement**

2 JW - conceptualization, literature search, figures and tables, writing original draft

3 AB - conceptualization, literature search, figures and tables, writing original draft

4 AP - conceptualization, literature search, figures and tables, writing original draft

5 DM - conceptualization, literature search, figures and tables, writing original draft

6 KP - conceptualization, writing - reviewing and editing

7 MAP - conceptualization, writing - reviewing and editing

8 FZ - conceptualization, writing - reviewing and editing

9 MGM - conceptualization, writing - reviewing and editing

10 VM - conceptualization, writing - reviewing and editing

11 GS - conceptualization, writing - reviewing and editing

12 MH - conceptualization, writing - reviewing and editing

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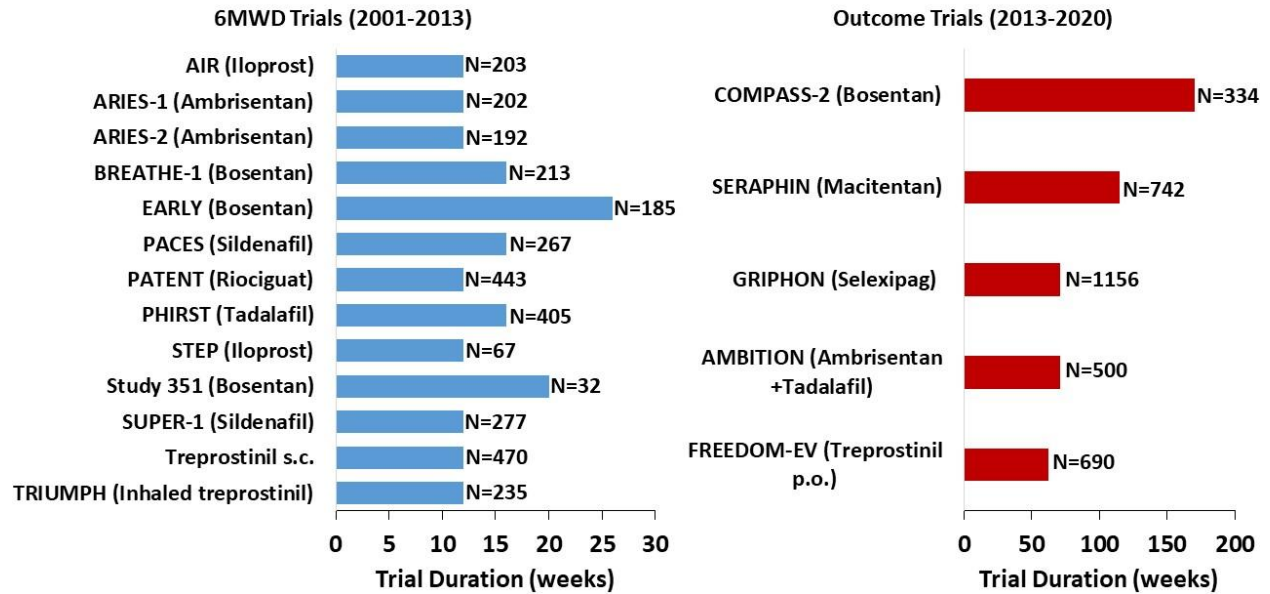
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1 **FIGURE LEGENDS**2 **Figure 1. Duration and size of pulmonary arterial hypertension randomized controlled trials.**

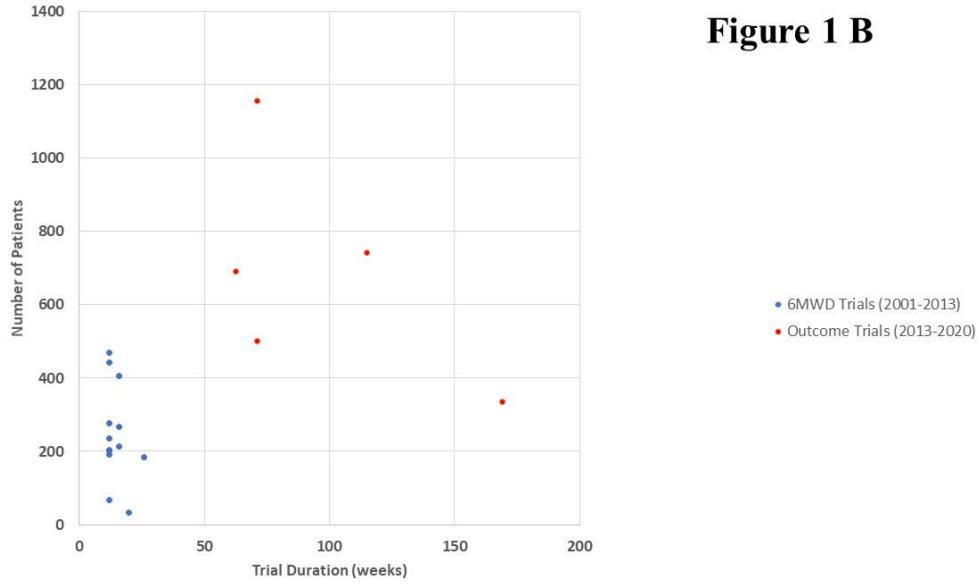
Figure 1 A



3

4 A) Pulmonary arterial hypertension clinical trials in the era of 6-minute walk distance primary

5 endpoint studies and studies that have used clinical outcome primary endpoints.



**Figure 1 B**

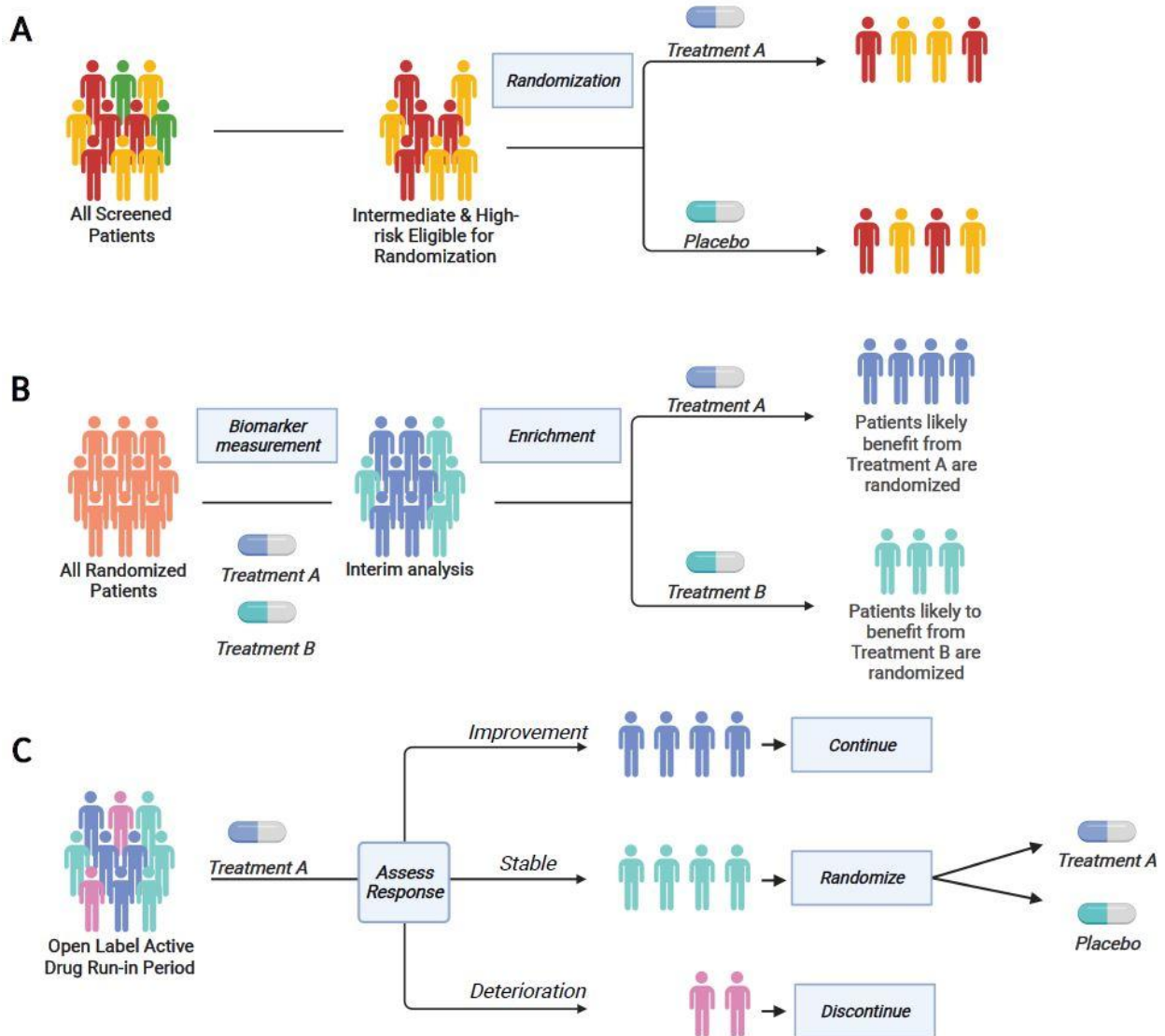
1

2 trial size vs duration. Abbreviations: p.o. – per os, s.c. - subcutaneous

3

B) Plot of

1 **Figure 2. Alternative clinical trial approaches.**



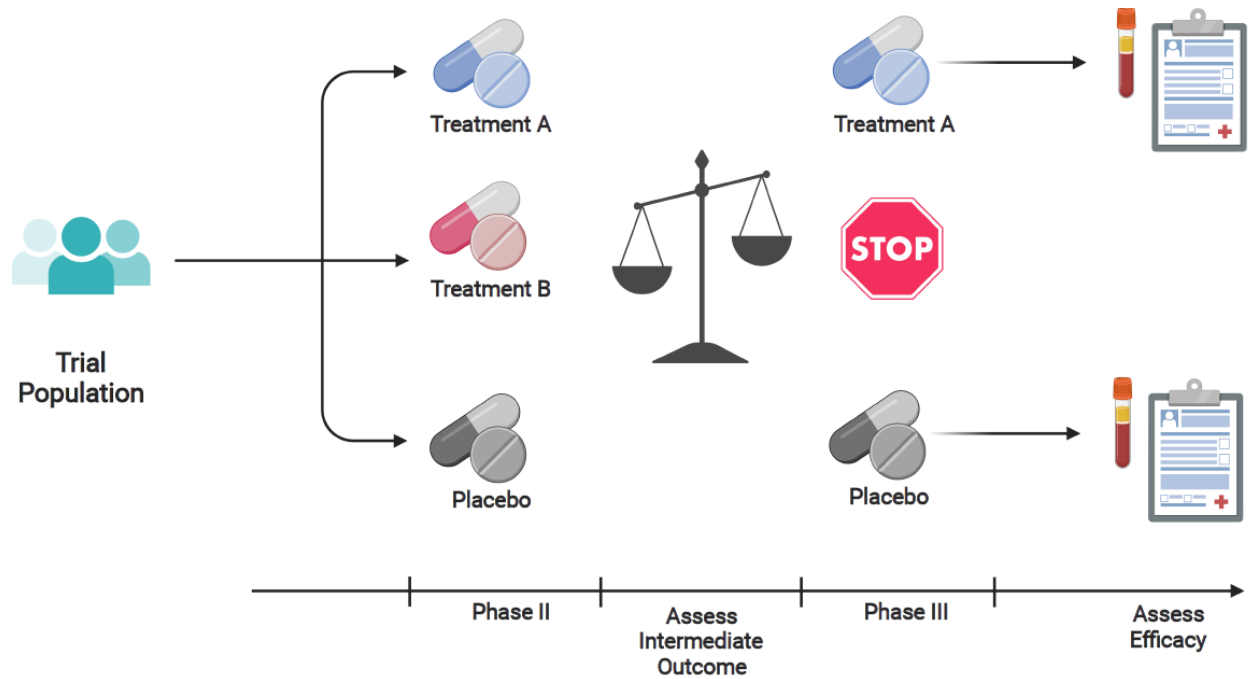
2

3 A) Risk-assessment based eligibility criteria for enrichment, B) adaptive enrichment recruitment based on

4 interim analysis response, and C) randomized discontinuation study design. Created with BioRender.com

5

1 **Figure 3. Adaptive seamless phase 2/3 trial design.**



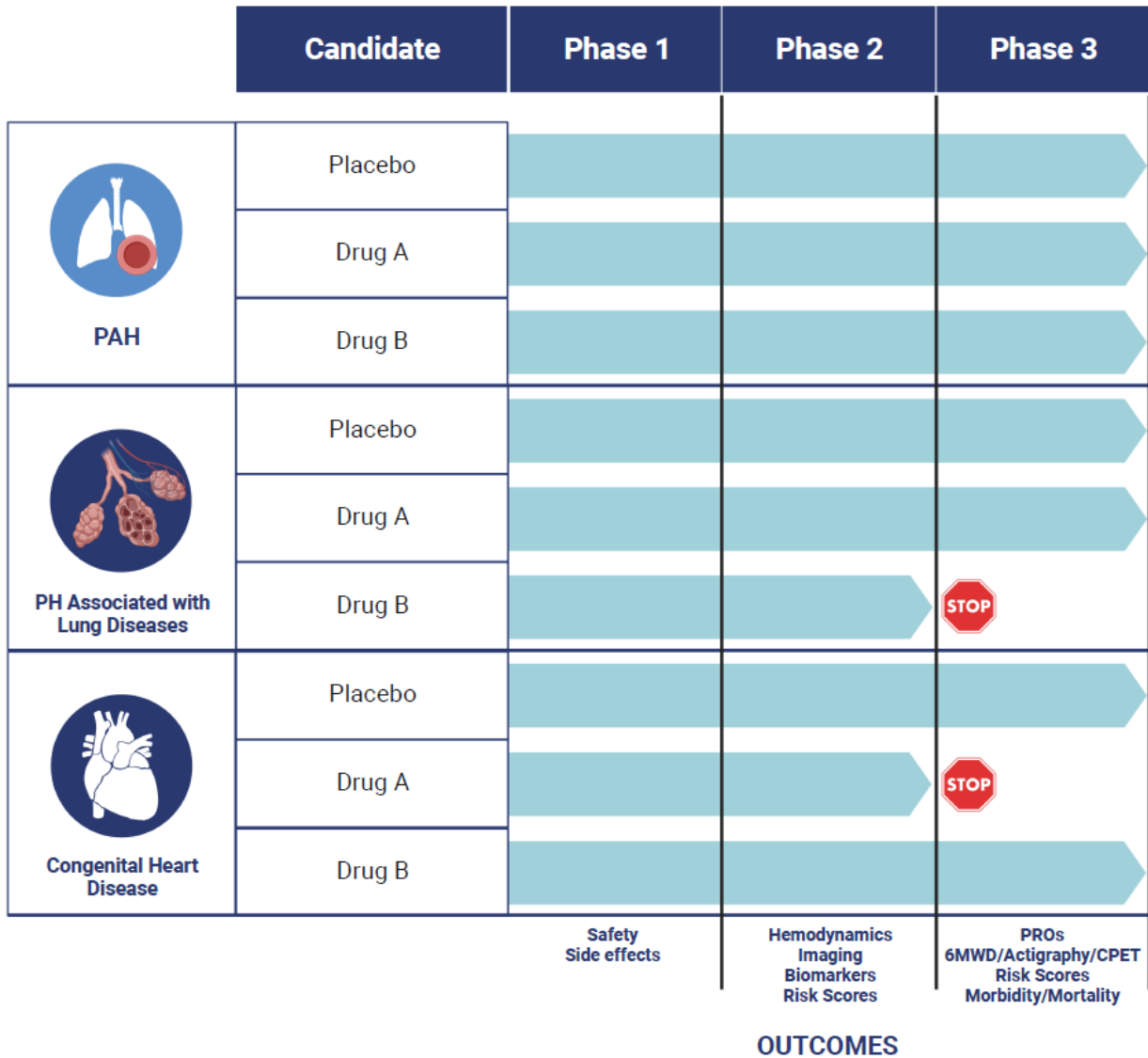
2

3 Participants are randomized to treatment A, treatment B or placebo. Assessment of the phase 2 outcome  
 4 indicates that treatment B is unlikely to benefit or is harmful. Treatment B is discontinued, and the phase  
 5 3 study continues with treatment A compared to placebo. Created with BioRender.com

6

7

1 **Figure 4. Theoretical design for an adaptive basket platform trial for therapeutics targeting right**  
 2 **ventricular failure due to pulmonary arterial hypertension and other conditions.**



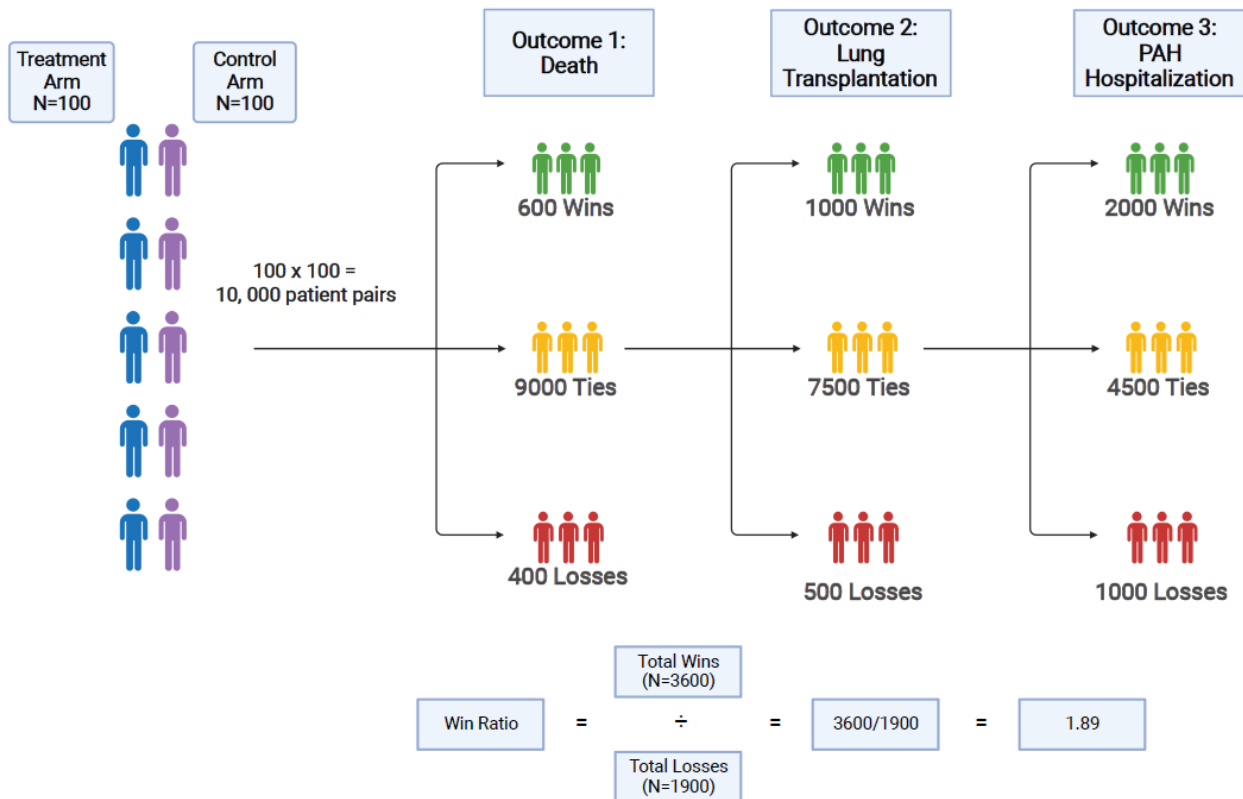
3  
 4 Participants within each condition would be randomized to Drug A, Drug B, or placebo. After assessment  
 5 of safety and side effects in Phase 1, candidate drugs are tested in Phase 2. Candidate treatments meeting  
 6 the primary endpoints in Phase 2 can proceed into Phase 3 using a seamless phase 2/3 design. Candidate  
 7 treatments that do not meet Phase 2 efficacy endpoints do not proceed to Phase 3, with efficacy that may  
 8 vary between conditions. Created with BioRender.com.



1 Abbreviations: PAH – pulmonary arterial hypertension, PH – pulmonary hypertension, PROs – patient  
 2 reported outcomes

3

4 **Figure 5. The Win Ratio method for a 3-component hierarchical composite outcome in a**  
 5 **hypothetical pulmonary arterial hypertension trial.**



6

7 In a hypothetical trial of 200 patients allocated 1:1 to an active treatment or control, pair-wise

8 comparisons are made between all patients in the treatment group and all patients in the comparator

9 group, yielding 10,000 patient pairs. Within each pair, the components of the composite outcome are

10 compared sequentially in an order that reflects the hierarchy of importance for the individual components.

11 If the patient in the comparator group of the pair dies and the patient in the treatment group does not, a

12 win is scored for the treatment group. If both die, it is a tie, or the one who dies later is designated as the

13 win. If neither patient dies, the next outcome of lung transplantation is compared similarly. If neither

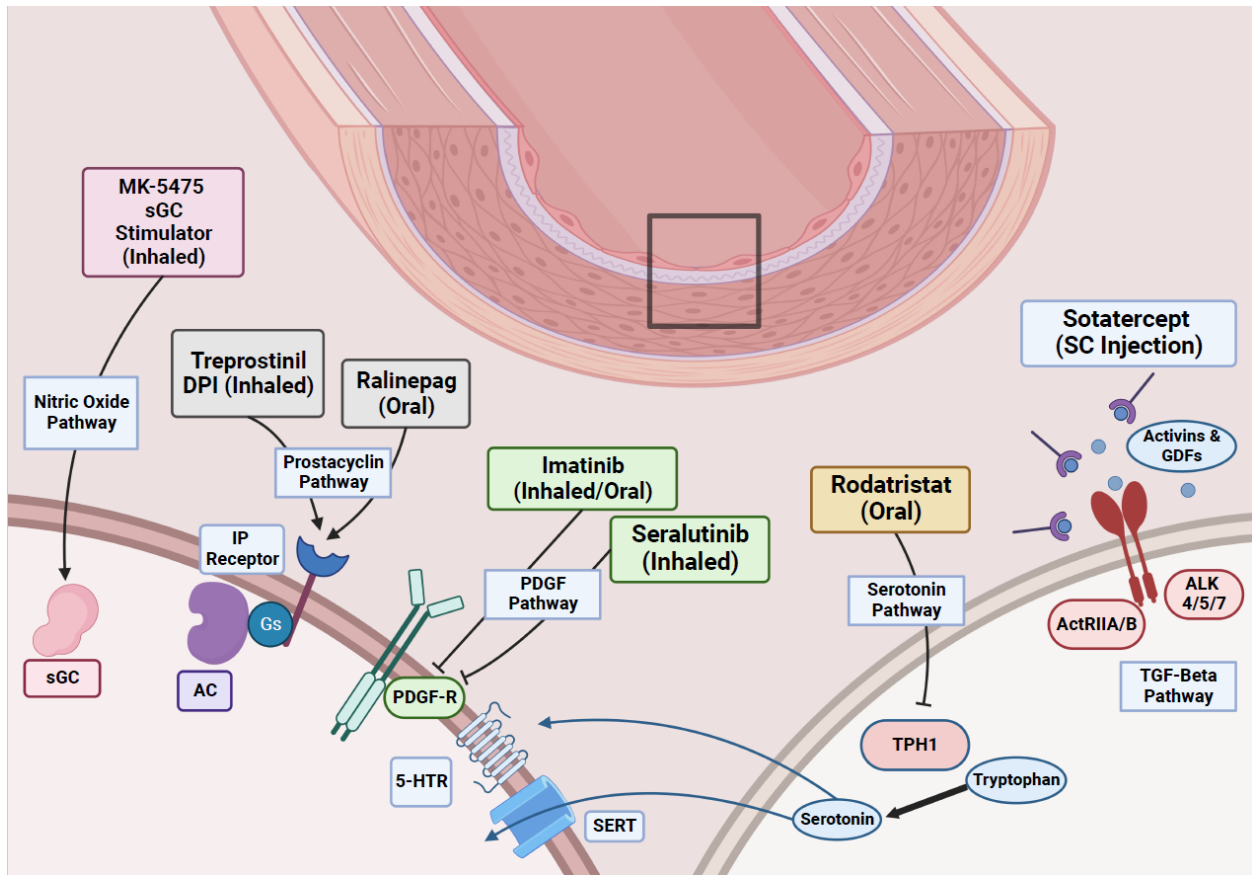
14 patient undergoes transplantation, the hospitalization outcome is compared. The number of total wins in

1 the treatment group divided by the number of number of total losses in the treatment group gives the win  
 2 ratio. Created with BioRender.com

3 Abbreviations: PAH – pulmonary arterial hypertension

4

5 **Figure 6. Novel pulmonary arterial hypertension therapies currently in phase 2 and 3 randomized**  
 6 **controlled trials**



7

8 Several investigational agents act predominantly through vasodilation by targeting existing pathways  
 9 (MK-5475, inhaled treprostinil DPI, and ralinepag). Several therapies under investigation, such as  
 10 imatinib, seralutinib, and sotatercept target the underlying proliferative component of pulmonary vascular  
 11 remodeling and may act through several other mechanisms and pathways not depicted in this image.

12 Abbreviations: 5-HTR – 5-hydroxytryptamine (serotonin) receptor, AC – adenylate cyclase, ActRIIA/B -

13 activin receptor type IIA/B, ALK - anaplastic lymphoma kinase, DPI – dry powder inhaler, GDF –

- 1 growth differentiating factor, IP – prostaglandin I<sub>2</sub>, PDGF – platelet derived growth factor, PDGF-R –
- 2 platelet derived growth factor receptor, SC – subcutaneous, SERT – serotonin transporter, sGC – soluble
- 3 guanylate cyclase, TGF-Beta – transforming growth factor-Beta, TPH1 – tryptophan hydroxylase.
- 4 Created with BioRender.com
- 5

1 **TABLES**2 **Table 1. Strengths and weaknesses of the novel trial designs and endpoints**

3 Abbreviations: 6MWD – 6-minute walk distance, PAH - pulmonary arterial hypertension, RCT –  
 4 randomized controlled trial

5

|   | <b>Strengths</b>   | <b>Weaknesses</b>   |
|---|--|---|
| <b>Novel trial designs</b>                    |  |   |
| Phenotype enrichment                          | <ul style="list-style-type: none"> <li>- Smaller sample size required</li> <li>- Target patient populations with a greater likelihood to respond mechanistically to the intervention</li> </ul>  | <ul style="list-style-type: none"> <li>- Can affect generalizability and applicability of trial results</li> </ul>  |
| Prognostic enrichment                         | <ul style="list-style-type: none"> <li>- Small sample size required</li> <li>- PAH risk scores already available</li> </ul>  | <ul style="list-style-type: none"> <li>- Can affect generalizability and applicability of trial results</li> </ul>  |
| Adaptative randomized discontinuation studies | <ul style="list-style-type: none"> <li>- Minimize drug exposure to groups that do not respond or experience progression</li> </ul>   | <ul style="list-style-type: none"> <li>- Phase 3 only</li> <li>- Pre-specified interim analysis</li> <li>- Risk of deterioration after investigational drug discontinuation</li> </ul>  |
| Adaptative trials                             | <ul style="list-style-type: none"> <li>- All phases of clinical research</li> <li>- Seamless phase 2/3 designs</li> <li>- Modifications of the design and statistical procedures based on observations gathered during the trial</li> <li>- Reduction of cost and study duration</li> <li>- Smaller sample size required in phase 3</li> </ul> | <ul style="list-style-type: none"> <li>- Pre-specified interim analysis</li> <li>- Need to determine what constitutes a reasonable prior and treatment effect if using Bayesian analysis framework</li> </ul>   |
| Pragmatic post approval trials                | <ul style="list-style-type: none"> <li>- Real-world population (minimization of exclusion criteria) which improves generalizability</li> <li>- Similar to usual care (eligibility of investigators and participants, flexibility of delivering the intervention, follow-up)</li> <li>- Evaluation of quality of life</li> </ul>                | <ul style="list-style-type: none"> <li>- Monitoring</li> <li>- Right heart catheterization less frequently available</li> <li>- Not blinded (reporting of adverse events and reasons for discontinuation may be biased)</li> <li>- Usual care may vary by treatment availability and reimbursement</li> </ul> |
| <b>Novel endpoints</b>                        |  |   |
| Composite endpoints                           | <ul style="list-style-type: none"> <li>- Currently used in PAH RCTs</li> </ul>   | <ul style="list-style-type: none"> <li>- Not designed to capture recurrent</li> </ul>   |

|   |   |  |
|---|---|--|
| in even-driven trials                                 | <ul style="list-style-type: none"> <li>- Possibility to use win ratio method</li> </ul>   | <ul style="list-style-type: none"> <li>events after the first clinical failure event</li> <li>- Not designed to capture improvement</li> </ul>   |
| Hemodynamic remote monitoring endpoints (CardioMEMS™) | <ul style="list-style-type: none"> <li>- Provide a continuous monitoring</li> </ul>   | <ul style="list-style-type: none"> <li>- Long-term safety issues (monitoring sensor implanted in the pulmonary artery)</li> <li>- Evaluates pulmonary artery pressure only, not cardiac output or stroke volume</li> </ul>   |
| Actigraphy  | <ul style="list-style-type: none"> <li>- Captures activity levels in daily life averaged over time (sedentary, moderate, vigorous)</li> <li>- Many tools available</li> </ul> | <ul style="list-style-type: none"> <li>- Changes in activity levels may be discordant from other measures of exercise capacity (6MWD)</li> <li>- Changes in activity levels may not necessarily mirror changes in other clinical outcomes</li> <li>- Minimal clinically meaningful difference not established</li> </ul> |
| Endpoints based on multiparametric risk assessment    | <ul style="list-style-type: none"> <li>- Predict death or lung transplantation</li> <li>- Reflect clinical improvement</li> </ul>   | <ul style="list-style-type: none"> <li>- Not yet accepted by regulatory authorities</li> <li>- Limited validation in clinical trials</li> <li>- Multiple tools, require standardization across trials</li> </ul>   |
| Patient reported outcomes                             | <ul style="list-style-type: none"> <li>- Relevant to patients and regulatory agencies</li> <li>- PAH-specific questionnaires available</li> </ul>                             | <ul style="list-style-type: none"> <li>- No tool captures the full spectrum of symptoms, quality of life and emotional well-being</li> <li>- Need for linguistic validation and cultural adaptation to varied population</li> </ul>  |

- 1 **Table 2. Primary endpoint definitions and components in outcome-driven pulmonary arterial**
- 2 **hypertension trials**
- 3 Abbreviations: 6MWD – 6-minute walking distance; PAH – Pulmonary arterial hypertension

| <b>Trial</b>  | <b>Primary Outcome Definition</b>  | <b>Definition of Worsening PAH</b>   |
|---------------|--|--|
| COMPASS-2(13) | Time to the first morbidity/mortality event. Defined as time to death from any cause, hospitalization for worsening PAH or start of intravenous prostanoid therapy, atrial septostomy, lung transplant, or worsening PAH.  | Worsening PAH, defined as either 1 or 2: <ol style="list-style-type: none"> <li>1) moderate or marked worsening of PAH symptoms on the patient global self-assessment together with the initiation of a subcutaneous or inhaled prostanoid or use of open-label bosentan;</li> <li>2) no change or mild worsening of PAH symptoms accompanied by a decrease in 6MWD by more than 20% from the previous visit or by more than 30% from the baseline visit, together with the initiation of a subcutaneous or inhaled prostanoid or use of open-label bosentan.</li> </ol> |
| SERAPHIN(14)  | Time to the first event related to PAH, defined as worsening of PAH, initiation of treatment with intravenous or subcutaneous prostanoids, lung transplantation, atrial septostomy, or death from any cause up to the end of treatment   | Worsening PAH, defined as the occurrence of all three of the following: <ol style="list-style-type: none"> <li>1) decrease in the 6MWD of at least 15% from baseline, confirmed by a second 6MWD performed on a different day within 2 weeks;</li> <li>2) worsening of symptoms of PAH;</li> <li>3) need for additional treatment for PAH</li> </ol>   |
| GRIPHON(15)   | Time to first event. Death or a complication related to PAH, whichever occurred first, up to the end of the treatment period.<br><br>Complications related to PAH were 1) disease progression or worsening of PAH that resulted in hospitalization, 2) initiation of parenteral prostanoid therapy or long-term oxygen therapy, 3) the need for lung transplantation, or 4) balloon atrial septostomy. | Disease progression, defined as a <ol style="list-style-type: none"> <li>1) decrease from baseline of at least 15% in the 6MWD (confirmed on a different day)</li> </ol> Plus <ol style="list-style-type: none"> <li>2) worsening in functional class (for the patients with functional class II or III at baseline) or the need for additional treatment of pulmonary arterial hypertension (for the patients with functional class III or IV at baseline)</li> </ol>   |
| AMBITION(17)  | Time to first occurrence of a composite end point of death, hospitalization for worsening pulmonary arterial hypertension, disease   | Disease progression, defined as a decrease of more than 15% from baseline in the 6MWD combined with functional class III or IV   |

|                |   |  |
|----------------|---|--|
|                | progression, or unsatisfactory long-term clinical response.   | <p>symptoms at two consecutive visits separated by at least 14 days</p> <p>Unsatisfactory long-term clinical response, defined as any decrease from baseline in 6MWD at two consecutive clinic visits after baseline separated by at least 14 days, and functional class III symptoms assessed at two clinic visits separated by at least 6 months (for those in the study at least 6 months)</p>  |
| FREEDOM-EV(16) | Time to first adjudicated clinical worsening event, which was defined as death from any cause, hospitalization for worsening PAH, disease progression, initiation of inhaled or infused prostacyclin therapy, or unsatisfactory long-term clinical response | <p>Disease progression, defined as a decrease in 6MWD at least 15% from baseline or too ill to walk directly related to PAH progression, confirmed by two 6MWD tests on different days, and worsening functional class or appearance of symptoms of right heart failure</p> <p>Unsatisfactory long-term clinical response, defined as decrease in 6MWD at week 24 or beyond at 2 consecutive visits on different days and sustained functional class III or IV symptoms for at least 24 consecutive weeks.</p> |

1 **Table 3. Comparison of risk assessment tools in pulmonary arterial hypertension**

2 Abbreviations: 6MWD – 6-minute walking distance, BNP – brain natriuretic peptide, COMPERA –  
 3 Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension, CI –  
 4 cardiac index, DLCO – diffusion capacity for carbon monoxide, HR – heart rate, NT-proBNP – N-  
 5 terminal pro-brain natriuretic peptide, NYHA FC – New York Heart Association Functional Class, PVR –  
 6 pulmonary vascular resistance, RAA – right atrial area, RAP – right atrial pressure, REVEAL - Registry  
 7 to Evaluate Early and Long-term Pulmonary Arterial Hypertension Disease Management, SBP – systolic  
 8 blood pressure, SPAHR – Swedish Pulmonary Arterial Hypertension Registry, SvO<sub>2</sub> – mixed venous  
 9 oxygen saturation, WHO – World Health Organization

10

|                      | <b>French invasive</b>   | <b>French Non-invasive</b>   | <b>SPAHR/<br/>COMPERA</b>   | <b>COMPERA 2.0</b>                  | <b>REVEAL 2.0</b>   | <b>REVEAL Lite 2</b>                             |
|----------------------|--|--|---|-------------------------------------|---|--|
| Variables            | NYHA FC I or II<br>6MWD > 440 m<br>RAP < 8 mmHg<br>CI ≥ 2.5 L·min <sup>-1</sup> ·m <sup>-2</sup> | NYHA FC I or II<br>6MWD > 440 m<br>NT-proBNP < 300 ng/L<br>or BNP < 100 ng/L | NYHA FC<br>6MWD<br>RAA (SPAHR only)<br>Pericardial effusion (SPAHR only)<br>NT-proBNP or BNP<br>RAP<br>CI<br>SvO <sub>2</sub> | NYHA FC<br>6MWD<br>NT-proBNP or BNP | WHO Group 1 subgroup<br>Demographics (age & male sex)<br>NYHA FC<br>SBP<br>HR<br>6MWD<br>NT-proBNP or BNP<br>DLCO<br>RAP<br>PVR | NYHA FC<br>SBP<br>HR<br>6MWD<br>NT-proBNP or BNP |
| Risk Strata          | 5 (number of low risk criteria present 0-4)  | 4 (number of non-invasive low-risk criteria present 0-3)                     | 3   | 4                                   | 8   | 3  |
| C-Index at baseline  | 0.61-0.62(42,106)  | ..   | ..  | 0.67(4)                             | 0.70-0.74(42,43)  | 0.71(108)  |
| C-index at follow-up | 0.64-0.72(42,106)  | 0.74(106)  | 0.62(42)  | 0.73(4)                             | 0.74-0.76(42,43)  | 0.70(108)  |



1 **Table 4. Summary of investigational pulmonary arterial hypertension therapies currently in phase**  
 2 **2, phase 2/3 or phase 3 trials.**

3 Abbreviations: 6MWD – 6-minute walking distance; BRD4 – bromodomain containing protein 4; c-KIT -  
 4 stem cell factor receptor; CSF1R - colony stimulating factor 1 receptor; DPI – dry powder inhaler; PDGF-  
 5 R – platelet-derived growth factor receptor; PETCO<sub>2</sub> – partial pressure of expired carbon dioxide; PVR –  
 6 pulmonary vascular resistance, TGF-B – transforming growth factor beta; V<sub>E</sub>/VCO<sub>2</sub> – minute ventilation  
 7 to carbon dioxide output ratio; VO<sub>2</sub> – oxygen consumption; WHO/NYHA – World Health  
 8 Organization/New York Heart Association; WU – Wood units

| Investigational Agent and Mechanism                                     | Trial Name and Registration       | Phase | Estimated Size | Key eligibility criteria   | Primary Outcome  |
|---|-----------------------------------|-------|----------------|--|--|
| Ralinepag<br>Prostacyclin receptor agonist                              | ADVANCE<br>(NCT03626688)          | 3     | 700            | WHO/NYHA Class II-IV   | Time to first clinical worsening event   |
|   | ADVANCE CAPACITY<br>(NCT04084678) | 3     | 193            | WHO/NYHA Class II or III<br>V <sub>E</sub> /VCO <sub>2</sub> ≥ 38<br>VO <sub>2</sub> ≥ 10 to < 18 mL·kg <sup>-1</sup> ·min <sup>-1</sup> | Change in peak VO <sub>2</sub> at Week 28  |
| Vardenafil DPI<br>(RT234)<br>Inhaled phosphodiesterase type 5 inhibitor | VIPAH-PRN<br>(NCT04266197)        | 2     | 40             | WHO/NYHA Class II-IV<br>PAWP or LVEDP ≤ 12 if PVR ≥ 3·75 and < 6·25 WU OR<br>PAWP or LVEDP ≤ 15 if PVR ≥ 6·25 WU                         | Treatment emergent adverse events, change in blood pressure, change in peak VO <sub>2</sub> , change in patient global impression of severity, change in V <sub>E</sub> /VCO <sub>2</sub> , change in PETCO <sub>2</sub> , change in exercise duration |
| MK-5475<br>Inhaled soluble guanylate cyclase stimulator                 | INSIGNIA-PAH<br>NCT04732221       | 2/3   | 450            | WHO/NYHA Class II-IV   | Phase 2: Change in PVR at Week 12<br><br>Phase 3: Change in 6MWD at Week 12  |
| Sotatercept   | STELLAR<br>(NCT04576988)          | 3     | 284            | WHO/NYHA II or III<br>PVR ≥ 5 WU   | Change in 6MWD at Week 24  |

|   |                             |      |     |   |  |
|---|-----------------------------|------|-----|---|--|
| TGF-B superfamily modulator   | HYPERION<br>(NCT04811092)   | 3    | 662 | Newly diagnosed<br>Intermediate and high<br>risk  | Time to Clinical Worsening,<br>defined as the first confirmed<br>morbidity event or death  |
|   | ZENITH                      | 3    | 166 | WHO/NYHA Class<br>III and IV at High-<br>Risk   | Time to first confirmed<br>morbidity or mortality event,<br>defined as all-cause death,<br>lung transplantation, or PAH<br>worsening-related<br>hospitalization of $\geq 24$ hours |
| <b>Seralutinib</b><br><br>Inhaled PDGF-R,<br>CSF1R, and c-KIT<br>inhibitor  | TORREY                      | 2    | 80  | WHO/NYHA Class II<br>or III<br><br>PAWP or LVEDP $\leq$<br>12 if PVR $\geq 5$ and $<$<br>6.25 WU OR<br><br>PAWP or LVEDP $\leq$<br>15 if PVR $\geq 6.25$ WU   | Change in PVR at Week 24   |
| <b>Imatinib DPI</b><br>(AV-101)<br><br>Inhaled tyrosine<br>kinase inhibitor | IMPAHCT<br>(NCT05036135)    | 2b/3 | 462 | WHO/NYHA Class<br>II-IV   | Phase 2b: Change in PVR at<br>Week 24<br><br>Phase 3: Change in 6MWD at<br>Week 24   |
| <b>Rodatristat ethyl</b><br><br>Tryptophan<br>hydroxylase inhibitor         | ELEVATE-2<br>(NCT04712669)  | 2    | 90  | WHO/NYHA Class II<br>or III<br><br>PAWP or LVEDP $\leq$<br>12 if PVR $\geq 4.4$ and $<$<br>6.25 WU OR<br><br>PAWP or LVEDP $\leq$<br>15 if PVR $\geq 6.25$ WU | Change in PVR at Week 24   |
| <b>Apabetalone</b><br><br>BRD4 inhibitor                                    | APPROACH-2<br>(NCT04915300) | 2    | 72  | WHO/NYHA Class<br>II or III<br><br>mPAP $> 20$ mmHg<br><br>PVR $> 5$ WU   | Change in PVR at Week 24   |

