Efficacy of phosphodiesterase type 5 inhibitors in univentricular congenital heart disease: the SV-INHIBITION study design

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Abstract

Aims   In univentricular hearts, selective lung vasodilators such as phosphodiesterase type 5 (PDE5) inhibitors would decrease pulmonary resistance and improve exercise tolerance. However, the level of evidence for the use of PDE5 inhibitors in patients with a single ventricle (SV) remains limited. We present the SV-INHIBITION study rationale, design, and methods.

Methods and results   The SV-INHIBITION trial is a nationwide multicentre, randomized, double blind, placebo-controlled, Phase III study, aiming to evaluate the efficacy of sildenafil on the ventilatory efficiency during exercise, in teenagers and adult patients ($>$15 years old) with an SV. Patients with a mean pulmonary arterial pressure $>$15 mmHg and a trans-pulmonary gradient $>$5 mmHg, measured by cardiac catheterization, will be eligible. The primary outcome is the variation of the VE/VCO_2 slope, measured by a cardiopulmonary exercise test, between baseline and 6 months of treatment. A total of 50 patients are required to observe a decrease of 5 ± 5 points in the VE/VCO_2 slope, with a power of 90% and an alpha risk of 5%. The secondary outcomes are clinical outcomes, oxygen saturation, 6 min walk test, SV function, NT-proBNP, peak VO_2, stroke volume, mean pulmonary arterial pressure, trans-pulmonary gradient, SF36 quality of life score, safety, and acceptability.

Conclusions   The SV-INHIBITION study aims to answer the question whether PDE5 inhibitors should be prescribed in patients with an SV. This trial has been built focusing on the three levels of research defined by the World Health Organization: disability (exercise tolerance), deficit (SV function), and handicap (quality of life).

Introduction

In the spectrum of complex congenital heart diseases (CHD), univentricular hearts or 'single ventricles' (SVs) are

characterized by the existence of only one functional ventricle. Physiologically, an SV provides both systemic and pulmonary blood flows, the circulation is in parallel, and mixed arterial and venous blood lead to desaturation at rest and

during exercise. Chronic ventricular volume overload results in progressive ventricular dysfunction.

Various palliative surgical procedures are performed in order to maintain the pulmonary blood flow (systemic-pulmonary artery anastomosis), to avoid pulmonary hypertension (pulmonary artery banding), and to eventually restore a circulation in series (Fontan repair).[1] In the Fontan circulation, the systemic venous return directly flows from the two vena cava to the pulmonary arteries, without any sub-pulmonary ventricle and thus without pulsatility. Surgical techniques have been progressively improved, and currently most children undergo a two-stage total cavo-pulmonary connection, using an extracardiac conduit. This palliative surgical approach corrects ventricular overload and cyanosis at a cost of a systemic venous hypertension and a cardiac output at the lower end of normal. This strategy improves survival of children born with an SV. Nevertheless, exercise capacity of these patients remains significantly impaired, and we recently showed that children with a Fontan circulation had a maximum oxygen uptake lowered by 30% compared with healthy matched subjects.[2] Furthermore, long-term evolution is inexorably marked by a failure of the Fontan circulation, and non-pulsatile pulmonary blood flow has been associated with the development of pulmonary vascular disease.[3] Any increase in resistance to pulmonary blood flow will aggravate effort intolerance and accelerate Fontan failure.[1]

Therefore, the use of a selective pulmonary vasodilator in SV may be of interest, in order to decrease trans-pulmonary gradient (TPG), increase pulmonary blood flow and ventricular preload, and, thus, improve cardiac output and exercise tolerance.[4–8] Recent studies have suggested that sildenafil, a phosphodiesterase type 5 (PDE5) inhibitor, would decrease pulmonary resistance, improve ventricular filling, and improve exercise tolerance, with low toxicity and good clinical tolerance.[6,7,9–11] However, the level of clinical evidence for sildenafil in this indication remains limited, with case reports, small and uncontrolled cohorts, retrospective studies, and studies with a short exposure time to treatment (e.g. maximum of 6 weeks).[12–16] Therefore, a better selection of patients who may benefit from pulmonary vasodilator is necessary and with a sufficiently long exposure time of treatment.

In the SV-INHIBITION trial, we aim to evaluate the efficacy of sildenafil on ventilatory efficiency during exercise assessed by the VE/VCO_2 slope, in patients with an SV and elevated pulmonary pressures. We also intend to assess the efficacy of sildenafil on functional status, SV function, haemodynamic parameters, health-related quality of life, and drug tolerance.

Study design

The SV-INHIBITION trial is a randomized, multi-centre, double blind, placebo-controlled, parallel arm, Phase III study, with a treatment period of 6 months, a follow-up of 9 months, and an expected recruitment duration of 24 months.

Randomization will be centralized, using a 1:1 ratio. Participants will be randomly allocated in a 1:1 ratio to either intervention or control group arms, with stratification on age and centre. Randomization numbers will be computer generated and assigned in strict sequence, using a secure, web-based randomization system (CS RANDOM module, Ennov clinical Software). Randomization will be managed by the Clinical Research Unit of Montpellier University Hospital, France, independently from the investigators. All screened subjects will be identifiable throughout the study by a unique subject number.

Eligible patients will be randomized into two groups (*Figure 1*):

- Group 1: patients receiving the study drug, e.g. sildenafil, for 6 months;
- Group 2: control subjects, receiving the placebo, for 6 months.

Setting

Patients will be recruited within the French national network of expert centres in complex CHD and/or severe pulmonary hypertension, labelled by health authorities (e.g. M3C and PH national health networks). Overall, 18 centres will participate in the study, and a total of 36 investigators (e.g. the SV-INHIBITION collaborative group) will oversee patient recruitment. These investigators are paediatric cardiologists ($n = 18$), adult congenital cardiologists ($n = 6$), or both ($n = 12$).

Conduct of the study will be led by a local principal investigator (supported, when necessary, by a co-investigator), a research nurse or fellow, and a clinical research assistant, all of whom are trained in Good Clinical Practice and in the requirements of the study protocol. Each site will be responsible for the recruitment and scheduled follow-up visits of participants.
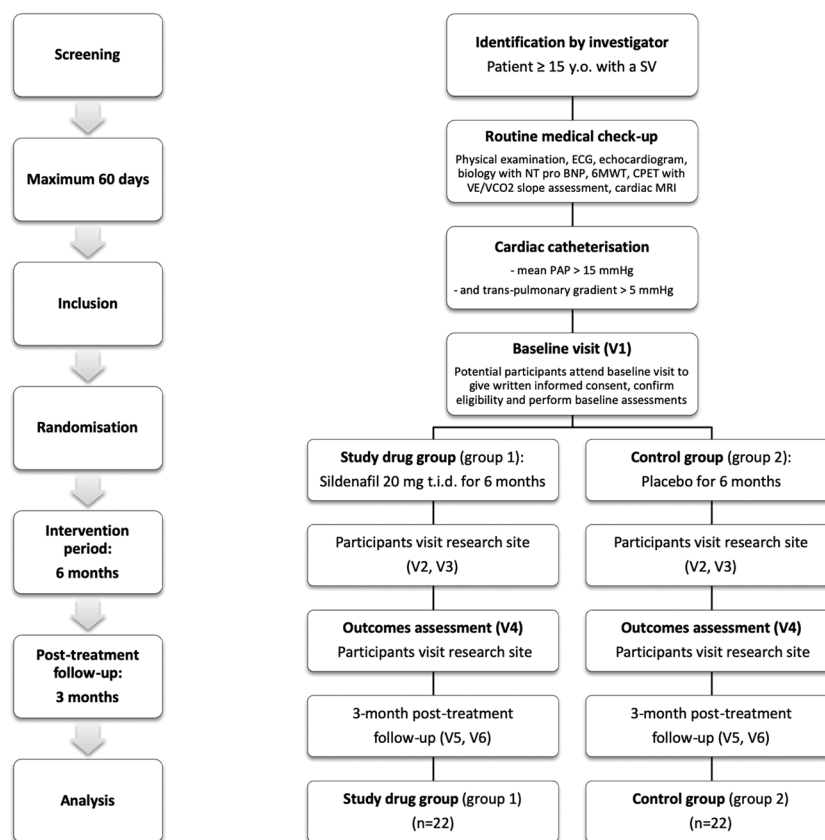
Sponsoring

Montpellier University Hospital is the sponsor of the SV-INHIBITION trial.

Study population

Patients with an SV (e.g. univentricular heart), as defined by the Anatomic and Clinical Classification of Congenital Heart Defects (ACC-CHD), and aged 15 years and above will be prospectively recruited in the participating centres during their regular follow-up. In the current guidelines, patients with an

Figure 1 Flow chart.

SV usually require an annual check-up, including a cardiology consultation, an electrocardiogram, a cardiac imaging examination (echocardiogram and/or cardiac magnetic resonance imaging), a blood test, a spirometry at rest, and a cardiopulmonary exercise test (CPET).[2] During the screening phase, patients with an SV referred for cardiac catheterization for heart failure, cyanosis, pre-transplantation assessment, exudative enteropathy, bronchial casts, and/or liver disease will be identified.

Patients with a mean pulmonary arterial pressure (mPAP) >15 mmHg and a TPG >5 mmHg, measured during cardiac catheterisation, will be eligible for the study. Catheterization will be performed through a standardized method that will be harmonized among centres before the study will start. Catheterization will be performed under local anaesthesia and conscious sedation in spontaneously breathing patient free from any oxygen or air administration in supine position at rest. The zero reference level will be placed at the mid-thoracic level. Intracardiac and vessels pressures [e.g. superior vena cava pressure (SVCP), inferior vena cava pressure, right and left mPAP, pulmonary capillary wedge pressure, SV end-diastolic pressure, SV systolic pressure, systolic, diastolic and mean aortic pressures (sAoP, dAoP, mAoP,

respectively)] will be measured using fluid-filled end hole catheter and a transducer. Measurements will be averaged over two to five consecutive steady-state beats and several respiratory cycles. Any pressure gradients within the circulation will be identified. Pulmonary artery oxygen saturation and aortic oxygen saturation (Ao-Sat) will be measured. Haemodynamic data will be measured at baseline and after fluid challenge (15 mL/kg of 0.9% sodium chloride injected in 10 min). Systemic (Qs) and pulmonary (Qp) blood flows will be calculated using the Fick formula. Oxygen consumption (VO_2) will be estimated using the LaFarge formula or measured using an indirect calorimeter collecting expired gas in a canopy hood, in centres with dedicated equipment. Cardiac index corresponds to Qs divided by body surface area. For Qp calculation, the Ao-Sat will be used or an assumed pulmonary vein saturation of 95% in case of veno-venous collaterals or fenestration.[17] Indexed pulmonary vascular resistance (PVRi) will be calculated as follows: PVRi = (mPAP − pulmonary capillary wedge pressure (PCWP)) ÷ (body surface area × Qp). Indexed systemic vascular resistance (SVRi) will be calculated as follow: SVRi = (mAoP − inferior vena cava pressure) ÷ (body surface area × Qs). If angiography images are required, they will be performed after haemodynamic measurements.

Table 1 Trial entry

Inclusion criteria
- 15 years of age and over
- Patients weight over 20 kg
- Patients with a single ventricle (e.g. univentricular heart) as defined by the ACC-CHD classification
- Mean pulmonary arterial pressure (mPAP) >15 mmHg and trans-pulmonary gradient (TPG) >5 mmHg, measured by cardiac catheterization[a]
- Written informed consent for adult patients or legal guardians for teenagers and formal assent for teenagers

Exclusion criteria
- Patient who is unable to perform a CPET
- Absolute contraindications for CPET: fever, uncontrolled asthma, respiratory failure, acute myocarditis or pericarditis, uncontrolled arrhythmias causing symptoms or haemodynamic compromise, uncontrolled heart failure, acute pulmonary embolus or pulmonary infarction, and patients with mental impairment leading to inability to cooperate
- Cardiac surgery planned during the study
- Patient treated by any pulmonary arterial vasodilator drug, within 6 months before inclusion, regardless the duration and the type(s) (oral, intravenous, subcutaneous, or inhaled) of administration, such as sildenafil, tadalafil, riociguat, bosentan, macitentan, ambrisentan, epoprostenol, iloprost, and treprostinil
- Patient treated by sildenafil within 6 months before inclusion, regardless the duration of administration
- Interventional cardiac catheterization planned during the trial (collateral occlusion, fenestration occlusion, stenting, angioplasty, ablation of rhythm disorder), other than during the screening[b]
- Participation in another clinical trial or administration of an off-label drug in the 4 weeks preceding the screening
- Pregnancy, desire for pregnancy, absence of contraception during the study period
- Severe hepatic insufficiency (Child-Pugh C class)
- Hypersensitivity to the active substance or to any of the excipients of the tablet: microcrystalline cellulose, calcium hydrogen phosphate anhydrous, croscarmellose sodium, stearate of magnesium, hypromellose, titanium dioxide (E171), monohydrate lactose, glycerol triacetate
- Combination with products called 'nitric oxide donors' (such as amyl nitrite) or with nitrates in any form, due to the hypotensive effects of nitrates
- Disposition to priapism, sclerosis of corpora cavernosa, disease of La Peyronie, sickle cell anaemia, multiple myeloma, leukaemia
- Uncontrolled hypotension or risk of hypotension: water depletion, obstruction to ejection of the left ventricle, dysfunction of the autonomic nervous system, and patient under alpha-blocker
- Severe cardiovascular events, recent (<3 months) or not stabilized: myocardial infarction, unstable angina, sudden cardiac death, ventricular arrhythmia, and cerebrovascular haemorrhage
- Active haemorrhagic disorders
- Active gastro-duodenal ulcer
- Patients with loss of vision of an eye due to non-arteritic anterior ischemic optic neuropathy, whether or not this event has been associated with previous exposure to a PDE5 inhibitor

CPET, cardiopulmonary exercise test.
[a]Patients with an SV referred for cardiac catheterization for heart failure, cyanosis, pre-transplantation assessment, exudative enteropathy, bronchial casts, and/or liver disease will be identified during the screening phase.
[b]If a patient requires an interventional catheterization (fenestration occlusion, stenting of Fontan circulation obstacle, collaterals embolization, etc.), a new hemodynamic cardiac catheterization will be required at least 3 months after procedure to confirm patient's eligibility (mPAP >15 mmHg and TPG >5 mmHg).

A core lab will analyse cardiac catheterization data before patient's enrolment.

The screening period will not exceed 60 days. Detailed inclusion and exclusion criteria are reported in *Table 1*.

Intervention

Patients randomized in the group 1 will receive sildenafil in three oral doses of 20 mg per day (t.i.d.), as defined in the marketing authorization indicated for pulmonary arterial hypertension (PAH) in adolescent and adult patients and for a period of 6 months. Patients in the Group 2 will receive a placebo, for the same period of 6 months. To guarantee the double blind, capsules will be similar in size and colour and will be differentiated only by a vial number regarding to the randomization list. They will be packed in pillboxes of 90 corresponding to 1 month of treatment. Pillboxes will be labelled in accordance with the Good Manufacturing Practices

(Annex 3, revised and adopted in July 2003 by the European Commission) and the 2006 decree on labelling content for investigational medicinal products. The clinical trials' unit of the sponsor's pharmacy will centralize treatment allocation and supply to the participating centres. Drug management (reception, storage, delivery, and traceability) will be ensured by the pharmacies of the participating centres.

After the 6 month treatment period, patients will be followed for 3 months and undergo at least two safety visits (1 and 3 months after intervention, and if necessary, any supplementary unscheduled visits). In accordance with the recommendations of the drug notice, the treatment will be suspended progressively over 1 week (20 mg b.i.d for 3 days, then 20 mg q.d. for 4 days, and then stopped) with a reinforcement of the surveillance. Patients will be able to contact an emergency number during this period, and the investigator may decide to continue open treatment with sildenafil if clinically justified.

Detailed visits of the study are reported in *Table 2*.

Table 2 Visits

Item Visit number Schedule (M: month)	Screening V0 Up to 60 days	Inclusion/Baseline V1 Day 1	Treatment period			Post-intervention follow-up period	
			V2 M1 ± 7 days	V3 M3 ± 7 days	V4 M6 ± 7 days	V5 M7 ± 7 days	V6 M9 ± 7 days
Informed consent/assent	X						
Eligibility criteria	X	X					
Medical and surgical history	X						
Demography	X						
Physical examination	X	X	X	X	X	X	X
Vital constant[a]	X	X	X	X	X	X	X
Randomization		X					
Routine laboratory testing[b]	X				X		X
NT-proBNP	X				X		
ECG	X	X	X	X	X	X	X
Echocardiography	X		X	X	X	X	X
6MWT	X				X		
CPET with VE/VCO$_2$ slope	X				X		
Cardiac MRI	X				X		
Cardiac catheterization	X				X		
Dispense study medication		X	X	X			
Returned study medication count			X	X	X		
Adverse events recording	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X
Quality of life assessment		X			X		X

CPET, cardiopulmonary exercise test; ECG, electrocardiogram; MRI, magnetic resonance imaging; NT-proBNP, N terminal pro brain natriuretic peptide; VE/VCO$_2$ slope, ventilatory efficiency (primary outcome); 6MWT, 6 min walk test.
Examinations specifically required for the study are indicated with a red cross; routine follow-up examinations are indicated with a black cross.
[a]Vital constant: body temperature, heart rate, arterial blood pressure, height, and body weight.
[b]Routine laboratory testing: blood count, platelets, blood ionogram, urea, serum creatinine, creatinine clearance, blood urea nitrogen, albumin, prothrombin time, INR if patient under VKA anticoagulants, ferritin, N terminal pro brain natriuretic peptide (NT-proBNP), liver function [alanine amino transferase (ALT), aspartate amino transferase (AST), gamma glutamyl transferase (gamma GT), bilirubin].

Sample size

We aim to recruit 50 patients (25 sidenafil: 25 placebo). The primary outcome is the change in the VE/VCO$_2$ slope. We used data from our preliminary study in which patients with CHD and PAH have an average VE/VCO$_2$ slope of 55 ± 5.[18] We hypothesized to observe a decrease of 10% in the VE/VCO$_2$ slope, e.g. a 5-point VE/VCO$_2$ slope decrease and no change in the placebo group. With a 90% power, a bilateral alpha risk of 5%, and potentially 10% of loss to follow-up and/or missing data on the primary outcome, we need to include 25 patients in Group 1 and 25 patients in Group 2. In order to guarantee the recruitment of 50 patients in the trial, all participating investigators have been selected according to the number of eligible patients within each centre.

Statistical analysis

All included subjects will be considered in the description of the population (baseline characteristics). An intention-to-treat analysis will be used, and each randomized subject will be analysed in his/her treatment arm. A per-protocol analysis, including all randomized subjects with a valid primary efficacy measurement and with no important protocol deviation that could affect the evaluation of the main outcome will also be carried out for parameters to study mechanisms of action.

A description of each group will be made by giving the frequencies of the different categories for the qualitative variables. In case of non-comparability of the groups on one of the confounding factors, an adjustment or stratification (in case of interaction) will be considered in the sensitivity analysis.

Primary outcome

The primary outcome will be the variation of the ventilatory efficiency, e.g. the VE/VCO$_2$ slope, measured by CPET,[19] between baseline (M0) and 6 months of treatment (M6). The VE/VCO$_2$ slope will be measured using the best-fit linear regression line relating minute ventilation (VE) and carbon dioxide output (VCO$_2$). The slope will be calculated from rest to peak exercise, the recuperation being eliminated.

As detailed in our previous multicentre CPET studies, exercise test procedures in all participating laboratories will be harmonized before the start of the study.[2,20,21] All centres will use the same CPET cycle ergometer protocol, to obtain a homogeneous incremental overall duration between 8

and 12 min: a 1 min rest; a 3 min warm-up (10 to 20 W) in increments of 10, 15, or 20 W each minute; a pedalling rate of 60 to 80 revolutions per minute; a 3 min active recovery (20 W); and a 2 min rest. The CPET will be considered as maximal when three out of the four following criteria will be reached: respiratory exchange ratio (RER = VCO_2/VO_2) ≥ 1, maximum heart rate $>85\%$ of maximal age-predicted heart rate, plateau of VO_2 (VO_{2max}) despite the increasing exercise intensity, and patient's inability to provide a minimum pedalling frequency of 60 per minute despite verbal encouragement. When a plateau of VO_2 will not be reached, as commonly observed in SV patients with submaximal exercise, the peak VO_2 will be informed.

Secondary outcomes

The following outcomes will be measured at baseline (M0) and after 6 months of treatment (M6):

- other CPET variables, VO_{2max} (e.g. maximal exercise test with plateau of VO_2), peak VO_2 (e.g. in submaximal exercise test), ventilatory anaerobic threshold (VAT) using Beaver's method, oxygen pulse (ratio VO_2/heart rate), oxygen uptake efficiency slope (OUES), and minimal oxygen saturation (SpO_2), will be recorded. VO_{2max}, peak VO_2, and VAT values will be normalized in a percentage of the predicted VO_{2max} using reference values for cycle ergometer test in the general paediatric and adult population, as in our previous CPET studies[2,20,21];
- The clinical outcomes: New York Heart Association (NYHA) functional class, blood pressure, SpO_2 at rest, health care usage (primary and secondary care contacts related to new symptoms and hospitalization), and medication;
- SV function evaluated by non-invasive cardiac imaging (echocardiography, magnetic resonance imaging);
- Biology: NT-proBNP;
- The 6 min walk test;
- Cardiac catheterization: mPAP, TPG, pulmonary capillary wedge pressure, pulmonary artery oxygen saturation, Ao-Sat, cardiac index, PVRi, SVRi.;
- The health-related quality of life score, using the SF36 questionnaire;
- The safety outcomes;
- The acceptability of the intervention to participants.

Detailed outcomes are reported in *Table 3*.

Data monitoring and quality control

Routine data monitoring visits will be made by the monitors designated by the sponsor to check compliance with the protocol, the completeness, accuracy and consistency of the

Table 3 Outcome measures

Primary outcome
- VE/VCO$_2$ slope

Secondary outcomes
- CPET: VO_{2max}; peak VO_2; VAT; oxygen pulse; OUES
- Spirometry: FEV1; FVC; FEV1/FVC ratio
- Clinical status: NYHA functional class; SpO_2; 6MWT
- Echocardiography: systemic blood flow, SV systolic ejection fraction, 2D Strain SV function
- Cardiac MRI: systemic and pulmonary blood flows in phase contrast, SV systolic ejection fraction and volumes
- NT-proBNP
- Cardiac catheterization: mPAP, TPG, PCWP, PA-Sat, Ao-Sat, CI, PVRi, SVRi
- SF36 quality of life questionnaire
- Safety outcomes
- Acceptability of the intervention to participants

Ao-Sat, aortic oxygen saturation; CI, cardiac index; CPET, cardiopulmonary exercise test; FEV1, flow volume curve and measurement of the forced expiratory volume in 1 second; FVC, forced vital capacity; mPAP, mean pulmonary arterial pressure; MRI, magnetic resonance imaging; OUES, oxygen uptake efficiency slope; PA-Sat, pulmonary artery oxygen saturation; PCWP, pulmonary capillary wedge pressure; PVRi, indexed pulmonary vascular resistance; SpO_2, pulse oximetry; SV, single ventricle; SVRi, indexed systemic vascular resistance; TPG, trans-pulmonary gradient; VAT, ventilatory anaerobic threshold; VO_2: oxygen uptake; 6MWT, 6 minute walk test.

data, and adherence to Good Clinical Practices. The investigator will agree to provide the monitor direct access to the subjects' source data, which may exist in the form of hospital records, patient files and notes, and laboratory assessment reports and results.

Furthermore, a Data and Safety Monitoring Board composed by a physician specialized in paediatric and congenital cardiology, a pharmacologist with skills on the mode of action and safety of the concerned product, and a methodologist or statistician independent has been set up. This consultative committee will be asked to express an opinion to the sponsor of the study on the benefit/risk ratio and the management of the clinical trial. The members of the Data and Safety Monitoring Board are as well responsible for safeguarding the interests of study participants, assessing the safety and efficacy of all study procedures, and shall monitor the overall conduct of the study. The committee makes recommendations about the future of the study (continuation, amendment, and stop).

Ethics

The study will be conducted in compliance with the Good Clinical Practices protocol and Declaration of Helsinki principles. It was approved by a drawn National Ethics Committee (South Mediterranean III - 2018-004828-11) and by the French National Agency of Medicine and Health Products Safety (ANSM). The study was registered on Clinicaltrials.

gov (NCT03997097). Informed consent will be obtained from all patients and their parents or legal guardians for minors.

Discussion

To our knowledge, the SV-INHIBITION study will be the first double blind, randomized, multicentre clinical trial to investigate the effects of a pulmonary arterial vasodilator in adolescents and adults with SV, mPAP >15 mmHg, and TPG >5 mmHg.

Univentricular heart failure is related with poor outcome, multisystemic organ disorders, decreased functional capacity, and impaired quality of life. Cardiac transplantation is the ultimate therapeutic option for the management of patients with failing Fontan. Unfortunately, it remains little performed given paucity of grafts and procedural challenges.[22] Thus, there is a need for a palliative medical approach to delay Fontan circulation failure.

Fontan failure has been related in some patients to increased pulmonary pressure and TPG, resulting in impaired ventricular preload and cardiac output. In such conditions, a pharmacological target strategy using pulmonary vasodilators is of interest. Recent studies have evaluated sildenafil in SV patients and suggested it would decrease pulmonary resistance, improve ventricular filling, and increase exercise tolerance, with low toxicity and good clinical tolerance.[6,7,9–11] A recent randomized study of 19 patients, using pressure/volume curves during cardiac catheterization,[23] and two recent echography studies[24,25] showed an improvement of ventricular function under sildenafil. However, results remain controversial,[16,26] and we need a stronger level of evidence for selective pulmonary vasodilators and particularly sildenafil in this indication.[12–16] Other oral selective pulmonary vasodilators, such as endothelin receptors antagonists (bosentan)[5,8] or soluble guanylate cyclase stimulator (riociguat)[27] are also of interest, but they are contraindicated in case of severe liver disease, which is not uncommon in failing Fontan.

The SV-INHIBITION trial intends to enrol SV patients aged 15 years and above. Indeed, decline of patients with Fontan circulation usually appears in late adolescence and during adulthood and manifests first by functional limitation during exercise and then at rest.[2] Including patients of various ages may provide a better identification of patients who will best benefit from pharmacological therapy.

The main outcome of the SV-INHIBITION trial is the ventilatory efficiency, e.g. the VE/VCO_2 slope. Indeed, the prognostic importance of VE/VCO_2 slope has been demonstrated in chronic heart failure and PAH.[19] Moreover, VE/VCO_2 slope is reproducible and easily measured, even for submaximal exercise test, in such conditions as SV. The current guidelines on CHD patients' follow-up recommend regularly measuring the VE/VCO_2 slope with a CPET. We recently showed that the VE/VCO_2 slope was associated with the quality of life of young patients with CHD.[20] We purposely chose this submaximal CPET variable, rather than the maximum oxygen uptake (VO_{2max}), as a maximal exercise, and thus a plateau of VO_2, are often difficult to obtain in the most serious SV patients, for which only the peak VO_2 can be measured. Indeed, from a cohort of 28 patients with an SV undergoing a CPET, Goldberg et al. failed to demonstrate in their randomized drug trial, any increase in peak VO_2, e.g. their primary outcome, but found that sildenafil improved ventilatory efficiency.[16]

The SV-INHIBTION trial aims to enrol patients with mPAP >15 mmHg and TPG >5 mmHg during cardiac catheterization. These criteria are currently used in clinical practice by some teams to indicate pharmacological therapy although there are currently no recommendations. The level of mPAP above 15 mmHg has already been suggested as a marker of poor outcome[28] and used as an inclusion criterion in other studies in patients with Fontan circulation.[29] This threshold was also one of the 'ten commandments' from the original Choussat criteria for Fontan surgery eligibility. In addition, a TPG above 5 mmHg avoids enrolling patients with isolated ventricular or atrio-ventricular valve dysfunction. Indeed, diastolic ventricular dysfunction seems to be aggravated by pulmonary vasodilators and may explain discrepancies in the results observed in previous studies.[7,17,26] We purposely did not use pulmonary vascular resistance to define patients eligible to the SV-INHIBITION trial, given the known difficulties to accurately measure pulmonary blood flow in SV physiology. Baseline World Health Organization (WHO)-New York Heart Association functional class and CPET data were purposely not included in the selection criteria. Indeed, we aim to investigate the effect of sildenafil in a wide spectrum of SV patients' clinical phenotype and therefore be as close as possible to the real life's clinical practice.

The use of empirical treatments remains too common in the field of CHD, and off-label drugs are routinely used in paediatric cardiology. Oral selective pulmonary vasodilators are increasingly used in SV because they are simple to manage, usually without major side effects, and analogy is made with the physiology of the PAH from vascular origin, whereas SV haemodynamic is more complex. Therefore, randomized controlled drug trials in this population become crucial, even if such trials may end up with negative results. The recent meta-analysis from Wang et al. analysed the efficacy and safety of pulmonary vasodilators in patients with Fontan circulation and counted only nine randomized controlled trials (sildenafil, n = 4; bosentan, n = 4; ambrisentan, n = 1), representing a total of 381 patients. As a result of small sample size studies, insufficient haemodynamic data and short-term follow-up, they concluded that further randomized controlled studies remained necessary to improve the level of evidence for the use of pulmonary vasodilators in patients with SV.[30] An on-going large randomized controlled

Phase III study (RUBATO) aims to assess the efficacy and safety of macitentan, a new oral endothelin receptor antagonist, in stable Fontan-palliated adolescent and adult subjects (NCT03153137).

Finally, the SV-INHIBITION trial was built taking into account the three health care levels defined by the World Health Organization: the deficit level (cardiac function, haemodynamic, etc.), the disability level (exercise tolerance, e.g. our primary endpoint), and the handicap level (health-related quality of life). Moreover, this study is financially supported by a grant of the French Ministry of Health, guarantying the absence of any conflict of interest with the pharmacological industry. If the results are positive, the SV-INHIBITION trial will open a major perspective in the treatment of SV patients.

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Conflict of interest

None declared.

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Author Contributions

Study concept and design: PA; Drafting of the manuscript: PA, SH, AG, AH; Critical revision of the manuscript for important intellectual content: all; Statistical analysis: MCP; Obtained funding: PA; Administrative, technical, or material support: PA, AH; Study supervision: PA, AG, DB, SH.

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