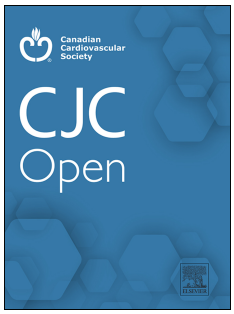

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Design of the Prospective comparison of Angiotensin Receptor-neprilysin inhibitor versus plAcebo in patients with Congenital sYStemic Right Ventricle

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Abstract

The presence of a systemic right ventricle (sRV) in patients with biventricular (biV) physiology is associated with increased morbidity and mortality. To date, no pharmacological therapy for heart failure has been proven effective for patients with systolic dysfunction of the sRV-biV. We designed a randomized, double-blind, placebo-controlled crossover trial to compare sacubitril/valsartan to placebo in adults (≥18 years) with moderate to severe sRV-biV dysfunction and New York Heart Association functional class II to III symptoms. Two primary efficacy endpoints are assessed in the trial: exercise capacity (sub-maximal exercise duration) and neurohormonal activation (NT-proBNP). Secondary objectives include assessing a change in the Kansas City Cardiomyopathy Questionnaire score and evaluating safety and tolerance of sacubitril/valsartan. A 6-week open run-in phase identifies the maximum tolerated dose of sacubitril/valsartan up to 97 mg/103 mg twice daily. After a 2-week washout period, patients are randomized 1:1 to sacubitril/valsartan versus placebo for a 24-week phase followed by another 2-week washout period and subsequent crossover to the alternative treatment arm for an additional 24-week phase. Data to assess primary and secondary endpoints are collected at baseline and end of each phase. A total of 48 patients is required to provide >80% power to detect a 30% difference in distance walked and in NT-proBNP levels with sacubitril/valsartan versus placebo, each with a two-sided P-value of 0.025. In summary, the ***PARACYS-RV*** trial should determine the role of sacubitril/valsartan in treating heart failure in patients with sRV-biV and carries the potential to alter management.

Keywords: Systemic right ventricle; angiotensin receptor neprilysin inhibitor; heart failure; systolic dysfunction; congenital heart disease

INTRODUCTION

A systemic right ventricle (sRV) associated with biventricular physiology (biV) occurs in the context of complete transposition of the great arteries with an atrial switch operation (DTGA/AS)[1, 2] and congenitally corrected transposition of the great arteries (ccTGA).[3] Despite the typical quiescent clinical course during childhood, many patients will develop complications in adulthood. The sRV-biV that is subject to systemic pressures is associated with severe morbidity and a shortened lifespan. After the 3rd decade of life, the sRV often begins to fail as manifested by progressively impaired exercise capacity, heart failure (HF), systemic atrioventricular valve regurgitation, and pulmonary hypertension.[4-10] The prevalence of HF reaches ~60% by age 40.[11] Moreover, a substantial number of patients develop end-stage HF resulting in premature death. To date, no pharmacological therapy for HF has been proven effective in patients with systolic dysfunction of the sRV-biV.[4, 12, 13]

In clinical trials of patients with sRV-biV, renin angiotensin aldosterone system (RAAS) inhibitors did not result in an increased ejection fraction or 6-minute walk test distance, nor in a reduction in NT-pro-BNP levels.[14, 15] However, a decrease in sRV end-diastolic and end-systolic volumes were observed by cardiac magnetic resonance imaging.[15] Post-trial follow-up of a 3-year placebo-controlled trial of valsartan in 87 symptomatic patients with a sRV-biV continued to demonstrate a reduction in adverse events (i.e., arrhythmias, worsening HF, and tricuspid valve surgery) at 8.3 years. A meta-analysis of studies assessing medical therapy for sRV-biV dysfunction did not identify a single effective treatment for HF associated with a sRV-biV, including angiotensin-converting enzyme inhibitors (ACEi) and angiotensin II receptor blockers (ARBs).[16] Therefore, no specific medical therapy for HF is currently endorsed by clinical practice guidelines for the treatment of systolic dysfunction of sRV-biV.[17-19]

Recent case reports support the safety and promising effect of the combination of sacubitril and valsartan in patients with sRV-biV.[20-22] An open-label single-center study comparing 18 patients with sRV-biV failure (ejection fraction <35%) at baseline and after 6 months of sacubritril/valsartan medication showed encouraging results. A significant decrease in NT-proBNP levels was observed along with improvements in echocardiographic parameters of sRV-biV function (fractional area change, global longitudinal strain), 6-minute walk test distance, and quality of life assessed by the Netherlands Organization for applied scientific research/Academic Hospital Leiden adult Quality Of Life questionnaire (TAAQOL).[23] No major adverse events, including renal dysfunction, were reported.[23] Similarly, a recent prospective open-label study of 50 patients (35% ccTGA) with sRV-biV reported an improvement in NYHA functional class, 6-minute walk test distance, and quality of life after one year of sacubitril/valsartan compared to baseline.[24] A reduction in NT-pro-BNP levels was observed one month after initiation of sacubitril/valsartan followed by a return to the baseline value at one year. Echocardiographic parameters of systolic function and dilatation of the sRV-RV improved after one year of sacubitril/valsartan compared to baseline.

A randomized clinical trial was deemed necessary to confirm the benefits of sacubitril/valsartan in patients with sRV-BiV systolic dysfunction. The Prospective comparison of Angiotensin Receptor-neprilysin inhibitor versus plAcebo in patients with Congenital sYStemic Right Ventricular heart failure trial (PARACYS-RV) is a randomized, double-blind, placebo-controlled, crossover trial designed for this purpose.

TRIAL DESIGN AND METHODS

STUDY POPULATION

Inclusion criteria are as follows: (i) age ≥18 years with clinical follow-up at the Montreal Heart Institute Adult Congenital Heart Center; (ii) presence of a sRV-biV; (iii) moderate to severe sRV-biV dysfunction by transthoracic echocardiography (TTE) or a sRV ejection fraction (sRVEF) <40% by magnetic resonance imaging; (iv) NYHA functional class II or III symptoms or peak exercise capacity <80% of predicted on a previous standard treadmill exercise stress test; (v) ability to provide informed consent to the study; (vi) access to a telephone and/or an internet connection for teleconference calls; (vii) a mailing address to receive the study drugs; and (viii) capacity to perform self-measurements of blood pressure using a blood pressure monitor provided. Exclusion criteria are listed **Table 1**.

STUDY DESIGN

The study consists of 3 phases. An overview of the study timeline is shown in **Figure 1**. The first phase includes the screening visit with baseline measurements (Table 2) followed by an open active run-in phase of 6 weeks to identify the maximum tolerated dose of sacubitril/valsartan and ensure the safety of patients under the active medication. The second phase begins by a two-week wash-out period. Patients are then randomized in a 1:1 ratio to the sequence of active therapy in the first 24-week arm of the trial (Phase 2) followed by the corresponding placebo in the second 24-week arm (Phase 3), or vice versa. Primary, secondary, and exploratory endpoints are measured at the end of each 24-week treatment period (Table 2). A two-week washout period is incorporated prior to crossover to the alternative treatment arm in the third phase. Safety monitoring is evaluated at the half-way time point for each treatment arm. The rationale for the

crossover design is addressed in the discussion.

Screening (visit 1)

At the screening visit, patient eligibility is assessed according to inclusion/exclusion criteria. A TTE performed within 6 months is deemed acceptable to assess eligibility barring a major intercurrent event (e.g., new onset of arrhythmia, electrophysiological intervention, HF deterioration with hospitalization, cardiac surgery). A blood pressure monitor to perform home self-measurements is provided. Following successful screening, the patient is enrolled in a run-in phase. Patients already treated by sacubitril/valsartan are excluded, as are those receiving an ACEi or ARB if replacement by another medication is considered contra-indicated. Otherwise, the ACEi or ARB is discontinued at the beginning of the run-in phase. For subjects previously on an ACEi, a 48-hour washout period is factored in prior to the run-in phase. Beta-blockers or calcium blockers are introduced or increased to control blood pressure if needed after interruption of an ACEi or ARB. Other therapies, including aldosterone, are continued. Doses of diuretics are titrated according to clinical circumstances throughout the trial.

Active run-in phase (Visits 2, 3, 4)

The first dose of sacubitril/valsartan is based on Canadian heart failure management guidelines.[25] Sacubitril/valsartan is then increased every 2 weeks until the maximum tolerated dose or 200 mg bid is reached. Ten days after initiation and after every change in dose, laboratory tests, self-measurements of blood pressure, and a nurse evaluation by phone are performed to verify safety criteria (**Table 3**). The dose is up-titrated consequent to this evaluation by an adult congenital heart disease physician investigator if all safety criteria are met.

Wash-out period (Visits 5, 6 and 10, 11)

A 2-week washout period where no study drug is administered prior to initiating each treatment phase of the trial allows each subject's condition to return to the baseline state. One week into the washout period, the patient is evaluated by phone by the nurse to ensure the absence of HF symptoms (Visit 5 and 10). At the end of the 2-week period (Visit 6 and 11), the patient is assessed during a conference call by a physician and blood tests are performed.

Double-blind 1:1 randomization to sacubitril/valsartan versus placebo (Visit 6)

A randomization sequence list was performed at the beginning of the study by the statistical department. Patients are randomized according to a computer-generated randomization sequence with 1:1 distribution using randomly permuted blocks of 4 and 6. Hospital pharmacists, who are blinded to patients' characteristics and baseline data, act as a third party and have access to the randomization sequence list. The randomization sequence remains in the possession of the pharmacy until all data are collected and analyzed. The randomization code is kept strictly confidential. Hospital pharmacists do not have any contact with the patients. Patients and their nurses and physicians are blinded to the sequence assignment. For the first treatment phase of the trial, each patient is randomized to active therapy (50, 100, or 200 mg bid of sacubitril/valsartan based on the run-in phase) or the corresponding placebo (matching tablets for the 50, 100 or 200 mg of sacubitril/valsartan), with crossover to the other treatment arm in the second phase. Upon reintroduction of sacubitril/valsartan after 2 weeks of washout during phases 2 and 3, the patient is instructed to take half the dose determined during the run-in phase (or matching placebo) for one week. The dose is then increased to the full amount and maintained for 24 weeks. If the dose determined by the run-in phase is 50 mg bid, it does not change throughout (i.e., no initial half-

dose is administered). A telephonic evaluation is conducted at the end of the first week to evaluate tolerance to the medication (Visit 7).

End of study (Visit 14)

The end of study for an individual subject will correspond to the last visit performed in the context of the trial. For subjects who complete the second treatment phase following crossover as per protocol, the end of study will occur at visit 14. For subjects who prematurely discontinue the study drug, the date of end of the study will be documented accordingly. For all subjects, the reason for discontinuing the study and (if applicable) the decider (physician, subject) will be noted.

Safety monitoring

Patients are assessed at each visit for potential side effects. Safety checks with evaluation of safety criteria (Table 3) will be performed at the halfway point of both phases of the trial (Visits 8 and 13). In case of mild symptomatic hypotension or postural symptoms, the study drug can be down-titrated to a lower dose at the investigator's discretion. In the presence of any serious adverse event, the study will be terminated. Occurrence of angioedema is monitored. At any time during the study, unscheduled site visits may be performed, as necessary, at the discretion of the investigator. All non-serious adverse events (AE), all serious adverse events (SAE), reports of drug exposure during pregnancy or lactation, all reports of misuse and abuse of the study drug, other medication errors and uses outside of what is foreseen in the protocol (irrespective of whether a clinical event occurred), all reports of overdose, medication error or occupational

exposure (irrespective of whether a clinical event occurred) and all reports of unusual lack of efficacy of study drugs are collected throughout the study.

Safety period (Visits 15, 16, 17)

A 4-week safety period will occur after the end of the second treatment phase with assessment of secondary safety endpoints. Remote evaluation of HF symptoms will be performed at 1, 2 and 4 weeks (Visits 15, 16, 17) after the end of study with safety criteria (Table 3) evaluated at 2 weeks (Visit 16).

STUDY OBJECTIVES

Primary objectives

The purpose of this study is to assess the efficacy of sacubitril/valsartan over placebo in improving exercise capacity and neurohormonal activation in adults with moderate to severe sRV-biV dysfunction and NYHA functional class II/III symptoms. The trial will assess two primary endpoints (each at an alpha of 0.025): (i) change in sub-maximal total exercise duration between baseline (Visit 1) and end of each treatment arm (Visits 9 and 14); and (ii) change in NT-proBNP levels between baseline (Visit 1) and end of each treatment arm (Visits 9 and 14).

Secondary objectives

The secondary efficacy objective is to test whether sacubitril/valsartan compared to placebo is superior in improving the Kansas City Cardiomyopathy Questionnaire (KCCQ) score.

The secondary safety objective is to evaluate the tolerance and safety of sacubitril/valsartan in patients with a sRV-biV by assessing the safety criteria (Table 3). Adverse clinical events of

symptomatic postural hypotension will be investigated, including fainting, dizziness, lightheadedness, blurred vision, weakness, fatigue, nausea, palpitations, and headache upon standing.

Exploratory objectives

The exploratory objectives are to evaluate the change in NYHA functional class, the impact on adverse clinical events (hospitalizations for HF, symptomatic and clinically significant supra-ventricular and ventricular arrhythmia), mortality, impact on myocardial injury (high-sensitivity troponin-T level), change in sRV-biV function and size (TAPSe, S'wave, fractional area change, global longitudinal strain, end diastolic area, end systolic area, tricuspid regurgitation) and complementary parameters of exercise capacity, and the impact on the metabolic profile.

STUDY MANAGEMENT AND COMMITTEES

PARACYS-RV is an investigator-initiated trial conducted by the Montreal Heart Institute and funded by Novartis. Safety will be monitored throughout the trial by a Data and Safety Monitoring Board (DSMB) composed of 3 independent members. While the trial is not assessing outcomes such as mortality or major morbidity for which a DSMB is advised, FDA guidelines recommend DSMBs for trials that involve high-risk populations. Patients with complex congenital heart disease and sRV-biV failure are deemed to fall into this "high-risk" category. Given the brief duration of the trial, the DSMB will be required to formally meet once when half of the study subjects are recruited to ensure their safety. Another meeting could be required at the steering committee's discretion.

STATISTICAL ASPECTS

Sample size and power calculations

The sample size was selected to demonstrate a treatment effect on at least one of 2 primary endpoints, while limiting the overall type I error rate to 0.05. For exercise duration, based on best available evidence, it is anticipated that the placebo-treated arm will have an average time walked of 9.3 minutes with a within-patient standard deviation (i.e., standard deviation of the difference between sacubitril/valsartan and placebo) of 4.1 minutes.[14] With the crossover design, a total of 24 patients would provide 80% power to detect a 30% difference in the distance walked between sacubitril/valsartan and placebo, with a 2-sided P-value of 0.025. For NT-proBNP endpoint, the anticipated mean value is 998 pg/mL in the placebo arm (value obtained from preliminary results of sRV-biV cohort followed in Montreal Heart Institute). The expected between-patient standard deviation is believed to be between 500–700 pg/mL. While there is no available data on within-patient variation, we conservatively assumed a within-patient standard deviation of 600 pg/mL. With these assumptions, a total of 41 patients would provide 80% power to detect a 30% difference in NT-proBNP levels between sacubitril/valsartan and placebo, with a 2-sided P-value of 0.025. Factoring in a 10% attrition rate, a sample size of 48 patients (24 per randomized sequence) will be required. Descriptive statistics will be provided for all study variables, overall and by treatment arm.

Statistical analyses

Prior to any analysis, the assumptions (e.g., normality) underlying planned models will be verified with data transformation (e.g., logarithmic transformation) performed as needed. The two co-primary endpoints will be analyzed by use of ANOVA models for repeated measures that

will account for assigned treatment arm and treatment phase (first 24 weeks versus second 24 weeks). The treatment effect will be tested at the 0.025 significance level for each co-primary endpoint. For illustrative purposes, the carry-over effect will be tested by adding to the above models a term for the sequence of treatment (sacubitril/valsartan followed by placebo versus placebo followed by sacubitril/valsartan). Analyses of secondary endpoints will use similar methods. Adverse events occurring during each phase of the study will be presented per treatment arm using descriptive statistics. All statistical testing will be two-sided and conducted at the 0.05 significance level except for the two co-primary endpoints. Statistical analysis will be performed using SAS software version 9.4 (SAS Institute).

APPROVAL AND REGISTRATION

The protocol was approved by the Ethics Committee/Institutional Review Board affiliated with the Montreal Heart Institute and by Health Canada. Enrollment in the ***PARACYS-RV*** trial began on March 15, 2022. The estimated enrollment was evaluated at two years. The study is conducted in accordance with Good Clinical Practice, Declaration of Helsinki 2002. The trial has been registered on Clinicaltrials.gov, NCT05117736.

DISCUSSION

We hypothesize that the combination of sacubitril and valsartan carries the potential to alter the sRV-biV's adaptive stress pathways and improve prognosis. The adaptive pathways to stress in the RV differ from those in the left ventricle, with RAAS activation not being the primary mechanism implicated.[26, 27] The RV is more susceptible to oxidative stress due to the absence of activation of antioxidant enzymes resulting in increased activation of cell death pathways and

RV fibrosis.[27] The metabolic adaptation process for the RV is marked by an acute and permanent shift of fatty acid metabolism to glycolysis.[27] Overactivation of growth factors including fibroblast growth factors and their receptors leads to early maladaptive hypertrophy.[26] The sRV-biV is more susceptible to functional ischemia by virtue of an inefficient coronary circulation, relying on a single coronary artery to irrigate a hypertrophied sRV-biV with a reduced angiogenic response even in the absence of coronary atherosclerosis.[26] ACEis or ARBs, by reducing RAAS activation, lead to a reduction in overall activation of vasoconstrictor neurohormones which in turn attenuate over activation of growth factors, reduce hemodynamic stress and improve cardiac metabolism. Sacubitril/valsartan, by inhibiting the metabolism of natriuretic peptides, and several other vasodilatory peptides, would be expected to enhance any beneficial effects of RAAS blockade and have particularly beneficial effects on coronary circulation and cardiac metabolism. The combination of the 2 molecules could theoretically have a substantial effect on mechanisms to prevent cell death and maladaptive lipidic metabolism that exceed what could be achieved by ACEi or ARB alone. Previous cases reports and the two recent open-label trials reported promising results of sacubitril/valsartan with good tolerance in patients with sRV-biV physiology. A double-blinded controlled randomized clinical trial is required to definitively demonstrate the benefits of sacubitril/valsartan in patients with sRV-biV dysfunction.

Several features of the design of ***PARACYS-RV*** merit discussion. A crossover design is particularly advantageous for the study of small and heterogeneous patient populations. It provides the major advantage of reducing variability in outcome measures resulting from extraneous confounders since each patient serves as his or her own control. By reducing variability measurements, precision and efficiency are enhanced, with smaller sample sizes

required. A crossover design also provides the opportunity for each research subject to receive active therapy, which could be attractive for subjects and critical to enhancing feasibility in the context of a limited population.

Patients recruited in ***PARACYS-RV*** are symptomatic with NYHA functional class II or III symptoms. Prior trials of RAAS inhibitors in patients with a sRV-biV comprised a majority of asymptomatic (NYHA I) patients.[14, 15, 28] Asymptomatic patients have normal levels of angiotensin-II, indicating minimal RAAS activation potentially contributing to the lack of effect of RAAS inhibitors.[14] These observations prompted the decision to limit recruitment to symptomatic patients. The choice of placebo as the comparator (as opposed to an ACEi or ARB) was made in the absence of clinical trials demonstrating efficacy with RAAS inhibitors in patients with sRV-biV combined with the fact that these therapies are not currently recommended by evidence-based management guidelines for this patient population.[17-19]

Wash-out periods where no therapy is administered prior to initiating the first and the second treatments arms of the trial were deemed necessary to allow each subject's condition to return to the state closest to baseline. A two-week duration was judged by the executive committee to be sufficient since the medication is eliminated within 3 days (5 half-lives). To mitigate against the risk of worsening HF symptoms during this period, follow-up remote visits at one week and at the end of the washout period were planned. Moreover, additional remote visits were incorporated one week after the beginning of each treatment phase (increase from half of the dose to full dose of sacubitril/valsartan or matched placebo).

The two primary endpoints comparing a change from screening to end of the treatment phase, i.e., sub-maximal exercise duration and NT-proBNP level, were chosen to capture HF associated with sRV-biV dysfunction. The sub-maximal cardiopulmonary exercise test protocol

is well established and has previously been used as a primary endpoint for clinical trials by our research team.[29-32] The submaximal treadmill test will be performed using a constant-load protocol at an intensity corresponding to 75% of the peak VO2 (maximal oxygen consumption) determined by the maximal cardiopulmonary exercise test performed previously. After a 2-minute warm-up, the slope and speed of the treadmill will be programmed to predetermined settings corresponding to 75% of the most recent peak VO2max. In the open label single-center study comparing 18 patients with sRV-biV failure (ejection fraction <35%) at baseline and after 6 months of sacubritril/valsartan medication, no change in VO2max was observed but the sub-maximal parameter, i.e., 6 minute walk test distance, improved significatively.[23] A more accurate sub-maximal parameter such as sub-maximal exercise duration is, therefore, believed to be advantageous. Sub-maximal exercise duration has excellent sensitivity in assessing therapeutic interventions (superior to VO_2max and 6-minute walk test distance) and reflects daily physical activities. Daily physical activities are defined by the activities normally undertaken in daily living such as feeding, bathing, dressing, grooming, work, homemaking, housecleaning, transportation, walking, and shopping. In contrast to the 6-minute walk test which is also a submaximal test, the submaximal exercise protocol in PARACYS-RV benefits from measuring cardiopulmonary exercise parameters to allow for a more comprehensive assessment of contractile reserve. Cardiopulmonary exercise testing is a powerful tool to gain insights into both cardiac and pulmonary efficiencies and functional reserve.

NT-proBNP is currently the most sensitive neurohormonal marker for HF that correlates with disease severity and prognosis. A reduction in NT-proBNP predicts clinical improvement and is indicative of therapeutic effectiveness. In the PARADIGM-HF trial, NT-proBNP fell acutely after initiation of sacubitril/valsartan and continued to drop over time until the end of the

trial. Zandstra et al. showed a significant decrease in NT-proBNP levels in 18 patients with sRV-biV after 6 months of sacubritril/valsartan therapy compared to baseline.[23] In contrast, in Fusco et al's study of 50 patients with sRV-biV, the significant drop in NT-proBNP one month after initiation was followed by a subsequent return to the baseline value after 3 months.[24]

CONCLUSION

In summary, the ***PARACYS-RV*** trial is the first double-blind randomized trial to assess the efficacy of sacubitril/valsartan in the treatment of HF in patients with systolic dysfunction of a morphologic right ventricle in the systemic position. Heart failure is a prevalent issue in this relatively young and unique patient population for whom there is currently no accepted evidenced-based guideline-directed medical therapy for this indication. As such, the trial carries the potential to alter clinical management and improve outcomes in this patient population.

FIGURE LEGENDS

Figure 1. ***PARACYS-RV*** trial study schema

This figure provides an overview of the study design. Phase 1 includes the screening visit and the open active run-in phase of 6 weeks. Phase 2 begins by a two-week wash-out period, then patients are randomized in the first arm of 24 weeks of active therapy or the corresponding placebo. Phase 3 is the mirror of the second phase, each patient receives the active therapy or the corresponding placebo depending on phase 2 after a two-week wash-out period. Safety monitoring is evaluated at half-way time point for each treatment arm. A safety period of 4 weeks ends the study.

W, Weeks

Table 1. Exclusion criteria

1. Participation in a clinical trial of an investigational drug, concurrently, or within the last 30 days prior enrolment
2. Planned cardiac surgery (e.g., severe tricuspid regurgitation with planned tricuspid valve replacement or repair)
3. Previous cardiac transplantation, or on heart transplant wait list
4. Myocardial infarction, stroke, or open-heart surgery in the previous 4 weeks
5. NYHA Functional class I or IV symptoms
6. Symptomatic hypotension (fainting, dizziness, lightheadedness, blurred vision, weakness, fatigue, nausea, palpitations, and headache) with a systolic blood pressure <100 mmHg at screening, or asymptomatic <90 mmHg at screening
7. eGFR <30 mL/min/1.73 m^2
8. Reduction in eGFR >35% from screening to randomization
9. Potassium >5.2 mmol/L at screening or >5.4 mmol/L at randomization
10. Known history of angioedema related to previous ACEI or ARB therapy or patients with a history of hereditary or idiopathic angioedema.
11. Patients who require concomitant treatment with an angiotensin converting enzyme inhibitor (ACEI) or an angiotensin receptor blocker (ARB) or a renin inhibitor for other indication than heart failure
12. Evidence of hepatic disease as determined by any one of the following: SGOT (AST) or SGPT (ALT) values exceeding 3x ULN, bilirubin >1.5 mg/dl at screening.
13. Unacceptable side effects with ACE-inhibitors or ARBs

14. Patient known with bilateral renal artery stenosis
15. Cyanosis; substantial left-to-right shunting (Qp/Qs >1.5); severe mitral, aortic, or pulmonary regurgitation; systemic or pulmonary inflow obstruction with a peak velocity >1.5 m/s by transthoracic echocardiography; and severe outflow tract obstruction with a peak systolic gradient >80 mm Hg.
16. Inability to provide informed consent
17. Unable to exercice
18. Pregnant or planned pregnancy during the study
19. Breastfeeding
20. Severe pulmonary hypertension defined as pulmonary pressure equal or superior to systemic pressure

Table 2. Endpoints collected during Paracys-RV

Endpoints	Description	Visits of endpoints collection
Primary-efficacy		
Exercise capacity and neurohormonal activation	1) Sub-maximal total exercise duration 2) NT-proBNP level	At screening (V1) and at the end of each treatment arm (V9 and 14)
Secondary-efficacy		
Quality of life	Kansas City Cardiomyopathy Questionnaire (KCCQ)	At screening (V1) and at the end of each treatment arm (V9 and 14)
Secondary-safety		
Safety of medication	Electrolytes (Serum potassium level), renal function (creatinine, eGFR, urea), blood pressure. Adverse clinical events occurred during each treatment arm: cough, postural symptoms, angioedema.	At screening (V1), at the half-way time point for each treatment arm (V8 and 13) and at the end of each treatment arm (V9 and 14). From screening (V1) until end of the follow-up (run in phase, two arms phases and safety period)
Exploratory		
NYHA functional class	NYHA class	At screening (V1) and at the end of each treatment arm (V9 and 14)
Occurrence of clinical events	Heart failure, hospitalizations, arrhythmias (supraventricular and ventricular), mortality	From screening (V1) until end of the follow-up (run in phase, two arms phases and safety period)
Myocardial injury biomarker	Hs Troponin T level	At screening (V1) and at the end of each treatment arm (V9 and 14)
sRv-biV size and function	TAPSe, S'wave, fractional area change, global longitudinal strain, end diastolic area, end systolic area by transthoracic echocardiography	At screening (V1) and at the end of each treatment arm (V9 and 14)
Exercise capacity complementary parameters	Anaerobic threshold, functional capacity METs, heart rate response, blood pressure response, oxygen saturation during exercise, respiratory exchange ratio VE/VO2 slope, VE/VCO2 slope	At screening (V1) and at the end of each treatment arm (V9 and 14)
Metabolic profile	Lipidomic analysis	At screening (V1) and at the end of each treatment arm (V9 and 14)

Table 3. Safety criteria

1) Potassium ≤5.4 mmol/L 2) No reduction in eGFR of >35% from Visit 0 screening; 3) No symptomatic hypotension with SBP<90mmHg; 4) Adverse events: **Postural symptoms** physical symptoms that occur or worsen when changing positions, such as standing up from a seated or lying position i.e. fainting, dizziness, lightheadedness, blurred vision, weakness, fatigue, nausea, palpitations, and headache. **Adverse events** include any unfavorable and unintended sign, including an abnormal laboratory finding, symptom or disease, that occurs during the study, whether or not considered related to the study drug. **Serious adverse events** are defined by any adverse event fulfilling at least one of the following criteria: fatal, life-threatening, requiring in-patient hospitalization, or prolongation of existing hospitalization, resulting in persistent or significant disability or incapacity or medically significant, or requires intervention to prevent at least one of the outcomes listed above.

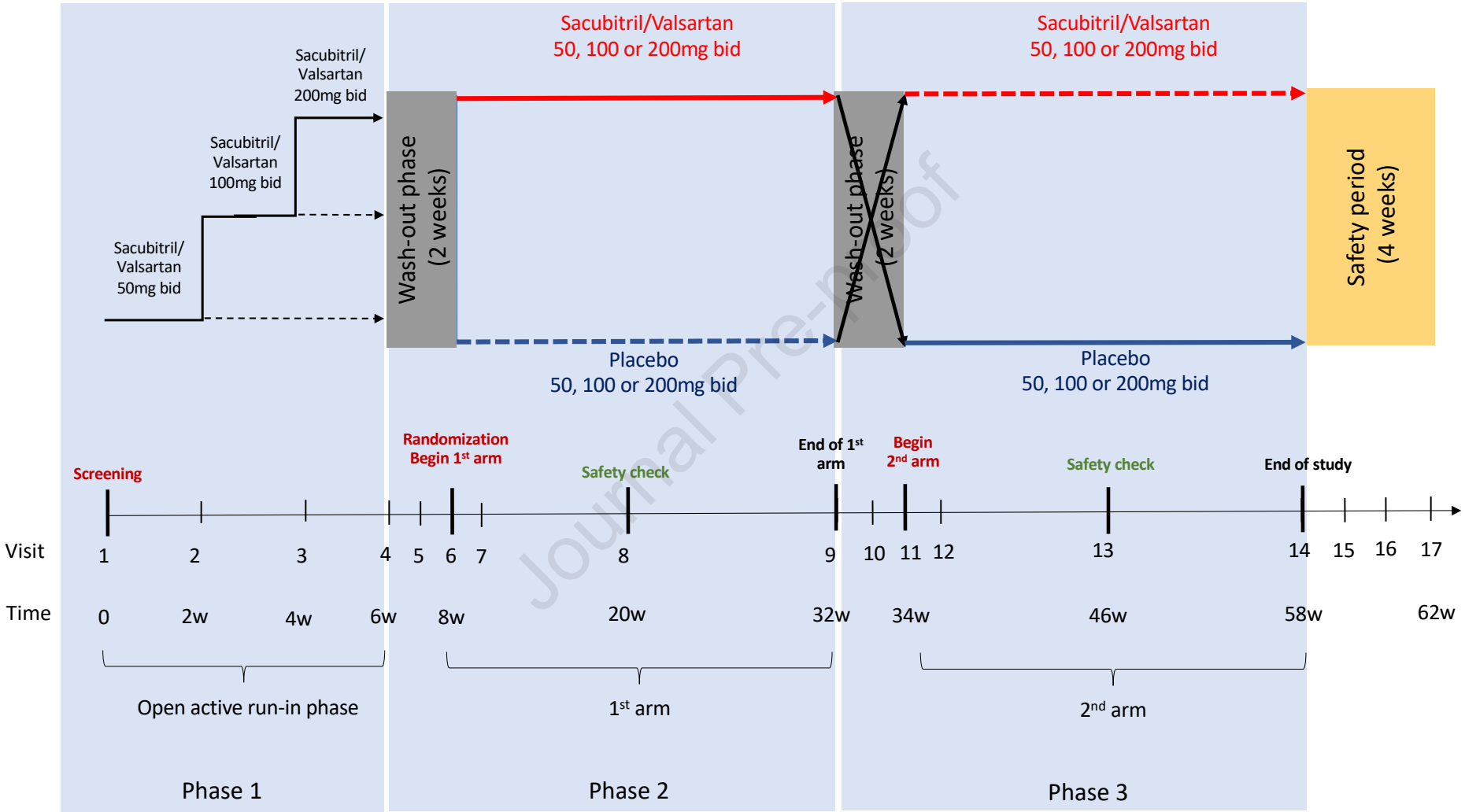

Figure 1. Overview of the ***PARACYS-RV*** trial

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