Rationale and design of the ranolazine PH–RV study: a multicentred randomised and placebo-controlled study of ranolazine to improve RV function in patients with non-group 2 pulmonary hypertension

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ABSTRACT

Introduction A major determining factor on outcomes in patients with pulmonary arterial hypertension (PAH) is right ventricular (RV) function. Ranolazine, which is currently approved for chronic stable angina, has been shown to improve RV function in an animal model and has been shown to be safe in small human studies with PAH. We aim to study the effect of ranolazine on RV function using cardiovascular magnetic resonance (CMR) in patients with pulmonary hypertension (non-group 2 patients) and monitor the effect of ranolazine on metabolism using metabolic profiling and changes of microRNA.

Methods and analysis This study is a longitudinal, randomised, double-blind, placebo-controlled, multicentre proof-of-concept study in 24 subjects with pulmonary hypertension and RV dysfunction treated with ranolazine over 6 months. Subjects who meet the protocol definition of RV dysfunction (CMR RV ejection fraction (EF) <45%) will be randomised to ranolazine or placebo with a ratio of 2:1. Enrolled subjects will be assessed for functional class, 6 min walk test and health outcome based on SF-36 tool. Peripheral blood will be obtained for N-terminal-pro brain natriuretic peptide, metabolic profiling, and microRNA at baseline and the conclusion of the treatment period. CMR will be performed at baseline and the conclusion of the treatment period. The primary outcome is change in RVEF. The exploratory outcomes include clinical, other CMR parameters, metabolic and microRNA changes.

Ethics and dissemination The trial protocol was approved by Institutional Review Boards. The trial findings will be disseminated in scientific journals and meetings.

Trial registration numbers NCT01839110 and NCT02829034; Pre-results.

INTRODUCTION

A major determining factor on outcomes in patients with pulmonary arterial hypertension (PAH) is right ventricular (RV) function.1 During the progression of PAH, many of the molecular mechanisms that drive transition from compensated RV hypertrophy (RVH) to dilatation and failure remain enigmatic. Recently, animal modelling of RVH and RV failure in PAH has revealed a substantial downregulation of mitochondrial oxidative metabolism in favour of glycolysis. The molecular mechanisms controlling this metabolic shift in the RV are unclear,2 but, in part, may involve alterations of potassium channel function.3–5 Importantly, in rodents with experimental PAH6,7 or chronic RV overload,8 RVH, RV electrical remodelling and RV dysfunction can be normalised with dichloroacetate (DCA), an inhibitor of pyruvate dehydrogenase kinase which in turn activates pyruvate dehydrogenase (PDH) to favour oxidative metabolism. These findings suggest that alterations in mitochondrial function, metabolism and energy substrate utilisation are keys to understanding the progression to RV failure. Observational human data through positron emission tomography corroborate these findings by revealing increased uptake of glucose in PAH-dependent RV dysfunction.9,10 However, data are sparse regarding the efficacy and safety profile of DCA in humans, and it is currently not an US Food and Drug Administration (FDA)-approved medication. Alternatively, ranolazine, which is currently approved for chronic stable angina,11,12 also activates PDH13–15 and has been shown to inhibit fatty acid oxidation, myocardial late sodium currents and sodium-dependent calcium overload, as previously reviewed.16 Recently, in a rodent model of RVH, ranolazine was reported to successfully reverse metabolic dysfunction and improve cardiac output and exercise capacity.15,17 A number of small
single-centred studies on the use of ranolazine in pulmonary hypertension (PH) have recently been completed. A study reported 12 patients with PAH (six ranolazine and six placebo) were given the drug acutely and followed for 12 weeks in a safety study of ranolazine in acute vasoactivity and found it to be safe without impact on haemodynamics (NCT01757808). Another study looking at 10 patients with 8 completing follow-up in an open-label ranolazine study in PAH patients with angina or angina equivalent showed symptomatic and functional improvement at 3 months (NCT01174173). A third small study looking at the effect of ranolazine in 10 patients with PH and diastolic LV dysfunction and follow-up in 6 months has not yet published results (NCT02133352). Thus, ranolazine may have therapeutic potential in RV dysfunction and PH, and could be readily ‘repurposed’ as an already FDA-approved medication.

Ranolazine is a racemic mixture and chemically described as 1-piperazineacetamide, N-((2,6-dimethylphenyl)-4-[2-hydroxy-3-(2-methoxyphenoxy)propyl]-, (±). It has an empirical formula of C_{24}H_{33}N_{3}O_{4}, a molecular weight of 427.54 g/mole. In the USA, ranolazine is available for oral administration as film-coated, extended-release tablets containing 500 or 1000mg of active ingredient. Ranolazine has antianginal and anti-ischaemic effects that do not depend on reductions in heart rate or blood pressure.

METHODS AND ANALYSIS

Design

This study is a randomised, double-blind, placebo-controlled, multi-centre proof-of-concept study in 24 male or female subjects with PH and RV dysfunction. Subjects who meet the protocol definition of RV dysfunction (cardiovascular magnetic resonance (CMR) imaging RV ejection fraction (EF) <45%) will be randomised to ranolazine or placebo 2:1.

The study includes a screening period (up to 4 weeks), a treatment period (up to 26±4 weeks) and a follow-up period (4 weeks). Subjects in the treatment period will be called every four weeks to assess any symptoms, any changes in health or medications, as well as study drug compliance. Subjects are encouraged to contact us with any adverse events (AEs) or issues during treatment period. Subjects will receive ranolazine or placebo at 500 mg orally two times per day and after 2 weeks to increase to 1000 mg orally two times per day. Subjects will continue at 1000 mg two times per day for the duration of the study. Subjects with adverse reactions that are difficult to tolerate will be down titrated to 500 mg two times per day. Subjects on moderate CYP3A inhibitors will be limited to 500 mg two times per day.

At baseline (week 0), interim (1–4 months post randomisation) and the conclusion of the treatment period (week 26±2), subjects will be assessed for functional class (FC), 6 min walk test (6MWT) and health outcome based on SF-36 tool. Peripheral blood will be obtained for metabolic profiling and microRNA at baseline and the conclusion of the treatment period. CMR will be performed at baseline and the conclusion of the treatment period. The complete study flow chart is included in table 1.

Recruitment and screening

The subjects were recruited from four academic centres (University of Pennsylvania (UPenn), Temple University (Temple), University of Maryland (UMD) and Brigham and Women’s Hospital (BWH)). All patients needed to have underwent a diagnostic catheterisation within 5 years of enrolment demonstrating PH but no evidence for diastolic heart failure. The inclusion and exclusion criteria are presented in boxes 1 and 2. Separate institutional review boards (UPenn, UMD and BWH) approved the study. Temple patients are enrolled through UPenn. There are two imaging centres (UPenn and BWH) with UMD sending patients to UPenn for CMR. The screening visit includes a CMR, a health assessment form, a 6MWT with Borg Dyspnea Index, an ECG, blood draw for liver function tests, N-terminal-pro brain natriuretic peptide, metabolic profiles, and microRNA, and a medical history including current medications.

Randomisation

A subject number is assigned to an individual at the screening visit. Randomisation of the subject proceeds through the use of a randomisation table at UPenn Investigational Drug Service (IDS), which prepares a randomisation table using random blocks of 3, at a 2:1 ratio of active to placebo. The table is computer-generated prior to the start of the trial and maintained securely within the IDS, which is not accessible to the rest of the study team. Subjects are assigned to treatment in sequential order (lowest to highest). After a subject is screened and determined to be eligible for the study (RVEF <45%) by the data coordinating centre (UPenn), the site personnel contact UPenn IDS and get a randomisation number. The randomisation number and the date the randomisation number is assigned will be recorded in the electronic case report form (CRF). Once randomisation numbers and registration numbers have been assigned, they cannot be reassigned.

INVESTIGATIONS

Primary objective

1. to demonstrate that treatment with ranolazine improves RV function in subjects with persistent RV dysfunction as measured by CMR

Exploratory objectives

1. to evaluate the clinical effect of ranolazine in subjects with PH on stable background therapy and persistent RV dysfunction, including 6MWT, WHO FC and clinical progression of disease;
2. to evaluate novel CMR markers such as changes in 4D flow and T1 mapping;
3. to evaluate changes in metabolism with ranolazine as measured by serum metabolites using metabolon;  
4. to evaluate changes in microRNA in peripheral blood;  
5. to evaluate changes in quality of life using questionnaire.  

Patients with high-risk profile are defined as patients with clinical worsening events or lack of clinical improvement at week 26.  
► Clinical improvement is defined as an increase in 6MWD ≥15% from baseline and an improvement (de-
Clinical worsening event (adjudicated), as defined by at least one of the events listed below:
- death (all causes)
- hospitalisation due to worsening PH defined as

| Box 1 Inclusion criteria |
|-------------------------|
| Have a current diagnosis of symptomatic pulmonary hypertension (PH) based on one of the following criteria: |
| a. Idiopathic PAH |
| b. Familial PAH |
| c. PAH associated with connective tissue disease |
| i. Systemic sclerosis |
| ii. Calcinosis, Raynaud phenomenon, oesophageal dysmotility, sclerodactyly and telangectasia syndrome |
| iii. Mixed connective tissue disease |
| iv. Systemic lupus erythematosus |
| d. Chronic thromboembolic pulmonary hypertension (CTEPH)-non-surgical/distal vessel disease or patients with CTEPH who are reluctant to go to surgery within 6-month period and are willing to participate. |
| e. Simple congenital such as repaired atrial septal defect (ASD)/ventricular septal defect (VSD) or unrepaired small ASD/VSD with persistent and out of proportion PAH. |
| f. Group 3 patients who have a component of PH and do not meet exclusion criteria (S) in 5.2. |
| g. PH caused by conditions affect the veins and small vessels of the lungs, sickle cell disease. |
| h. Group 5 PH such as polycythemia vera, essential thrombocythemia, sarcoidosis, or vasculitis, or metabolic disorder. Sarcoid with known cardiac involvement (left ventricle (LV) and/or right ventricle (RV)) will be excluded. |
| WHO functional class II, III or IV. |
| Age >18 and <80 years of age. |
| For incident cases, a right heart catheterisation (RHC) performed within 100 days prior to enrolment (defined as randomisation) that shows the following (prevalent cases require a historical RHC within the past 60 months): |
| a. Mean pulmonary artery pressure >25 mm Hg at rest. |
| b. Pulmonary capillary wedge pressure (PCWP) or LV end diastolic pressure <15 mm Hg. If the PCWP is >15 but <20 mm Hg, then the transpulmonary gradient must be >25 mm Hg. |
| c. Pulmonary vascular resistance >3 mm Hg/L/min |
| CMR RVEF <45% obtained from a CMR done within 28 days of enrolment. |
| 6 min walk test distance (6MWD) >50 m within 90 days prior to enrolment. |
| No dual upfront therapies permitted for patients with stratum I (incident). |
| No addition or discontinuation of PAH-specific medication within 90 days and no change in PAH-specific medication dose within 28 days prior to baseline imaging procedures. Note: Adjustment of diuretic dose (increase or decrease of 100% or less) is permissible. Switches from same class of medication may only require a stable dose 28 days prior to baseline imaging procedures at the discretion of the Investigator. |
| Subjects must be capable of giving informed consent. |

| Box 2 Exclusion criteria |
|-------------------------|
| Previous treatment with or prior sensitivity to any formulation of ranolazine. |
| Any family history of QTc prolongation, congenital long QT syndrome or receiving drugs that prolong the QTc interval such as class la (eg, quinidine) or class III (eg, dofetilide, sotalol, amiodarone) antiarrhythmic agents, erythromycin and certain antipsychotics (eg, thioridazine, ziprasidone). |
| For patients who have a prolonged QTc of >480 ms that is not due to the above exclusion #2 and an increased QRS duration of >120 ms, QTrr,qrs formula$^{20}$ will be used to calculate an adjusted QTc. Patient will be excluded if an adjusted QTc is >460 ms. |
| Subject receiving intravenous inotropes within 2 weeks prior to the baseline imaging procedures. |
| Parenchymal lung disease based on pulmonary function testing within the past 12 months prior to baseline imaging procedures showing any of the following: |
| a. Total lung capacity <50% of predicted and a high-resolution CT that does not demonstrate clinically severe interstitial lung disease based on the discretion of the Investigator |
| b. FEV1/forced vital capacity <50% |
| Subjects currently on a strong CYP3A inhibitor or inducer, or hepatic enzymes >3 x upper limits of normal, or moderate to severe liver disease. |
| Portal hypertension associated with either cirrhotic or non-cirrhotic chronic liver disease. |
| Left-sided heart disease including any of the following: |
| a. Moderate or greater aortic or mitral valve disease |
| b. Any left ventricular (LV) cardiomyopathy (including but not limited to restrictive, amyloid, hypertrophic) |
| c. LV systolic dysfunction defined as an ejection fraction <50% by echocardiography |
| Uncontrolled systemic hypertension (systolic blood pressure (BP)>160 mm Hg or diastolic BP>100 mm Hg) with or without treatment. |
| Inability to perform a 6 min walk test because of a mechanical problem such as arthritis, morbid obesity or musculoskeletal problem. |
| The subject has the presence, or history, of malignancy that required significant medical intervention within the preceding three months and/or is likely to result in death within the next two years (exception of basal cell or non-metastatic squamous cell carcinoma of the skin and carcinoma in situ of the cervix). |
| The receipt of any investigational medication within 14 days prior to baseline imaging or the need for another investigational drug during the course of this study. |
| Pregnancy or lactation: women of childbearing potential and non-vasectomised men must agree to use a barrier method of contraception during screening and for the entire study period. |
| Implantable cardioverter defibrillator, pacemaker, hazardous metallic implants or any other contraindication to MRI. |
| Severe anxiety or claustrophobia prohibiting completion of cardiac MRI. |
| Psychiatric disorder that compromises the ability to provide informed consent. |
- non-elective hospitalisation lasting at least 24 hours in duration caused by clinical conditions directly related to PH and/or right heart failure
- lung or heart/lung transplantation
- atrial septostomy
- de novo intravenous initiation of a prostacyclin for the treatment of worsening PH
- disease progression (all criteria required):
  - a decrease in 6MWD of at least 15% from baseline (or too ill to walk) directly related to PH progression with other comorbidities ruled out, confirmed by two 6MWTs performed on different days
  - worsening of PH symptoms, which must include either
    - an increase in FC
    - new onset of at least one symptom which did not respond to oral diuretic therapy (syncope, near syncope, chest pain, chest discomfort, orthopnoea and dizziness)

**Withdrawal**
A subject may voluntarily discontinue participation in this study at any time. The investigator may also, at his or her discretion, discontinue the subject from participating in this study at any time. If a subject is prematurely discontinued from participation in the study for any reason, at any time, at either the investigator’s discretion or the subject’s request, an effort must be made to document the reason(s) why a subject fails to return to the study clinic for necessary visits or is discontinued from the study. The primary reason for discontinuing participation in the study must be stated in the CRF and may include, but is not limited to, one of the following:
- progressive disease as determined by the investigator;
- use of unapproved concomitant medications (initiation of a strong CYP3A inhibitor or inducer without any alternative therapies; initiation of a moderate CYP3A inhibitor would warrant dose reduction);
- occurrence of intolerable AEs;
- withdrawal of consent by subject;
- non-compliance with protocol, for example, the subject fails to appear at one or more visits;
- development of an intercurrent illness, injury or medical condition likely to interfere with subject safety, the overall assessment or the required administration of study medication;
- pregnancy;
- development of any condition for which the investigator feels treatment withdrawal is justified;
- termination of the study.

When a subject discontinues or is withdrawn, the investigator will perform the procedures indicated for the end of treatment visit when possible. An effort will be made to determine why a subject failed to return for the necessary visits or is dropped from the study.

**Data monitoring committee**
An independent data safety monitoring board (DSMB) with three physicians (one PAH expert, one CMR expert and one clinical trials expert) is established to assure the safety of participants in this trial. The DSMB will review the study for safety and overall study conduct. At the end of the study, they may adjudicate final outcome based on the clinical information. The membership of the DSMB as well as the responsibilities and procedures used to carry out these responsibilities are described separately in the DSMB charter.

**Sample size**
Approximately 24 subjects with PH and RV dysfunction will be randomised in 2:1 ratio to ranolazine or placebo. We aim to have 18 evaluable subjects with 12 evaluable subjects for ranolazine and 6 for placebo, after accounting for 20% dropout/non-evaluable.

The imaging analyses will be combined at all sites. Each site will assess for image quality after the first enrolled subject to adjust imaging parameters as necessary. Image quality will be assessed for combined analysis. We will be examining different imaging markers as continuous variables comparing the difference pre-drug and post-drug treatment. With 12 treated patients and 12 untreated patients (six in the randomised group and six in the observational group, obtained from a similarly designed study without drug administration), assuming the effect size is 40% with an SD of 50%, we will have 87.0% power to detect the difference between groups with a sample size of 12. If the effect size is lower at 35% with an SD of 50%, we will have 78.2% power to detect the difference between groups with a sample size of 12. The unequal randomisation is to ensure minimum number of subjects are exposed to the treatment to provide sufficient information for the study.

**STATISTICAL ANALYSIS**

**Primary outcome analysis**
Change in CMR RVEF is the primary endpoint for assessment of the treatment outcome. All CMR images will be transmitted to the CMR core laboratory (UPenn) for analyses. RV function is difficult to assess using methods such as echocardiography. CMR is the gold standard for assessment of RV function. However, heavy trabeculations and RV enlargement often seen with patients with PAH pose additional challenges for RV assessment. We will include phase-contrast assessment for pulmonic and aortic flows and using biventricular volumes to correlate in cases of absence of regurgitations to ensure accuracy in the assessment of RV function. All variables from CMR imaging will be summarised and listed. Treatment effect will be tested using analysis of covariance, with treatment in the model. If the normality assumption fails, non-parametric methods will be employed. Difference between drug versus placebo pre treatment and post treatment will be summarised and tested using t-test. Significance
will be established at alpha level of 0.05. The efficacy analysis will be conducted on the all-treated population.

**Exploratory outcome analysis**
The exploratory efficacy endpoint is the estimate and a confidence interval (CI) for the difference in proportions between the treatment groups. Number and percentage of subjects with high-risk profile for each treatment group at week 26 will be provided. Fisher’s exact test will be employed to detect the difference between placebo versus active. Patients with high-risk profile are defined as patients with clinical worsening events or lack of clinical improvement at the end of the study (week 26). The efficacy analysis will be conducted on the all-randomised population.

Clinical worsening is evaluated by two independent clinicians at each visit, from date of first dose to end of treatment visit. To minimise investigator bias, the data manager will compare the assessed outcome between the two independent clinicians. Shall the assessment be different between the two independent clinicians, the third clinician will be involved to adjudicate the case. The evaluation from the adjudicator will be used for analysis. At any given time, if the difference exceeds >30%, the investigator will have a conversation with the two independent clinicians to narrow the difference.

For subjects who do not experience clinical worsening, the end of the treatment visit (week 26) with 6MWT and FC assessment would determine if there is no clinical improvement or if there is clinical improvement. All efforts should be made to collect the death information in the follow-up period.

**Quality-of-life health outcome**
The objective is to assess the improvement in quality of life of the subjects after being treated with ranolazine. Ordinal regression will be employed using SF-36 responses to predict a general health perception variable (response options ‘excellent’, ‘very good’, ‘good’, ‘fair’ and ‘poor’). Items that significantly predicted this variable were candidates for inclusion in the utility exercise. The efficacy analysis will be conducted on the all-randomised population.

Additional exploratory endpoints including additional CMR imaging such as 4D flow and T1 mapping, metabolic data and microRNA data will be summarised and tested using t-test (paired for pre data and post data on the same patient, unpaired for ranolazine treated and non-treated patients). If the normality assumption fails, non-parametric method will be employed.

**SAFETY EVALUATION**

**Adverse event**
An adverse event (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. The study period is defined as the period from the randomisation to 4 weeks following the last administration of study drug. Some common AEs that had been described for ranolazine at a rate of up to 6% include dizziness, nausea, asthenia, constipation and headache. Additional adverse reactions at an incidence of 0.5%–4% include bradycardia, palpitations, tinnitus, vertigo, blurred vision, abdominal pain, dry mouth, vomiting, dyspepsia, asthenia, peripheral oedema, anorexia, syncope, confusion, state, haematuria, dyspnoea, hyperhidrosis and hypotension. Others (<0.5%) include angioedema, renal failure, eosinophilia, chromaturia, increased blood urea, hypoesthesia, paraesthesia, tremor, pulmonary fibrosis, thrombocytopenia, leucopenia and pancytopenia. Intercurrent illnesses or injuries are regarded as AEs. Abnormal results of diagnostic procedures are considered to be AEs if the abnormality

- results in study withdrawal
- is associated with a serious AE
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

A serious AE (SAE) is any AE that is
- fatal
- life-threatening
- requires or prolongs hospital stay
- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect
- an important medical event

**General physical examination findings**
At screening, any clinically significant abnormality should be recorded as a pre-existing condition. At the end of the study, any new clinically significant findings/abnormalities that meet the definition of an AE must also be recorded and documented as an AE.

**Abnormal laboratory values**
A clinical laboratory abnormality should be documented as an AE if any one of the following conditions is met:

- The laboratory abnormality is not otherwise refuted by a repeat test to confirm the abnormality
- The abnormality suggests a disease and/or organ toxicity
- The abnormality is of a degree that requires active management; for example, change of dose, discontinuation of the drug, more frequent follow-up assessments, further diagnostic investigation, etc.

**Hospitalisation, prolonged hospitalisation or surgery**
Any AE that results in hospitalisation or prolonged hospitalisation should be documented and reported as a SAE. Neither the condition, hospitalisation, prolonged hospitalisation, nor surgery are reported as an AE in the following circumstances:

- Hospitalisation or prolonged hospitalisation for diagnostic or elective surgical procedures for a pre-existing condition. Surgery should not be reported as an
outcome of an AE if the purpose of the surgery was elective or diagnostic and the outcome was uneventful.

- Hospitalisation or prolonged hospitalisation required to allow efficacy measurement for the study.
- Hospitalisation or prolonged hospitalisation for therapy of the target disease of the study, unless it is a worsening or increase in frequency of hospital admissions as judged by the clinical investigator.

**Reporting of serious AEs and unanticipated problems**

Site investigators must report AEs that are
- related to study participation
- unexpected
- serious or involve risks to subjects or others

Any study-related unanticipated problem posing risk of harm to subjects or others, and any type of SAE, must be reported to Penn PI within 24 hours using SAE form. The drug will be immediately discontinued on identification of the SAE if not earlier. For other AEs, the drug may be lowered in dosage or discontinued by the site investigator depending on the tolerability of the AE by the patient.

**Reporting procedures for potential endpoints and endpoints**

Events that are potential endpoints: hospitalisation for PH, death, worsening of PH, lung or heart–lung transplant, atrial septostomy or other interventional procedure specifically for RV failure or PH, decline of 6MWD, increase in Borg Dyspnea Index and increase in WHO FC initially will not be considered as serious AEs but will be handled as efficacy endpoints. They will not be subject to the immediate submission requirements for SAEs in this study and will not require the investigator’s causality assessment. The site investigator will make the initial determination to classify these events as endpoints or SAEs. For these potential endpoints, an SAE electronic case report form will only be completed if the DSMB determines that a specific event does not meet the criteria for the relevant endpoint (ie, the potential endpoint is negatively adjudicated). The DSMB will review all fatal endpoints to evaluate whether the cause of death is due to a SAE that is a specific concern for the study drug or which may be individually informative.

**Trial status**

The study is registered on the clinicaltrials.gov as NCT01839110 and NCT02829034. The study is currently ongoing and recruited a total of 22 subjects. The mean age is 54.7±15.6; years. Nine patients were male (41%). Fifteen patients were whites and five were African-Americans and two others. Eleven patients had baseline WHO FC II and eight were class III and three were class IV. Nineteen patients (86%) were patients with group I PAH and two were group 4 CTEPH and one group 3 patient. Baseline medications include riociguat monotherapy (n=1), phosphodiesterase 5 inhibitor (PDE5i) monotherapy (n=1), PDE5i and endothelin receptor antagonist (ERA) dual therapy (n=7), prostanoid and ERA (n=1), prostanoid, PDE5i and ERA (n=6).

**Impact**

Ranolazine is an FDA-approved agent that is safe to use in patients with PH, and if proven to be beneficial to improve RV function in non-group 2 patients with PH, it could be readily ‘repurposed’ and added to the armamentarium of treatment for patients with PH. It would also be a first drug that is targeted to improve RV function without significant haemodynamic effect.

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**Competing interests** SYC reports consultancy agreements with Actelion, Gilead, Pfizer and Vivos. MHP reports consultant/scientific advisory, Actelion, Bayer, United Therapeutics and speakers’ bureau for Bayer.

**Patient consent** Obtained.

**Ethics approval** Institutional Review Board of University of Pennsylvania, University of Maryland and Brigham Women’s Hospital.

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**Data sharing statement** The full data set is available from the corresponding author upon reasonable request.

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REFERENCES

1. van de Veerdonk MC, Kind T, Marcus JT, et al. Progressive right ventricular dysfunction in patients with pulmonary arterial hypertension responding to therapy. J Am Coll Cardiol 2011;58:2511–9.
2. Tuder RM, Davis LA, Graham BB. Targeting energetic metabolism: a new frontier in the pathogenesis and treatment of pulmonary hypertension. Am J Respir Crit Care Med 2012;185:260–6.
3. Lee JK, Kodama I, Honjo H, et al. Stage-dependent changes in membrane currents in rats with monocrotaline-induced right ventricular hypertrophy. Am J Physiol 1997;272(6 Pt 2):H2833–H2842.
4. Storey JD, Tibshirani R. Statistical significance for genomewide studies. Proc Natl Acad Sci U S A 2003;100:9440–5.
5. Kleiman RB, Houser SR. Outward currents in normal and hypertrophied feline ventricular myocytes. Am J Physiol 1989;256(5 Pt 2):H1450–61.
6. Bonnet S, Michelakis ED, Porter CJ, et al. An abnormal mitochondrial-hypoxia inducible factor-1alpha-Kv channel pathway disrupts oxygen sensing and triggers pulmonary arterial hypertension in fawn hooded rats: similarities to human pulmonary arterial hypertension. Circulation 2006;113:2630–41.
7. Michelakis ED, McMurtry MS, Wu XC, et al. Dichloroacetate, a metabolic modulator, prevents and reverses chronic hypoxic pulmonary hypertension in rats: role of increased expression and activity of voltage-gated potassium channels. Circulation 2002;105:244–50.
8. Piao L, Fang YH, Cadete VJ, et al. The inhibition of pyruvate dehydrogenase kinase improves impaired cardiac function and electrical remodeling in two models of right ventricular hypertrophy: resuscitating the hibernating right ventricle. J Mol Med 2010;88:47–60.
9. Oikawa M, Kagaya Y, Otani H, et al. Increased [18F] fluordeoxyglucose accumulation in right ventricular free wall in patients with pulmonary hypertension and the effect of epoprostenol. J Am Coll Cardiol 2009;45:1849–55.
10. Basu S, Alzeair S, Li G, et al. Etiopathologies associated with intercostal muscle hypermetabolism and prominent right ventricle visualization on 2-deoxy-2[18F]fluoro-D-glucose-positron emission tomography: significance of an incidental finding and in the setting of a known pulmonary disease. Mol Imaging Biol 2007;9:333–9.
11. Chaitman BR, Skettino SL, Parker JO, et al. Anti-ischemic effects and long-term survival during ranolazine monotherapy in patients with chronic severe angina. J Am Coll Cardiol 2004;43:1375–82.
12. Chaitman BR, Pepine CJ, Parker JO, et al. Effects of ranolazine with atenolol, amlodipine, or diltiazem on exercise tolerance and angina frequency in patients with severe chronic angina: a randomized controlled trial. JAMA 2004;291:309–16.
13. Clarke B, Speeding M, Patmore L, et al. Protective effects of ranolazine in guinea-pig hearts during low-flow ischaemia and their association with increases in active pyruvate dehydrogenase. Br J Pharmacol 1993;109:748–50.
14. Chaitman BR, Skettino SL, Parker JO, et al. Anti-ischemic effects and long-term survival during ranolazine monotherapy in patients with chronic severe angina. J Am Coll Cardiol 2004;43:1375–82.
15. Cai CL, Liang X, Shi Y, et al. Isl1 identifies a cardiac progenitor population that proliferates prior to differentiation and contributes a majority of cells to the heart. Dev Cell 2003;5:877–89.
16. De Rosa S, Fichtlscherer S, Lehmann R, et al. Transcoronary concentration gradients of circulating microRNAs. Circulation 2011;124:1936–44.
17. Gomberg-Mattland M, Schilz R, Mediratta A, et al. Phase I safety study of ranolazine in pulmonary arterial hypertension. Pulm Circ 2015;5:691–700.
18. Khan SS, Cuttica MJ, Beussink-Nelson L, et al. Effects of ranolazine on exercise capacity, right ventricular indices, and hemodynamic characteristics in pulmonary arterial hypertension: a pilot study. Pulm Circ 2015;5:547–56.
19. Rautaharju PM, Zhang ZM, Prineas R, et al. Assessment of prolonged QT and JT intervals in ventricular conduction defects. Am J Cardiol 2004;93:1017–21.