Statistical Analysis Plan

Study: Effect of phosphodiesterase-5 inhibition with Tadalafil on SystEmic Right VEntricular size and function – a multi-center, double-blind, randomized, placebo-controlled clinical trial – **SERVE** Trial

CTU project number: **636**

Protocol: Version 3 / 20.09.2017

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Date: 26.03.2018

Version: 1.0

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Change history:

Version	Date	Major changes

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Contents

1. Study synopsis

Currently, there are an estimated 300-600 adults living in Switzerland with congenital heart disease (CHD) and a right ventricle (RV) in subaortic (systemic) position. This includes adults with prior atrial switch operations for complete transposition of the great arteries (D-TGA) and adults with congenitally corrected transposition of the great arteries (ccTGA). Although midterm survival is favourable, late outcome is compromised by ventricular dysfunction of the systemic RV, end-stage heart failure, and premature death. Medical heart failure therapy (ACE-inhibitors, beta-blockers, aldosterone antagonists) has been shown to improve ventricular function and survival in patients with left heart failure from acquired heart disease. Unfortunately, case-reports and studies failed to show similar clinical benefits of these drugs in adults with a failing systemic RV. Currently, the only established end-stage therapy for a failing systemic RV is heart transplantation. Given the ubiquitous shortage of donor organs and the number of adults at risk, medical options to improve the fate of patients with a systemic RV are urgently needed.

The RV and left ventricle (LV) have different embryological origins, myocardial architecture and contractile properties. In response to increased afterload, as in an RV in systemic position, the RV expresses a fetal gene pattern, with an increase in phosphodiesterase (PDE)-5 expression. PDE-5 is not expressed in the normal RV, but is up-regulated in the hypertrophied RV. PDE-5 inhibition increases contractility in experimental models of RV hypertrophy, but not in the normal RV. In clinical practice, the effects of PDE-5 inhibition on systemic RV function and exercise capacity in adults with TGA have not been tested.

This study assesses in a double-blind, randomized, **placebo**-controlled multi-center pilot trial the effect of PDE-5 inhibition with **Tadalafil** on RV size and function, exercise capacity and neurohumoral activation in adults with a systemic RV over a 3-year follow-up period.

2. Study objectives

2.1. Primary objective

The prrimary endpoint is **change in mean end-systolic RV volumes** (RV ESV) from baseline to study end at 3 years of follow-up, measured by cardiovascular magnetic resonance imaging (CMR) or cardiac multirow detector computed tomography (CMDCT) in patients with contraindications for CMR, or at the time of permanent discontinuation of the randomized treatment if stopped before 3 years of follow-up.

2.2. Secondary objectives

Secondary endpoint are change in **mean systemic RV ejection fraction** (RV EF) from baseline to study end at 3 years of follow-up, measured by CMR or CMDCT in patients with contraindications for CMR, or at the time of permanent discontinuation of the randomized treatment if stopped before 3 years of follow-up.

Secondary endpoints are change in exercise capacity measured as **peak VO_2** during cardiopulmonary exercise testing and change in **serum neurohormonal activation** from baseline to study end at 3 years of follow-up, or at the time of permanent discontinuation of the randomized treatment if stopped before 3 years of follow-up. The eight serum neurohormonal hormones included are: BNP: brain natriuretic peptide; NT-proBNP: NT-proB-type natriuretic peptide; soluble ST2: ST2 interleukin (IL)-1 receptor, hs Troponin: high sensitivity Troponin T, MR-proANP: Mid-regional pro-atrial natriuretic peptide; Pro-Adrenomedullin; Copeptin; Proendothelin-α; soluble ST2: ST2 interleukin (IL)-1 receptor.

2.3. Assessment of objectives

The primary endpoint is measured with CMR or CMDCT in patients with contraindications for CMR, both at baseline and at follow-up 3 years (or earlier if the randomized treatment is stopped prematurely), and the change is the value of mean end-systolic RV volume at follow-up minus the value of mean end-systolic RV volume at baseline, i.e. positive changes indicate an improved geometry of the RV.

The secondary endpoint is measured with CMR or CMDCT in patients with contraindications for CMR, both at baseline and at follow-up 3 years (or earlier if the randomized treatment is stopped prematurely), and the change is the value of mean RV ejection fraction at follow-up

minus the value of mean RV EF at baseline, i.e. positive changes indicate an improved function of the RV

Peak VO2 is measured by cardiopulmonary exercise testing and analyzed in a central core lab.

The concentrations of the eight secondary endpoints - neurohormones are measured according to central laboratory protocols. It is expected that not all neurohormones will be reported inside the primary publication, but instead will be reported inside separate secondary publications.

2.4. Changes of the primary objective during the conduct of the study

No changes in the primary and secondary objectives during the conduct of the study are expected to occur.

3. Study design

3.1. General design and plan

Double-blind, randomized placebo controlled multicenter superiority study, parallel group design.

3.2. Sample size

Sample size calculation is based on the change in mean RV ESV. In a representative sample of n=79 TGA patients with a systemic RV from Bern and Zurich with CMR data, the mean RV ESV was 122±34 ml. Assuming that mean RV ESV improves or remains stable in the Tadalafil group and increases in the Placebo group by 20% to 146±39 ml, 78 patients are required to obtain an 80% power with a two-sided alpha set at 0.05 to detect a 20% change in volumes between the 2 treatment groups. Considering a possible dropout of 20%, 98 patients will be required (49 patients for each group).

3.3. Randomization

Randomization will be stratified by permanent pacemaker device or ICD at baseline at screening.

The randomized allocation lists (Tadalafil vs Placebo in 1:1 ratio) were be generated by an independent statistician using a random seed, with the help of a computer program, and lists will be generated stratified according to the presence or absence of pacemaker at baseline (with randomly varying block sizes of 2, 4 or 6 patients). Lists were deposited password protected in a dedicated folder on a central GCP-compliant server.

Afterwards, the randomized allocation lists were used by Pharmacy Inselspital (per site and presence/absence of permanent pacemaker device PPM or ICD at baseline) to prepare the IMP products in the order as specified by the list (randomized sequences of either IMP containing Tadalafil or Placebo) and these IMPs were provided inside two boxes (one box for presence of PPM/ICD and one box for absence of these devices) and delivered to the study site. The study site would then select the next IMP from the appropriate box to randomize the patient blinded.

3.4. Blinding

All study personnel, including patients, investigators, CMR or CMDCT assessors, study nurses, trial statistician, monitors and central data monitors will remain blinded after the

assignment of the treatments. Packages containing the drugs (Tadalafil pills or similarly looking Placebo pills) will only contain identifiers to allow emergency unblinding.

The trial statistician will remain blinded and produce blinded results (e.g. by allocating patients 1, 3, 5 etc per site as arm A and patients 2, 4, 6 etc. per site as arm B) for the initial tables. The initial tables containing the primary and secondary endpoints (see 2.1 and 2.2) is reprogrammed independently by another independent statistician and a signed quality check QC documentation is filed after the results of these reprogrammed tables are compared with the tables from the trial statistician and discrepancies have been resolved.

After all queries, plausibility and validation checks have been resolved, the trial statistician will ask permission from the SC to produce all tables with the unblinded information, correctly assigning the patients to treatment **Tadalafil** or **Placebo**. The primary and secondary endpoints cannot be changed after these final tables have been produced. Note that the secuTrial EDC system will never show the real randomized arm assignments, as these are not stored within the system.

3.5. Study assessments

The following study assessments are planned, note the additional safety follow-up one month after the study drug has been discontinued (PC6 Safety FU):

Visit	**BL***	**Visit 1**	**PC1****	**PC2****	**PC3****	**Visit 2**	**PC4****	**Visit 3**	**PC5****	**Visit 4**	**PC 6 Safety FU**
Time (months)	0	1	3	6	9	12	18	24	30	36	37
Window (weeks)	0	+ 2	+2	+2	+2	+ 4	+2	+ 4	+2	+ 4	± 1
Informed Consent	X										
Eligibility criteria	X										
Demography	X										
Medical history	X										
QoL	X					X				X	
Randomization	X										
Clinical examination	X	X				X		X		X	
IMP delivery	X					X		X			
IMP accountability		X				X		X		X	
ECG	(X)	X				(X)		(X)		(X)	
Holter	(X)									(X)	
CMR / CMDCT	X					X				X	
CPET	X									(X)	
Blood analysis	(X)	X				(X)		(X)		(X)	
Neurohormones	X					X				X	
TTE	(X)					(X)		(X)		(X)	
Concomitant Medication	X	X	X	X	X	X	X	X	X	X	
Adherence			X	X	X		X		X		
AE/SAE		X	X	X	X	X	X	X	X	X	X

(X) Not study specific, only collected if performed per routine

* Baseline (BL) exams

**Phone call (PC) to control adherence to IMP

4. Data management

4.1. Data export

Data are captured inside the secuTrial EDC system:

https://secutrial.insel.ch/apps/WebObjects/ST21-productive-DataCapture.woa/wa/

Data will be exported using the secuTrial data export tool:

https://secutrial.insel.ch/apps/WebObjects/ST21-productive-ExportSearchTool.woa/wa/

Data are exported as comma delimited files, and are labelled using the codebook provided by secuTrial in the same export.

The unblinded treatment assignments will be received (see **3.4.** when this occurs) from the CTU Data Management. The list is password protected inside the following zipped folder:

R:\Clinical studies\636_SERVE\10_Randomisation_Decoding_636**02_ProductiveRandomization_636.zip**

and the password is securely stored by CTU Data Management.

4.2. Data validation

The following data validation checks will be performed:

1.All tables with sample sizes per item for Steering Committee SC to check for plausibility of missing data.

2.All items containing dates will be checked whether they occurred on/after the date of randomization, the only exception being items from the medical history (e.g. date of atrial switch procedure) which occurred year(s) before the randomization.

5. Study populations

5.1. Patient flow

The number of patients randomized (blinded) will be taken from the Randomization eCRF, item: **IMP number assigned to patient**.

Received intended study drug at randomization with dosage is taken from Baseline Medication eCRF item: **Date patient will start taking IMP** with dosage **What dose is patient taking** (**20 mg** = one pill / day, **10 mg** = half pill / day)

Received intended study drug at follow-up visit {number of months} with dosage is taken from **Follow-up month** {number of months} Medication eCRF item: **Patient is taking IMP without interruption** with dosage **What dose is patient taking** (**20 mg** = one pill / day, **10 mg** = half pill / day).

Detailed information on stopping and if applicable restarting dates or dosage changes (with dates) can be found in the eCRF **IMP Adherence**.

The following flow chart will be produced:

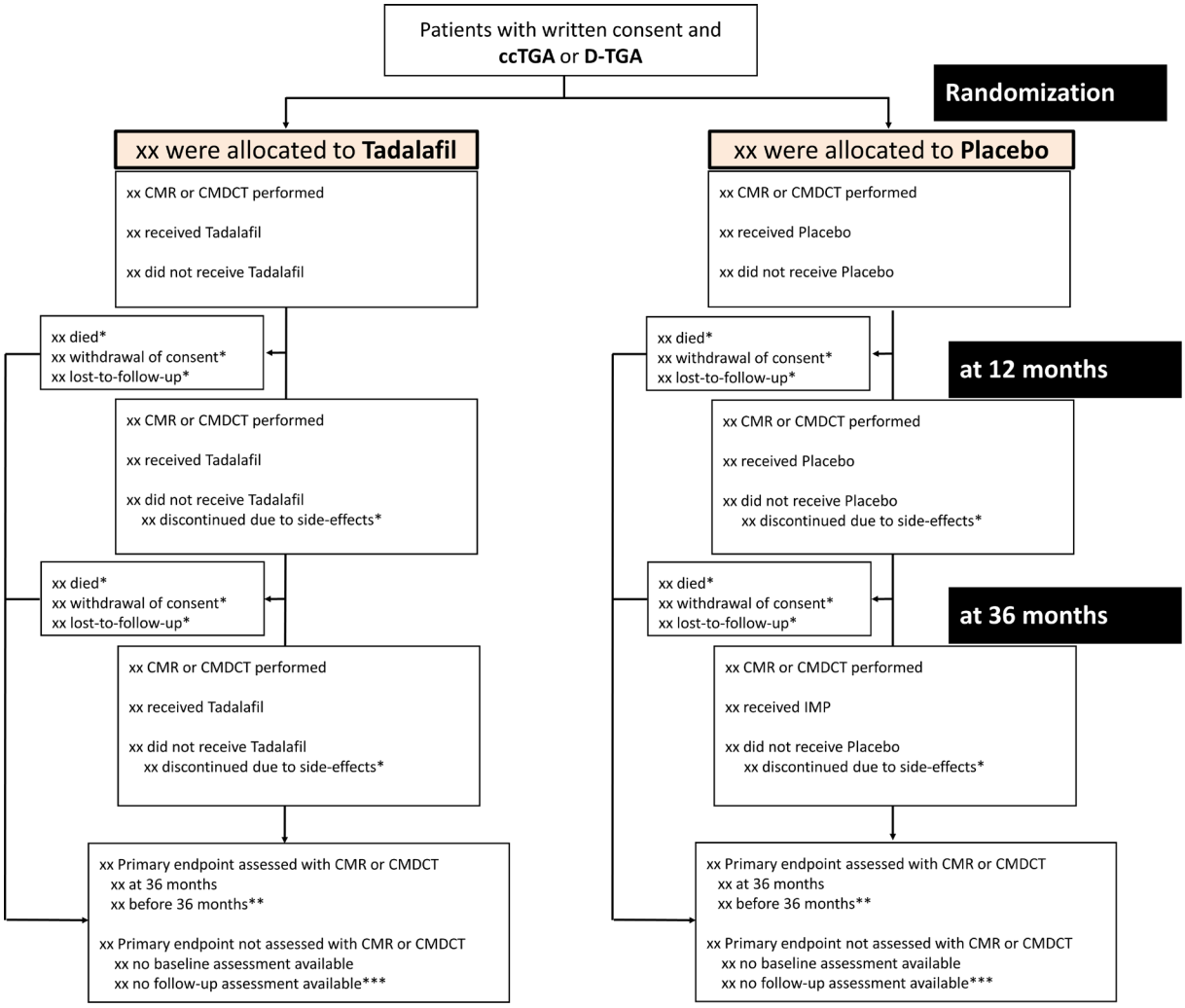

Figure 1: Flowchart

5.2. Definition of populations for analysis

All patients with ccTGA or D-TGA are known to the local Principal Investigators and will be individually invited to participate in the SERVE Trial, and can potentially be enrolled if they satisfy all inclusion and exclusion criteria.

5.3. Full analysis set (FAS)

The full-analysis population consists of all patients randomized. The primary and secondary endpoints of patients randomized to Tadalafil will be compared to the patients randomized to Placebo by the intention-to-treat principle, the last assessment of the primary or secondary endpoints will be used in case of early termination of the study drug.

Patient without a follow-up assessment needed for the primary endpoint are reported (see flowchart), but do not contribute to mean difference comparing Tadalafil vs Placebo. See also **Sensitivity analyses**.

5.4. Per-protocol (PP)

The per-protocol population PP consists of all patients randomized, who ingested at least one (half) pill of the study drug (Tadalafil or Placebo) and had a baseline plus follow-up assessment (36 months or last assessment if early drug discontinuation) of the primary endpoint. No PP analyses are currently planned.

5.5. Safety population

The safety population consist of all patients randomized, which received at least one dose of the randomized drug (Tadalafil or Placebo), and the patient's time at risk for safety endpoints are censored at the termination of the randomized drug intake.

5.6. Definition of sub-group populations in different analyses

The primary endpoint and secondary endpoints Tadalafil vs Placebo will be compared separately for patients without a previous permanent pacemaker implant or ICD at randomization, and separately for patient with a permanent pacemaker implant or ICD at randomization.

6. Statistical analysis

6.1. General

The general approach is to show descriptive means and standard deviations of the primary endpoints and secondary endpoints (including follow-up minus baseline difference as mean change with standard deviation), and then show the mean difference of the change Tadalafil (follow-up minus baseline) vs the change of Placebo (follow-up minus baseline) using an adjusted ANCOVA approach, or Tobit approach in case of lower and/or upper detection limits.

Statistical analyses will be performed with Stata version 14.2 or higher, or R version 3.4 or higher. Type I error rate, alpha, is set to 5% throughout.

6.2. Pooling of sites

Considering the very low number of patients per site and the possibility that by coincidence some sites do not get a patient randomized into the Tadalafil arm or do not get a patient randomized into the Placebo arm, no correction for random site effects is proposed. See also **Sensitivity analyses**.

6.3. Interim analyses

No interim analyses are planned.

6.4. Time-points for analysis

Time-points for primary and secondary endpoint assessments are the follow-up at 12 and 36 months, of which the 36 months assessments contains the primary and secondary endpoints analyses.

6.5. Methods for handling missing data and Sensitivity analyses

The main analyses will exclude the patients without any follow-up assessment of the primary endpoint, and again this process of exclusion is repeated also for the secondary endpoints.

Sensitivity analyses will be conducted by imputing the missing data for the primary and secondary endpoints (as applicable what is actually missing) using chained equations and the Baseline Clinical Characteristics (lumping rare categories), the non-missing primary and secondary endpoints from the previous visit (baseline if none available) and the (minimum known) last date (in days since randomization) the drug was confirmed taken.

6.6. Statistical analytical issues

6.6.1. Assessment of statistical assumptions

The neurohormones and other potential biomarkers will be evaluated for the presence of values below the lower detection threshold, and for values above the upper detection threshold. If no values are recorded below the lower or above the upper detection threshold, adjusted ANCOVA will be used (see described below). If less than 30% of the values are recorded below the lower or above the upper detection threshold at follow-up, Tobit regression will be used (i.e. model with left and/or right censoring at the detection thresholds). If more than 30% of the values are recorded below the lower or above the upper detection threshold at follow-up, or if any baseline value is recorded below the lower or above the upper detection threshold, follow-up values and baseline values fulfilling these criteria will be multiple imputed using chained equations (see **Sensitivity analyses**, .i.e. to impute in the range below or above the thresholds, as appropriate) and accordingly 20 data-sets will be created.

Note that the analyses are on non-missing data, see **Sensitivity analyses** for the additional analyses dealing with missing data.

6.6.2. Adjustments for covariates

The primary endpoint will be analysed using ANCOVA (Analysis of Covariance), with RV ESV (in ml) at 3 years (or earlier if drug withdrawal) as the response variable, randomized treatment as main independent variable, baseline RV ESV (ml) and time between baseline and follow-up RV volume measurement (in months since baseline) as covariates.

Secondary endpoints will be analysed using ANCOVA (Analysis of Covariance) or Tobit regression, with the secondary endpoint (RV EF, peak VO2, BNP, NT-pro BNP, hs-cTn, MR-proANP, Pro-adrenomedullin, Copeptin or Pro-endothelin-1) at 3 years (or earlier if drug withdrawal) as the response variable, randomized treatment as main variable, baseline measurement (RV EF, peak VO2, BNP, NT-pro BNP, hs-cTn, MR-proANP, Pro-adrenomedullin, Copeptin or Pro-endothelin-1; respectively) and time between baseline and follow-up measurement time (in months since baseline) as covariates.

Specifically: ANCOVA (Analysis of Covariance), with secondary endpoint at 3 years (or earlier if drug withdrawal) as the response variable, randomized treatment as main independent variable, baseline secondary endpoint and time between baseline and follow-up measurement (in months since baseline) as covariates. In case of ANOCVA, adjusted mean differences with 95% confidence intervals of the Tadalafil vs Placebo comparison will be reported from the Tobit regression model.

If applicable, Tobit regression with secondary endpoint at 3 years (or earlier if drug withdrawal) as the response variable (with as applicable the lower and/or upper detection threshold(s)), randomized treatment as main independent variable, baseline secondary endpoint and time between baseline and follow-up measurement (in months since baseline) as covariates. In case of adjusted Tobit regression, adjusted mean differences with 95% confidence intervals of the Tadalafil vs Placebo comparison will be reported from the Tobit regression model.

If more than 30% of the values are recorded below the lower or above the upper detection threshold at follow-up, or if any baseline value is recorded below the lower or above the upper detection threshold, follow-up values and baseline values fulfilling these criteria will be multiple imputed using chained equations (see **Sensitivity analyses**, i.e. to impute in the range below or above the thresholds, as appropriate) and accordingly 20 data-sets will be created and analysed using Tobit regression with secondary endpoint at 3 years (or earlier if drug withdrawal) as the response variable (with as applicable the lower and/or upper detection threshold(s)), randomized treatment as main independent variable, baseline secondary endpoint and time between baseline and follow-up measurement (in months since baseline) as covariates. In case of adjusted Tobit regression, adjusted mean differences with 95% confidence intervals of the Tadalafil vs Placebo comparison will be estimated from the Tobit regression model. These estimates of the twenty different Tobit models will be combined using Rubin's rule.

6.6.3. Multicenter studies

No adjustment of center effects are reported, except in the **Sensitivity analyses**. See **Sensitivity analyses**.

6.6.4. Multiple comparisons

No multiple comparisons are needed.

6.6.5. Use of efficacy subset

All patients will be analysed by intention-to-treat and reported according to their randomized arm, irrespective of whether and how much of the study drug they received, but note that each endpoint will be assessed after discontinuation of the drugs. Also note that the last assessment of the endpoint will be used if otherwise no measurement of the endpoint could be conducted at 36 months, including due to death, due to withdrawal of consent, due to lost to follow-up incl. failure to come to the clinic for assessment, or due to discontinuation of the drug without an immediate assessment.

6.6.6. Active-control studies intended to show equivalence

Not applicable.

6.6.7. Examination of subgroups

Due to the low number of patients included no subgroups have been defined, but the mean difference of Tadalafil vs Placebo for the primary and secondary endpoints will be explored for patients with and again separately also for patients without a permanent pacemaker implant or ICD at randomization.

7. Evaluation of characteristics and medication

7.1. Baseline clinical characteristics

Please note that P-values, standard errors, and confidence intervals are not be shown in baseline tables according to the CONSORT Statement, since any significant difference can be explained by the play of chance if the randomization was performed properly.

The following baseline table will be produced:

Table 1. Baseline Clinical Characteristics and Medical History

	Tadalafil (N=)	Placebo (N=)
Age — years (±SD)	xx ± xx	xx ± xx
Male gender — no. (%)	xx (xx%)	xx (xx%)
Cardiac anatomy — no. (%)		
ccTGA	xx (xx%)	xx (xx%)
D-TGA and Mustard	xx (xx%)	xx (xx%)
D-TGA and Senning	xx (xx%)	xx (xx%)
Pacemaker PM or ICD implantation— no. (%)	xx (xx%)	xx (xx%)
Medical history		
Additional lesions — no. (%)	xx (xx%)	xx (xx%)
VSD	xx (xx%)	xx (xx%)
Pulmonary stenosis	xx (xx%)	xx (xx%)
VSD and Pulmonary stenosis	xx (xx%)	xx (xx%)
Other	xx (xx%)	xx (xx%)
Palliation procedure prior to repair — no. (%)	xx (xx%)	xx (xx%)
Atrial septostomy	xx (xx%)	xx (xx%)
Atrial septectomy	xx (xx%)	xx (xx%)
Atrial septostomy and septectomy	xx (xx%)	xx (xx%)
None	xx (xx%)	xx (xx%)
Atrial switch procedure — no. (%)	xx (xx%)	xx (xx%)
Performed years before randomization — years (SD)	xx ± xx	xx ± xx
Additional interventions performed* — no. (%)	xx (xx%)	xx (xx%)
Last intervention before randomization — years (±SD)	xx ± xx	xx ± xx
Residual LVOTO >20mmHg — no. (%)	xx (xx%)	xx (xx%)
LVOTO gradient— mmHg (±SD)	xx ± xx	xx ± xx
Resiudal atrial shunt — no. (%)	xx (xx%)	xx (xx%)
Qp:Qs— no (%)		
>1.5	xx (xx%)	xx (xx%)
≤1.5	xx (xx%)	xx (xx%)
not determined	xx (xx%)	xx (xx%)
Qp:Qs— median ratio (25-75% IQR)	xx (xx - xx)	xx (xx - xx)
Previous stroke — no. (%)	xx (xx%)	xx (xx%)
History of tachyarrhythmias — no. (%)	xx (xx%)	xx (xx%)

Data expressed as n (%) or means±standard deviations SD or median (25% to 75% interquartile range IQR).

ccTGA: congenitally corrected transposition of the great arteries (L-TGA); D-TGA: regular transposition of the great arteries (TGA)

PM: Permanent Pacemaker implant; VSD: ventricular septal defect, PS: pulmonary stenosis

CRT: Cardiac Resynchronization Therapy device; ICD: Implantable Cardioverter-Defibrillator

LVOTO: left ventricular outflow tract obstruction; NYHA: New York Heart Association

*One or more additional interventions performed

Table 1. Baseline Clinical Characteristics and Medical History

7.2. Clinical examinations

Please note that P-values are not shown for the Clinical examinations at Baseline.

Table 2. Clinical examinations from Baseline to 36 months of Follow-up

	Clinical examination at Baseline		Clinical examination at 12 Months of Follow-up			Clinical examination at 36 Months of Follow-up		
	Tadalafil (N=)	Placebo (N=)	Tadalafil (N=)	Placebo (N=)	p-value	Tadalafil (N=)	Placebo (N=)	p-value
Nr of patients assessed	N = xx	N = xx	N = xx	N = xx		N = xx	N = xx	
Body mass index — kg/m² (±SD)	xx ± xx	xx ± xx	xx ± xx	xx ± xx	x.xx	xx ± xx	xx ± xx	x.xx
Body surface area — m² (±SD)	xx ± xx	xx ± xx	xx ± xx	xx ± xx	x.xx	xx ± xx	xx ± xx	x.xx
Heart rate — beats/min (±SD)	xx ± xx	xx ± xx	xx ± xx	xx ± xx	x.xx	xx ± xx	xx ± xx	x.xx
Oxygen saturation (Biox) — % (±SD)	xx ± xx	xx ± xx	xx ± xx	xx ± xx	x.xx	xx ± xx	xx ± xx	x.xx
Systolic blood pressure — mmHg (±SD)	xx ± xx	xx ± xx	xx ± xx	xx ± xx	x.xx	xx ± xx	xx ± xx	x.xx
Diastolic blood pressure — mmHg (±SD)	xx ± xx	xx ± xx	xx ± xx	xx ± xx	x.xx	xx ± xx	xx ± xx	x.xx
NYHA class — no. (%)					x.xx			x.xx
I or II	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	x.xx	xx (xx%)	xx (xx%)	x.xx
III or IV	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	x.xx	xx (xx%)	xx (xx%)	x.xx

Data expressed as n (%) or means±standard deviations SD.

Table 2. Clinical examinations from Baseline to 36 months of Follow-up

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7.3. ECG

Please note that P-values are not shown for the ECG at Baseline.

Table 3. ECG from Baseline to 36 Months

	ECG at Baseline		ECG at 12 Months of Follow-up			ECG at 36 Months of Follow-up		
	Tadalafil (N=)	Placebo (N=)	Tadalafil (N=)	Placebo (N=)	p-value	Tadalafil (N=)	Placebo (N=)	p-value
Nr of patients assessed	N = xx	N = xx	N = xx	N = xx		N = xx	N = xx	
Pacemaker rhythm — no. (%)					x.xx			x.xx
no	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	x.xx	xx (xx%)	xx (xx%)	x.xx
atrial stimulation only	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	x.xx	xx (xx%)	xx (xx%)	x.xx
ventricular stimulation	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	x.xx	xx (xx%)	xx (xx%)	x.xx
Rhythm if not paced — no. (%)					x.xx			x.xx
junctional	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	x.xx	xx (xx%)	xx (xx%)	x.xx
sinus rhythm	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	x.xx	xx (xx%)	xx (xx%)	x.xx
atrial flutter	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	x.xx	xx (xx%)	xx (xx%)	x.xx
atrial fibrillation	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	x.xx	xx (xx%)	xx (xx%)	x.xx
other	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	x.xx	xx (xx%)	xx (xx%)	x.xx
QRS duration — ms (±SD)	xx ± xx	xx ± xx	xx ± xx	xx ± xx	x.xx	xx ± xx	xx ± xx	x.xx
Ventricular heart rate — beats/min (±SD)	xx ± xx	xx ± xx	xx ± xx	xx ± xx	x.xx	xx ± xx	xx ± xx	x.xx

Data expressed as n (%) or means±standard deviations SD.

Table 3. ECG from Baseline to 36 Months

8. Evaluation of treatment compliance and exposure

8.1. Compliance to study drug and treatment

The study drugs are delivered to the patient in boxes of 56 pills each at baseline and again at 1, 6, 12, 18, 24, 30 months.

Pills of the IMP are counted at each follow-up visit (either count provided by the patient during the telephone call, or together with the study personnel during a clinical visit) and in the main text we will report the median percentage of pills IMP (25% and 75% interquartile range) taken for the patients randomized to **Tadalafil** (percentage from all the pills which should have been taken up to the date of 36 months - end of study; or up to an earlier date if: death, discontinued, lost-to-follow-up or withdrawal of consent); and also median percentage of pills IMP (25% and 75% interquartile range) taken for the patients randomized to **Placebo** (percentage from all the pills which should have been taken up to the date of 36 months - end of study; or up to an earlier date if: death, discontinued, lost-to-follow-up or withdrawal of consent). These two percentages will be compared with a Mann-Whitney U-test.

8.1.1. Compliance to study drug

Compliance to the study drug is recorded cross-sectional inside each follow-up visit (at 1, 3, 6, 12, 18, 24, 30 and 36 months (the 37 months visit is a safety visit to record reactions after the drug has been discontinued): yes or not taken with any interruption of 3 days or more and the dosage (one pill or half pill). This cross-sectional compliance is recorded in the follow-up Table 4 for the primary visits at 1, 12, 24 and 36 months only. Details of the other visits can be provided in Supplement on request.

Table 4. Medication and Investigational Medical Product use

	Medications at Baseline		Medications at 1 Month of Follow-up			Medications at 12 Months of Follow-up			Medications at 24 Months of Follow-up			Medications at 36 Months of Follow-up		
	Tadalafil (N=)	Placebo (N=)	Tadalafil (N=)	Placebo (N=)	p-value	Tadalafil (N=)	Placebo (N=)	p-value	Tadalafil (N=)	Placebo (N=)	p-value	Tadalafil (N=)	Placebo (N=)	p-value
Nr of patients assessed	N = xx	N = xx	N = xx	N = xx		N = xx	N = xx		N = xx	N = xx		N = xx	N = xx	
IMP	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	x.xx	xx (xx%)	xx (xx%)	x.xx	xx (xx%)	xx (xx%)	x.xx	xx (xx%)	xx (xx%)	x.xx
interruption of 3 days or more	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	x.xx	xx (xx%)	xx (xx%)	x.xx	xx (xx%)	xx (xx%)	x.xx	xx (xx%)	xx (xx%)	x.xx
one pill/day	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	x.xx	xx (xx%)	xx (xx%)	x.xx	xx (xx%)	xx (xx%)	x.xx	xx (xx%)	xx (xx%)	x.xx
half pill/day	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	x.xx	xx (xx%)	xx (xx%)	x.xx	xx (xx%)	xx (xx%)	x.xx	xx (xx%)	xx (xx%)	x.xx
Acetylsalycilic acid	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	x.xx	xx (xx%)	xx (xx%)	x.xx	xx (xx%)	xx (xx%)	x.xx	xx (xx%)	xx (xx%)	x.xx
$P2Y_{12}$ inhibitor	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	x.xx	xx (xx%)	xx (xx%)	x.xx	xx (xx%)	xx (xx%)	x.xx	xx (xx%)	xx (xx%)	x.xx
Vitamin K antagonists	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	x.xx	xx (xx%)	xx (xx%)	x.xx	xx (xx%)	xx (xx%)	x.xx	xx (xx%)	xx (xx%)	x.xx
Novel oral anticoagulants	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	x.xx	xx (xx%)	xx (xx%)	x.xx	xx (xx%)	xx (xx%)	x.xx	xx (xx%)	xx (xx%)	x.xx
Calcium channel blocker	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	x.xx	xx (xx%)	xx (xx%)	x.xx	xx (xx%)	xx (xx%)	x.xx	xx (xx%)	xx (xx%)	x.xx
Beta-blocker	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	x.xx	xx (xx%)	xx (xx%)	x.xx	xx (xx%)	xx (xx%)	x.xx	xx (xx%)	xx (xx%)	x.xx
ACE inhibitor or AT-II blocker	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	x.xx	xx (xx%)	xx (xx%)	x.xx	xx (xx%)	xx (xx%)	x.xx	xx (xx%)	xx (xx%)	x.xx
Potent CYP3A4 inhibitor*	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	x.xx	xx (xx%)	xx (xx%)	x.xx	xx (xx%)	xx (xx%)	x.xx	xx (xx%)	xx (xx%)	x.xx
PDE-5 inhibitor*	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	x.xx	xx (xx%)	xx (xx%)	x.xx	xx (xx%)	xx (xx%)	x.xx	xx (xx%)	xx (xx%)	x.xx
Nitrates*	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	x.xx	xx (xx%)	xx (xx%)	x.xx	xx (xx%)	xx (xx%)	x.xx	xx (xx%)	xx (xx%)	x.xx
Diuretics	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	x.xx	xx (xx%)	xx (xx%)	x.xx	xx (xx%)	xx (xx%)	x.xx	xx (xx%)	xx (xx%)	x.xx
Cordarone	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	x.xx	xx (xx%)	xx (xx%)	x.xx	xx (xx%)	xx (xx%)	x.xx	xx (xx%)	xx (xx%)	x.xx
Digoxin	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	x.xx	xx (xx%)	xx (xx%)	x.xx	xx (xx%)	xx (xx%)	x.xx	xx (xx%)	xx (xx%)	x.xx

Data expressed as n (%) and p-values are from Fisher's tests.

IMP: double-blinded investigational drug taken.

*IMP to be interrupted during the intake of this medication, included Ketoconazol (n=xx at xx follow-up), Ritonavir (n=xx at xx follow-up), Rifampicin (n=xx at xx follow-up) or other potent CYP3A4 inhibitor (n=xx at xx follow-up).

Table 4. Medication

Measurement of treatment compliance

All patients who took **one pill** or **half pill** of the study drug is considered compliant at each follow-up visit (at 1, 3, 6, 12, 18, 24, 30 and 36 months. This cross-sectional compliance is recorded in the follow-up Table 3.

Detailed analyses of drug intake with exact discontinuation date (in months since randomization), or exact first interruption date (in months since randomization) or exact dose halving date (in months since randomization) can be reported in the main text of the manuscript; if enough of such cases are accumulated, otherwise case reports are recommended for a Supplementary Appendix table, incl. reasons (see **IMP Adherence CRF**).

8.2. Exposure to study drug

8.2.1. Extent of exposure

Experimental Group: Tadalafil 20 mg p.o. once per day (OD) for 3 years

Control Group: placebo p.o. OD for 3 years.

The study medication (verum and placebo) will be provided by the pharmacy of the University Hospital Bern.

All participants will be started on Tadalafil 20 mg or placebo OD without any titration period.

8.2.2. Duration of exposure

Three years (36 months, additional 37 month visit to record reactions after discontinuation of the study drug).

8.2.3. Dose of exposure and concentration

Tadalafil: 20 mg p.o. once per day (OD). Tadalafil has a half-live of approximately 18 hours.

Placebo: p.o. once per day (OD).

9. Evaluation of patients at follow-up

Patient are contacted at 1, 3, 6, 9, 12, 18, 24, 30 and 36 months follow-up (12, 24 and 36 months are clinical visits, remainder telephone calls), during all visits patients will be asked about medication and drug compliance (see above), additionally follow-up examinations will be conducted during the clinical visits, which are recorded in the following tables.

9.1. Follow-up at 12 months

The follow-up 12 months contains a clinical examination and ECG and Quality of Life assessment (CMR/CMRCT data are reported under the primary and secondary endpoints). See Tables 2 and 3 above; and Table 9 below.

9.2. Follow-up at 24 months

If requested, produced as Supplementary Material, following the same outline as the Tables 2 and 3.

9.3. Follow-up at 36 months

The follow-up 36 months contains a clinical examination and ECG and Quality of Life assessment (CMR/CMRCT data are reported under the primary and secondary endpoints). See Tables 2 and 3 above; and Table 9 below.

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10. Evaluation of efficacy parameters

10.1. Analysis of primary, secondary, and other efficacy endpoints

10.1.1. Analysis of primary endpoint

The primary endpoint will be analysed using ANCOVA (Analysis of Covariance), with RV ESV (in ml) at 3 years (or earlier if drug withdrawal) as the response variable, randomized treatment as main independent variable, baseline RV ESV (ml) and time between baseline and follow-up RV volume measurement (in months since baseline) as covariates.

10.1.2. Analysis of secondary endpoints

Secondary endpoints will be analysed using ANCOVA (Analysis of Covariance) or Tobit regression, with the secondary endpoint (RV EF, peak VO2, BNP, NT-pro BNP, hs-cTn, MR-proANP, Pro-adrenomedullin, Copeptin or Pro-endothelin-1) at 3 years (or earlier if drug withdrawal) as the response variable, randomized treatment as main variable, baseline measurement (RV EF, peak VO2, BNP, NT-pro BNP, hs-cTn, MR-proANP, Pro-adrenomedullin, Copeptin or Pro-endothelin-1; respectively) and time between baseline and follow-up measurement time (in months since baseline) as covariates.

Specifically: ANCOVA (Analysis of Covariance), with secondary endpoint at 3 years (or earlier if drug withdrawal) as the response variable, randomized treatment as main independent variable, baseline secondary endpoint and time between baseline and follow-up measurement (in months since baseline) as covariates. In case of ANOCVA, adjusted mean differences with 95% confidence intervals of the Tadalafil vs Placebo comparison will be reported from the Tobit regression model.

If applicable, Tobit regression with secondary endpoint at 3 years (or earlier if drug withdrawal) as the response variable (with as applicable the lower and/or upper detection threshold(s)), randomized treatment as main independent variable, baseline secondary endpoint and time between baseline and follow-up measurement (in months since baseline) as covariates. In case of adjusted Tobit regression, adjusted mean differences with 95% confidence intervals of the Tadalafil vs Placebo comparison will be reported from the Tobit regression model.

If more than 30% of the values are recorded below the lower or above the upper detection threshold at follow-up, or if any baseline value is recorded below the lower or above the upper detection threshold, follow-up values and baseline values fulfilling these criteria will be multiple imputed using chained equations (see **Sensitivity analyses**, i.e. to impute in the range below or above the thresholds, as appropriate) and accordingly 20 data-sets will be created and analysed using Tobit regression with secondary endpoint at 3 years (or earlier if drug withdrawal) as the response variable (with as applicable the lower and/or upper detection threshold(s)), randomized treatment as main independent variable, baseline secondary endpoint and time between baseline and follow-up measurement (in months since baseline)

as covariates. In case of adjusted Tobit regression, adjusted mean differences with 95% confidence intervals of the Tadalafil vs Placebo comparison will be estimated from the Tobit regression model. These estimates of the twenty different Tobit models will be combined using Rubin's rule.

10.1.3. Analysis of other endpoints

All other endpoints, including novel biomarkers or neurohormones not yet specified in the protocol will be analysed using the same approach as for the **Secondary endpoints**.

10.1.4. Endpoint tables

The following Tables will be produced, Tables 5 and 6 will be provided in the main publication:

Table 5. Baseline and Follow-up CMR/CMDCT assessments

	Tadalafil				Placebo				Tadalafil vs Placebo	
	Baseline (N=)	Follow-up FUP (N=)	Change FUP vs Baseline	p-value	Baseline (N=)	Follow-up FUP (N=)	Change FUP vs Baseline	p-value	Mean difference of the change*	p-value
CMR/CMDCT assessed at 12 months	N = xx	N = xx			N = xx	N = xx				
CMR modality	N = xx	N = xx			N = xx	N = xx				
CMDCT modality	N = xx	N = xx			N = xx	N = xx				
RV enddiastolic volume — ml (±SD)	xx ± xx	xx ± xx	xx ± xx	x.xx	xx ± xx	xx ± xx	xx ± xx	x.xx	xx ± xx	x.xx
RV endsystolic volume — ml (±SD)	xx ± xx	xx ± xx	xx ± xx	x.xx	xx ± xx	xx ± xx	xx ± xx	x.xx	xx ± xx	x.xx
RV enddiastolic volume index — ml (±SD)	xx ± xx	xx ± xx	xx ± xx	x.xx	xx ± xx	xx ± xx	xx ± xx	x.xx	xx ± xx	x.xx
RV endsystolic volume index — ml (±SD)	xx ± xx	xx ± xx	xx ± xx	x.xx	xx ± xx	xx ± xx	xx ± xx	x.xx	xx ± xx	x.xx
RV mass — mg (±SD)	xx ± xx	xx ± xx	xx ± xx	x.xx	xx ± xx	xx ± xx	xx ± xx	x.xx	xx ± xx	x.xx
RV stroke volume— ml (±SD)	xx ± xx	xx ± xx	xx ± xx	x.xx	xx ± xx	xx ± xx	xx ± xx	x.xx	xx ± xx	x.xx
RV ejection fraction — % (±SD)	xx ± xx	xx ± xx	xx ± xx	x.xx	xx ± xx	xx ± xx	xx ± xx	x.xx	xx ± xx	x.xx
LV enddiastolic volume — ml (±SD)	xx ± xx	xx ± xx	xx ± xx	x.xx	xx ± xx	xx ± xx	xx ± xx	x.xx	xx ± xx	x.xx
LV endsystolic volume — ml (±SD)	xx ± xx	xx ± xx	xx ± xx	x.xx	xx ± xx	xx ± xx	xx ± xx	x.xx	xx ± xx	x.xx
LV enddiastolic volume index - ml (SD)										
LV endsystolic volume index - ml (SD)										
LV stroke volume — ml (±SD)	xx ± xx	xx ± xx	xx ± xx	x.xx	xx ± xx	xx ± xx	xx ± xx	x.xx	xx ± xx	x.xx
LV ejection fraction — % (±SD)	xx ± xx	xx ± xx	xx ± xx	x.xx	xx ± xx	xx ± xx	xx ± xx	x.xx	xx ± xx	x.xx
LV mass — mg (±SD)	xx ± xx	xx ± xx	xx ± xx	x.xx	xx ± xx	xx ± xx	xx ± xx	x.xx	xx ± xx	x.xx
Ascending aorta flow — l/sec (±SD)	xx ± xx	xx ± xx	xx ± xx	x.xx	xx ± xx	xx ± xx	xx ± xx	x.xx	xx ± xx	x.xx
Right and left PA flow — l/sec (±SD)	xx ± xx	xx ± xx	xx ± xx	x.xx	xx ± xx	xx ± xx	xx ± xx	x.xx	xx ± xx	x.xx
Tricuspid regurgitation fraction (%)	xx ± xx	xx ± xx	xx ± xx	x.xx	xx ± xx	xx ± xx	xx ± xx	x.xx	xx ± xx	x.xx
CMR/CMDCT assessed at 36 months or last assessment**	N = xx	N = xx			N = xx	N = xx				
CMR modality	N = xx	N = xx			N = xx	N = xx				
CMDCT modality	N = xx	N = xx			N = xx	N = xx				
RV enddiastolic volume — ml (±SD)	xx ± xx	xx ± xx	xx ± xx	x.xx	xx ± xx	xx ± xx	xx ± xx	x.xx	xx ± xx	x.xx
RV endsystolic volume — ml (±SD)	xx ± xx	xx ± xx	xx ± xx	x.xx	xx ± xx	xx ± xx	xx ± xx	x.xx	xx ± xx¶	x.xx
RV enddiastolic volume index — ml (±SD)	xx ± xx	xx ± xx	xx ± xx	x.xx	xx ± xx	xx ± xx	xx ± xx	x.xx	xx ± xx	x.xx
RV endsystolic volume index — ml (±SD)	xx ± xx	xx ± xx	xx ± xx	x.xx	xx ± xx	xx ± xx	xx ± xx	x.xx	xx ± xx	x.xx
RV mass — mg (±SD)	xx ± xx	xx ± xx	xx ± xx	x.xx	xx ± xx	xx ± xx	xx ± xx	x.xx	xx ± xx	x.xx
RV stroke volume— ml (±SD)	xx ± xx	xx ± xx	xx ± xx	x.xx	xx ± xx	xx ± xx	xx ± xx	x.xx	xx ± xx	x.xx
RV ejection fraction — % (±SD)	xx ± xx	xx ± xx	xx ± xx	x.xx	xx ± xx	xx ± xx	xx ± xx	x.xx	xx ± xx§	x.xx
LV enddiastolic volume — ml (±SD)	xx ± xx	xx ± xx	xx ± xx	x.xx	xx ± xx	xx ± xx	xx ± xx	x.xx	xx ± xx	x.xx
LV endsystolic volume — ml (±SD)	xx ± xx	xx ± xx	xx ± xx	x.xx	xx ± xx	xx ± xx	xx ± xx	x.xx	xx ± xx	x.xx
LV enddiastolic volume index - ml (SD)	xx ± xx	xx ± xx	xx ± xx	x.xx	xx ± xx	xx ± xx	xx ± xx	x.xx	xx ± xx	x.xx
LV endsystolic volume index - ml (SD)	xx ± xx	xx ± xx	xx ± xx	x.xx	xx ± xx	xx ± xx	xx ± xx	x.xx	xx ± xx	x.xx
LV stroke volume — ml (±SD)	xx ± xx	xx ± xx	xx ± xx	x.xx	xx ± xx	xx ± xx	xx ± xx	x.xx	xx ± xx	x.xx
LV ejection fraction — % (±SD)	xx ± xx	xx ± xx	xx ± xx	x.xx	xx ± xx	xx ± xx	xx ± xx	x.xx	xx ± xx	x.xx
LV mass — mg (±SD)	xx ± xx	xx ± xx	xx ± xx	x.xx	xx ± xx	xx ± xx	xx ± xx	x.xx	xx ± xx	x.xx
Ascending aorta flow — l/sec (±SD)	xx ± xx	xx ± xx	xx ± xx	x.xx	xx ± xx	xx ± xx	xx ± xx	x.xx	xx ± xx	x.xx
Right and left PA flow — l/sec (±SD)	xx ± xx	xx ± xx	xx ± xx	x.xx	xx ± xx	xx ± xx	xx ± xx	x.xx	xx ± xx	x.xx
Tricuspid regurgitation fraction (%)	xx ± xx	xx ± xx	xx ± xx	x.xx	xx ± xx	xx ± xx	xx ± xx	x.xx	xx ± xx	x.xx

Data expressed as n (%) or means±standard deviations SD.

RV: right ventricular; LV: left ventricular; PA: pulmonary artery.

*Estimates from ANCOVA or Tobit regression (for xx) with the follow-up assessment as response, baseline assessment and time between follow-up assessment and baseline assessment (months) as covariates.

**Last assessment used if IMP was prematurely completely discontinued, if available and at least 3 months IMP taken. ¶ Primary endpoint. § Secondary endpoint.

Table 5. Baseline and Follow-up CMR/CMDCT assessments

Table 6. Baseline and Follow-up CPET assessments

	Tadalafil				Placebo				Tadalafil vs Placebo	
	Baseline (N=)	Follow-up FUP (N=)	Change FUP vs Baseline	p-value	Baseline (N=)	Follow-up FUP (N=)	Change FUP vs Baseline	p-value	Mean difference of the change	p-value
Nr of patients assessed	N = xx	N = xx	N = xx		N = xx	N = xx	N = xx		N = xx	
Heart rates — beats/min (±SD)										
resting	xx ± xx	xx ± xx	xx ± xx	x.xx	xx ± xx	xx ± xx	xx ± xx	x.xx	xx ± xx	x.xx
peak	xx ± xx	xx ± xx	xx ± xx	x.xx	xx ± xx	xx ± xx	xx ± xx	x.xx	xx ± xx	x.xx
recovery	xx ± xx	xx ± xx	xx ± xx	x.xx	xx ± xx	xx ± xx	xx ± xx	x.xx	xx ± xx	x.xx
Systolic blood pressure — mmHg (±SD)										
resting	xx ± xx	xx ± xx	xx ± xx	x.xx	xx ± xx	xx ± xx	xx ± xx	x.xx	xx ± xx	x.xx
peak	xx ± xx	xx ± xx	xx ± xx	x.xx	xx ± xx	xx ± xx	xx ± xx	x.xx	xx ± xx	x.xx
Diastolic blood pressure — mmHg (±SD)										
resting	xx ± xx	xx ± xx	xx ± xx	x.xx	xx ± xx	xx ± xx	xx ± xx	x.xx	xx ± xx	x.xx
peak	xx ± xx	xx ± xx	xx ± xx	x.xx	xx ± xx	xx ± xx	xx ± xx	x.xx	xx ± xx	x.xx
Peak Watt output — W (±SD)	xx ± xx	xx ± xx	xx ± xx	x.xx	xx ± xx	xx ± xx	xx ± xx	x.xx	xx ± xx	x.xx
Peak Watt output in % of predicted — % (±SD)	xx ± xx	xx ± xx	xx ± xx	x.xx	xx ± xx	xx ± xx	xx ± xx	x.xx	xx ± xx	x.xx
Metabolic Equivalent of Task MET — ratio (±SD)	xx ± xx	xx ± xx	xx ± xx	x.xx	xx ± xx	xx ± xx	xx ± xx	x.xx	xx ± xx	x.xx
Respiratory Exchange Ratio RER — ratio (±SD)	xx ± xx	xx ± xx	xx ± xx	x.xx	xx ± xx	xx ± xx	xx ± xx	x.xx	xx ± xx	x.xx
Peak VO_2 — ml/min/kg (±SD)	xx ± xx	xx ± xx	xx ± xx	x.xx	xx ± xx	xx ± xx	xx ± xx	x.xx	xx ± xx§	x.xx
Peak VO_2 in % of predicted — % (±SD)	xx ± xx	xx ± xx	xx ± xx	x.xx	xx ± xx	xx ± xx	xx ± xx	x.xx	xx ± xx	x.xx
VO_2 workload slope — mean (±SD)	xx ± xx	xx ± xx	xx ± xx	x.xx	xx ± xx	xx ± xx	xx ± xx	x.xx	xx ± xx	x.xx
O_2 / heart rate — ml/beat (±SD)	xx ± xx	xx ± xx	xx ± xx	x.xx	xx ± xx	xx ± xx	xx ± xx	x.xx	xx ± xx	x.xx
VE/VCO_2 workload slope — mean (±SD)	xx ± xx	xx ± xx	xx ± xx	x.xx	xx ± xx	xx ± xx	xx ± xx	x.xx	xx ± xx	x.xx
Partial pressure CO_2 — mmHg (±SD)	xx ± xx	xx ± xx	xx ± xx	x.xx	xx ± xx	xx ± xx	xx ± xx	x.xx	xx ± xx	x.xx

Data expressed as n (%) or means±standard deviations SD or median (25% to 75% interquartile range IQR).

Peak VO_2: Peak oxygen consumption; VE/VCO_2 slope: minute ventilation carbon dioxide production relationship.

**Last assessment used if IMP was prematurely completely discontinued, if available and at least 3 months IMP taken. § Secondary endpoint.

Table 6. Baseline and Follow-up CPET assessments

It is expected that the Neurohormones data will be reported in secondary publications, except for NT-proBNP which will be reported in the main publication:

Table 7. Baseline and Follow-up Neurohormones assessments

	Tadalafil				Placebo				Tadalafil vs Placebo	
	Baseline (N=)	Follow-up FUP (N=)	Change FUP vs Baseline	p-value	Baseline (N=)	Follow-up FUP (N=)	Change FUP vs Baseline	p-value	Mean difference of the change	p-value
Neurohormones assessed at 12 months	N = xx	N = xx	N = xx		N = xx	N = xx	N = xx		N = xx	
BNP — pg/ml (±SD)	xx ± xx	xx ± xx	xx ± xx	x.xx	xx ± xx	xx ± xx	xx ± xx	x.xx	xx ± xx	x.xx
NT-proBNP — pg/ml (±SD)	xx ± xx	xx ± xx	xx ± xx	x.xx	xx ± xx	xx ± xx	xx ± xx	x.xx	xx ± xx	x.xx
hs Troponin T — ng/l (±SD)	xx ± xx	xx ± xx	xx ± xx	x.xx	xx ± xx	xx ± xx	xx ± xx	x.xx	xx ± xx	x.xx
MR-proANP — pmol/l (±SD)	xx ± xx	xx ± xx	xx ± xx	x.xx	xx ± xx	xx ± xx	xx ± xx	x.xx	xx ± xx	x.xx
Pro-Adrenomedullin — nmol/l (±SD)	xx ± xx	xx ± xx	xx ± xx	x.xx	xx ± xx	xx ± xx	xx ± xx	x.xx	xx ± xx	x.xx
Copeptin — pmol/l (±SD)	xx ± xx	xx ± xx	xx ± xx	x.xx	xx ± xx	xx ± xx	xx ± xx	x.xx	xx ± xx	x.xx
Proendothelin-α — pmol/l (±SD)	xx ± xx	xx ± xx	xx ± xx	x.xx	xx ± xx	xx ± xx	xx ± xx	x.xx	xx ± xx	x.xx
soluble ST2 — ng/ml (±SD)	xx ± xx	xx ± xx	xx ± xx	x.xx	xx ± xx	xx ± xx	xx ± xx	x.xx	xx ± xx	x.xx
Neurohormones assessed at 36 months or last assessment**	N = xx	N = xx	N = xx		N = xx	N = xx	N = xx		N = xx	
BNP — pg/ml (±SD)	xx ± xx	xx ± xx	xx ± xx	x.xx	xx ± xx	xx ± xx	xx ± xx	x.xx	xx ± xx	x.xx
NT-proBNP — pg/ml (±SD)	xx ± xx	xx ± xx	xx ± xx	x.xx	xx ± xx	xx ± xx	xx ± xx	x.xx	xx ± xx	x.xx
hs Troponin T — ng/l (±SD)	xx ± xx	xx ± xx	xx ± xx	x.xx	xx ± xx	xx ± xx	xx ± xx	x.xx	xx ± xx	x.xx
MR-proANP — pmol/l (±SD)	xx ± xx	xx ± xx	xx ± xx	x.xx	xx ± xx	xx ± xx	xx ± xx	x.xx	xx ± xx	x.xx
Pro-Adrenomedullin — nmol/l (±SD)	xx ± xx	xx ± xx	xx ± xx	x.xx	xx ± xx	xx ± xx	xx ± xx	x.xx	xx ± xx	x.xx
Copeptin — pmol/l (±SD)	xx ± xx	xx ± xx	xx ± xx	x.xx	xx ± xx	xx ± xx	xx ± xx	x.xx	xx ± xx	x.xx
Proendothelin-α — pmol/l (±SD)	xx ± xx	xx ± xx	xx ± xx	x.xx	xx ± xx	xx ± xx	xx ± xx	x.xx	xx ± xx	x.xx
soluble ST2 — ng/ml (±SD)	xx ± xx	xx ± xx	xx ± xx	x.xx	xx ± xx	xx ± xx	xx ± xx	x.xx	xx ± xx	x.xx

Data expressed as n (%) or means±standard deviations SD. All neurohormones were predefined secondary endpoints of the study.

BNP: brain natriuretic peptide; NT-proBNP: NT-proB-type natriuretic peptide; hs Troponin: high sensitivity Troponin T, MR-proANP: Mid-regional pro-atrial natriuretic peptide; soluble ST2: ST2 interleukin (IL)-1 receptor.

**Last assessment used if IMP was prematurely completely discontinued, if available and at least 3 months IMP taken. § Secondary endpoint.

Table 7. Baseline and Follow-up Neurohormones assessments

It is expected that the Holter data will be reported in secondary publications:

Table 8. Holter at Baseline and 36 Months of Follow-up

	Tadalafil				Placebo				Tadalafil vs Placebo	
	Baseline (N=)	Follow-up FUP (N=)	Change FUP vs Baseline	p-value	Baseline (N=)	Follow-up FUP (N=)	Change FUP vs Baseline	p-value	Mean difference of the change	p-value
Holter assessed at 36 months of Follow-up	N = xx	N = xx	N = xx		N = xx	N = xx	N = xx		N = xx	
Underlying rhythm — no. (%)										
sinus rhythm	xx (xx%)	xx (xx%)	xx (xx%)	x.xx	xx (xx%)	xx (xx%)	xx (xx%)	x.xx	xx (xx%)	x.xx
paced	xx (xx%)	xx (xx%)			xx (xx%)	xx (xx%)				
atrial flutter	xx (xx%)	xx (xx%)			xx (xx%)	xx (xx%)				
atrial fibrillation	xx (xx%)	xx (xx%)			xx (xx%)	xx (xx%)				
other	xx (xx%)	xx (xx%)			xx (xx%)	xx (xx%)				
Heart rates — beats/min (±SD)										
Mean	xx ± xx	xx ± xx	xx ± xx	x.xx	xx ± xx	xx ± xx	xx ± xx	x.xx	xx ± xx	x.xx
Minimum	xx ± xx	xx ± xx	xx ± xx	x.xx	xx ± xx	xx ± xx	xx ± xx	x.xx	xx ± xx	x.xx
Maximum	xx ± xx	xx ± xx	xx ± xx	x.xx	xx ± xx	xx ± xx	xx ± xx	x.xx	xx ± xx	x.xx
AV-block — no. (%)	xx (xx%)	xx (xx%)	xx (xx%)	x.xx	xx (xx%)	xx (xx%)	xx (xx%)	x.xx	xx (xx%)	x.xx
AV-block I	xx (xx%)	xx (xx%)			xx (xx%)	xx (xx%)				
AV-block II	xx (xx%)	xx (xx%)			xx (xx%)	xx (xx%)				
AV-block III	xx (xx%)	xx (xx%)			xx (xx%)	xx (xx%)				
Pauses	xx (xx%)	xx (xx%)	xx (xx%)	x.xx	xx (xx%)	xx (xx%)	xx (xx%)	x.xx	xx (xx%)	x.xx
>2 to 3 seconds	xx (xx%)	xx (xx%)			xx (xx%)	xx (xx%)				
>3 seconds	xx (xx%)	xx (xx%)			xx (xx%)	xx (xx%)				
VT	xx (xx%)	xx (xx%)	xx (xx%)	x.xx	xx (xx%)	xx (xx%)	xx (xx%)	x.xx	xx (xx%)	x.xx
non-sustained	xx (xx%)	xx (xx%)			xx (xx%)	xx (xx%)				
sustained	xx (xx%)	xx (xx%)			xx (xx%)	xx (xx%)				

Data expressed as n (%) or means±standard deviations SD.

Table 8. Holter at Baseline and 36 Months of Follow-up

It is expected that the Quality of Life data will be reported in secondary publications:

Table 9. Quality of Life assessments at Baseline and Follow-up

	Tadalafil				Placebo				Tadalafil vs Placebo	
	Baseline (N=)	Follow-up FUP (N=)	Change FUP vs Baseline	p-value	Baseline (N=)	Follow-up FUP (N=)	Change FUP vs Baseline	p-value	Mean difference of the change	p-value
Quality of Life assessed at 12 months	N = xx	N = xx	N = xx		N = xx	N = xx	N = xx		N = xx	
LAS scale — mean score (±SD)	xx ± xx	xx ± xx	xx ± xx	x.xx	xx ± xx	xx ± xx	xx ± xx	x.xx	xx ± xx	x.xx
Satisfaction scale — mean score (±SD)	xx ± xx	xx ± xx	xx ± xx	x.xx	xx ± xx	xx ± xx	xx ± xx	x.xx	xx ± xx	x.xx
General self-efficacy — mean score (±SD)	xx ± xx	xx ± xx	xx ± xx	x.xx	xx ± xx	xx ± xx	xx ± xx	x.xx	xx ± xx	x.xx
Quality of Life assessed at 36 months	N = xx	N = xx	N = xx		N = xx	N = xx	N = xx		N = xx	
LAS scale — mean score (±SD)	xx ± xx	xx ± xx	xx ± xx	x.xx	xx ± xx	xx ± xx	xx ± xx	x.xx	xx ± xx	x.xx
Satisfaction scale — mean score (±SD)	xx ± xx	xx ± xx	xx ± xx	x.xx	xx ± xx	xx ± xx	xx ± xx	x.xx	xx ± xx	x.xx
General self-efficacy — mean score (±SD)	xx ± xx	xx ± xx	xx ± xx	x.xx	xx ± xx	xx ± xx	xx ± xx	x.xx	xx ± xx	x.xx

Data expressed as mean scores ±standard deviations of the score SD.

Table 9. Quality of Life assessments at Baseline and Follow-up

10.1.5. Sensitivity Analyses of endpoints

To deal with missing data in the baseline assessment of the endpoint (using as covariate in the adjusted analyses, e.g. ANCOVA, Tobit), and to deal with missing data of the follow-up assessment of the endpoint, sensitivity analyses will be conducted, where missing follow-up values and baseline values will be multiple imputed using chained equations.

The missing data for the primary and secondary endpoints (as applicable what is actually missing, including baseline and follow-ups) are imputed using chained equations, 20 data-sets will be created. The equations include the Baseline Clinical Characteristics (lumping rare categories), the non-missing primary and secondary endpoints from the previous visit (baseline if none available) and the (minimum known) last date (in days since randomization) the drug was confirmed taken at that time point as predictor variables (e.g. 12 months for the 12 months data if drug was still taken at 12 months, or 36 months for 36 months of data if the drug was still taken at 36 months; normalized to 0 = not taken to a maximum of 1 – taken whole period). Endpoints are taken from baseline and all the follow-ups, as applicable (typically baseline, 12 months, 24 months and 36 months).

Afterwards all sensitivity analyses are conducted on the 20 data-sets for each endpoint separately, where also a random effect of hospital identifier will be explored (using clustering or nested analyses as appropriate). The sensitivity analyses will be shown in the Supplementary Material following the same structure as the Tables 5 – 8, except if the main analyses could only be conducted on the multiple imputed Tobit regression model, in which case this endpoint will be reported in the Supplementary Material, but also redundantly be reported in the main Table 5 or 6 or 7 or 8 (as applicable) with a comment.

10.2. Method for analysis

10.2.1. Binary data

Binary data will be compared Tadalafil vs Placebo using Fisher's exact test for 2 x 2 tables with two-sided p-values.

10.2.2. Count data

Count data will be compared Tadalafil vs Placebo using Poisson regression with two-sided p-values.

10.2.3. Continuous scale data

Continuous data will be compared Tadalafil vs Placebo using t-tests with two-sided p-values. Exceptions are the primary and secondary endpoints, see above.

10.2.4. Time-to-event data

Time to event data will reported as total nr of events per patient and compared Tadalafil vs Placebo using Poisson regression with time to last assessment as offset (i.e. days between baseline and 3 years follow-up, or discontinuation of the drugs, or last contact), with two-sided p-values.

10.2.5. Ordinal scales and non-ordered scales data

Ordered data will be reported as counts, compared Tadalafil vs Placebo using chisquare tests for 2 x n tables with two-sided p-values, no specific ordered test is recommended considering the low sample sizes.

11. Evaluation of safety parameters

11.1. Adverse events

During the entire duration of the study, specific adverse events (AE) (see xx) and all serious adverse events (SAEs) will be collected, fully investigated and documented in source documents and case report forms (CRF). Study duration encompasses the time from when the participant signs the informed consent until the last protocol-specific procedure has been completed, including a safety follow-up period of 1 month after the last visit (36 month Follow-up visit).

11.1.1. Brief summary of adverse events

The following AEs will be collected:

- headache

- deterioration in renal function defined as an increase of 50% in serum Creatinine on at least two measurements (at least 6 days apart), or a drop in GFR below 30ml/min on two measurements (at least 6 days apart)

- allergic reactions

- epipharyngitis

- nausea and dyspepsia

- symptomatic arterial hypotension

The occurrence of these AEs together with the study discontinuation rate due to AE will be part of the annual safety report (see 10.1.2).

The following SAEs will be collected:

- Hospitalization for heart failure

- Death

11.1.2. Display of adverse events

A Supplementary Material table will be produced with all adverse events; if applicable and requested, also separate for the Safety population:

Supplemental Table 1. Events in all Patients

	Tadalafil (N=)			Placebo (N=)			
	Nr of patients with event	Total nr of events	% of events Tadafil stopped	Nr of patients with event	Total nr of events	% of events Placebo stopped	p-valiue
Serious adverse events							
Death	xx (xx%)	xx	xx%	xx (xx%)	xx	xx%	x.xx
Worsening heart failure	xx (xx%)	xx	xx%	xx (xx%)	xx	xx%	x.xx
Vascular event*	xx (xx%)	xx	xx%	xx (xx%)	xx	xx%	x.xx
SAE other then any of the above	xx (xx%)	xx	xx%	xx (xx%)	xx	xx%	x.xx
Adverse events							
Headache	xx (xx%)	xx	xx%	xx (xx%)	xx	xx%	x.xx
Allergic reaction	xx (xx%)	xx	xx%	xx (xx%)	xx	xx%	x.xx
Epipharyngitis	xx (xx%)	xx	xx%	xx (xx%)	xx	xx%	x.xx
Nausea and dyspepsia	xx (xx%)	xx	xx%	xx (xx%)	xx	xx%	x.xx
Symptomatic arterial hypertension	xx (xx%)	xx	xx%	xx (xx%)	xx	xx%	x.xx
Renal function impairment	xx (xx%)	xx	xx%	xx (xx%)	xx	xx%	x.xx
New or worsening arrhythmias	xx (xx%)	xx	xx%	xx (xx%)	xx	xx%	x.xx
Other AE leading to discontinuation of study drug	xx (xx%)	xx	xx%	xx (xx%)	xx	xx%	x.xx

Data expressed as nr of patients with event (% of all patients) and total nr of events reported. P-value from Poisson regression comparing the event rates, with time to last assessment as offset (i.e. days between baseline and 3 years follow-up or discontinuation of the drugs or last contact).

Only (S)AE listed above had to be reported.

*Stroke, TIA, Myocardial infarction, Peripheral embolism, other Vascular events.

Supplemental Table 1. Events in all Patients

Supplemental Table 2. Events in Safety Population¥

	Tadalafil (N=)			Placebo (N=)			
	Nr of patients with event	Total nr of events	% of events Tadafil stopped	Nr of patients with event	Total nr of events	% of events Placebo stopped	p-valiue
Serious adverse events							
Death	xx (xx%)	xx	xx%	xx (xx%)	xx	xx%	x.xx
Worsening heart failure	xx (xx%)	xx	xx%	xx (xx%)	xx	xx%	x.xx
Vascular event*	xx (xx%)	xx	xx%	xx (xx%)	xx	xx%	x.xx
SAE other then any of the above	xx (xx%)	xx	xx%	xx (xx%)	xx	xx%	x.xx
Adverse events							
Headache	xx (xx%)	xx	xx%	xx (xx%)	xx	xx%	x.xx
Allergic reaction	xx (xx%)	xx	xx%	xx (xx%)	xx	xx%	x.xx
Epipharyngitis	xx (xx%)	xx	xx%	xx (xx%)	xx	xx%	x.xx
Nausea and dyspepsia	xx (xx%)	xx	xx%	xx (xx%)	xx	xx%	x.xx
Symptomatic arterial hypertension	xx (xx%)	xx	xx%	xx (xx%)	xx	xx%	x.xx
Renal function impairment	xx (xx%)	xx	xx%	xx (xx%)	xx	xx%	x.xx
New or worsening arrhythmias	xx (xx%)	xx	xx%	xx (xx%)	xx	xx%	x.xx
Other AE leading to discontinuation of study drug	xx (xx%)	xx	xx%	xx (xx%)	xx	xx%	x.xx

Data expressed as nr of patients with event (% of all patients) and total nr of events reported. P-value from Poisson regression comparing the event rates, with time to last assessment as offset (i.e. days between baseline and 3 years follow-up or discontinuation of the drugs).

Only (S)AE listed above had to be reported.

*Stroke, TIA, Myocardial infarction, Peripheral embolism, other Vascular events.

¥Safety population are the patients who took at least once the drug (Tadalafil or Placebo), and events are reported up to last confirmed intake of the allocated study drug.

Supplemental Table 2. Events in Safety Population

11.1.3. Analysis of adverse events

Full analyses set: Adverse events will be reported as rates: total nr of events per patient and compared Tadalafil vs Placebo using Poisson regression with time to last assessment as offset (i.e. days between baseline and 3 years follow-up, or discontinuation of the drugs, or last contact), with two-sided p-values.

Safety population are the patients who took at least once the drug (Tadalafil or Placebo), and events are reported up to last confirmed intake of the study drug. Adverse events will be reported as rates: total nr of events per patient and compared Tadalafil vs Placebo using Poisson regression with time to last known intake of the study drug as offset (i.e. days between baseline and 3 years follow-up – temporary stops disregarded, or confirmed discontinuation of the drugs, or last known intake of the drug if unclear at 36 months), with two-sided p-values.

11.1.4. Listing of adverse events by patient

Listing of adverse events per patient are provided on request.

11.2. Concomitant medications

Concomitant medications are reported inside the Medication tables, of which some medications may trigger a halving of the study drug (from one pill to half a pill per day) or (temporary) discontinuation of the study drug.

Potent CYP3A4 inhibitor: study drug has to be interrupted during intake of this inhibitor.

PDE-5 inhibitor: study drug has to be interrupted during intake of this inhibitor.

Nitrates: study drug has to be interrupted during intake of nitrates.

11.3. Vital signs and physical examination

11.3.1. Findings in vital signs and physical examinations

Clinical examinations are conducted at baseline and again at 12, 24 and 36 months follow-up, including assessments of heart rate, oxygen saturation, blood pressures, NYHA class, crackles, peripheral edema and jugular venous pressure and ECG. Holter is performed at baseline and 36 months.

See Tables 4 and 5 (and if needed Supplementary Material for 24 months using the same structure as Table 4).

11.4. Other safety evaluations

11.4.1. Other observations related to safety

No other safety observations, assessments or analyses are currently defined and planned for this statistical analysis plan.

12. Appendix: planned substudies

The following substudies have been predefined:

Planned SERVE substudies

Proposal No.	Working title	Research question	Responsible investigator	Submitted by	Center Data
BIOMARKERS					
1	Cardiomyocyte damage in systemic RV	Functional determinants of hs-cTn in systemic RV	DT / CM	DT	all
2	Cardiomyocyte damage in systemic RV	Utility of hs-cTn in prediction of outcome	DT / CM	DT	all
3	Cardiomyocyte damage in systemic RV	Determinants of progression (i.e. increase in hs-cTn > 50% or median)	DT / CM	DT	all
4	Hemodynamic cardiac stress in systemic RV assessed by nt-proBNP	Functional determinants of nt-proBNP in systemic RV	DT / CM	DT	all
5	Hemodynamic cardiac stress in systemic RV assessed by nt-proBNP	Utility of nt-proBNP in prediction of outcome	DT / CM	DT	all
6	Hemodynamic cardiac stress in systemic RV assessed by nt-proBNP	Determinants of progression (i.e. changes in nt-proBNP over time)	DT / CM	DT	all
7	Endothelial dysfunction in systemic RV	Functional determinants of endothelin 1 or pro-endothelin in systemic RV	DT / CM	DT	all
8	Endothelial dysfunction in systemic RV	Utility of endothelin-1 in prediction of outcome	DT / CM	DT	all
9	Endothelial dysfunction in systemic RV	Determinants of progression (i.e. changes in endothelin 1 over time)	DT / CM	DT	all
10	Mirocvascular dysfunction in systemic RV	Functional determinants of MR-pro-Adrenomedullin in systemic RV	DT / CM	DT	all
11	Mirocvascular dysfunction in systemic RV	Utility of MR-pro-Adrenomedullin in prediction of outcome	DT / CM	DT	all
12	Mirocvascular dysfunction in systemic RV	Determinants of progression (i.e. changes in MR-pro-Adrenomedullin over time)	DT / CM	DT	all
13	Enodgenous stress in systemic RV	Functional determinants of copeptin 1 or pro-endothelin in systemic RV	DT / CM	DT	all
14	Enodgenous stress in systemic RV	Utility of copeptin in prediction of outcome	DT / CM	DT	all
15	Enodgenous stress in systemic RV	Determinants of progression (i.e. changes in endothelin copeptin over time)	DT / CM	DT	all
16	Biomarkers of myocardial fibrosis in systemic RV	Functional determinants of ST-2 or Galactin-3 in systemic RV	DT / CM	DT	all
17	Biomarkers of myocardial fibrosis in systemic RV	Utility of ST-2 or Galactin-3 in prediction of outcome	DT / CM	DT	all
18	Biomarkers of myocardial fibrosis in systemic RV	Determinants of progression (i.e. changes in ST-2 or Galactin-3 over time)	DT / CM	DT	all
19	Neurohormones as surrogate markers for modulaters of Tadalafil	Is Tadalafil less effective in certain subgroups of patients based on the neurohormonal profile	DT / CM	DT	all
22	Renal function in systemic RV	Biomarker determinants of impaired renal function in patients with a systemic RV	DT / CM	CM	all
23	Renal function in systemic RV	Biomarker determinants of renal function deterioration in patients with a systemic RV	DT / CM	CM	all
24	Renal function in systemic RV	cMRI determinants of impaired renal function in patients with a systemic RV	DT / CM	CM	all
25	Renal function in systemic RV	cMRI determinants of renal function deterioration in patients with a systemic RV	DT / CM	CM	all
26	Renal function in systemic RV	Prognostic importance of impaired renal function deterioration in patients with a systemic RV	DT / CM	CM	all
27	Renal function in systemic RV	Prognostic importance of renal function impairement in patients with a systemic RV	DT / CM	CM	all
IMAGING					
28	CMR feature tracking in systemic RV	Comparison of changes in feature tracking between sub-groups at baseline exam and follow-up	KW / EV	KW	all
29	Ventriculo-aterial coupling in systemic RV measured by CMR	Non-invasive assessment of ventriculo-aterial coupling and aortic stiffness	KW	KW	all
30	MultiMask analysis Substudy	Comparison of semiautomatic RV segmentation (Mask Method) of the systemic RV	EV	EV	all
31	Diffuse fibrosis development quantified by T1 mapping CMR	Development of diffuse fibrosis under Tadalafil vs placebo measured by T1 mapping CMR	TR / JS	TR	all
32	Correlation of echo measures with CMR findings	To find surrogates for RV-EF on conventional 2-Dimensional TTE	MG	MG	all
33	RV diastolic function and neurohormones	Correlation of echocardiographic measurements of RV diastolic dysfunction with Pro-BNP and hs-cTn	MG	MG	all
34	Grading of TR severity by TTE and MRI	Correlation of measurements of severity of tricuspid regurgitation between TTE and MRI	MG	MG	all
35	Reproducibility of echo measures in systemic RVs	To define the reproducibility of echocardiographic measurements of systemic right ventricular size and function	MG	MG	all
36	Feasibility of TTE to detect changes in RV size and function	To define the role of echocardiography to detect changes in systemic right ventricular size and function	MG	MG	all
37	Correlation of RV strain measured by echo vs. MRI	To compare strain measurements by MRI and echocardiography in patients with systemic right ventricles	MG	MG	all
38	Contraction pattern of a systemic RV assessed by TTE	Comparion of longitudinal vs. radial strain in a systemic RV and their relative contribution to RV-EF and VO2max	MS	MS	all
ARRHYTHMIAS/EP					
39	Arrhythmia substudy	Prevalence and incidence of arrhythmias in systemic RV over a 3 year period	JB	JB	all
40	Dyssynchrony and QRS-duration in systemic RVs	Define the impact of biventricular function on QRS-duration and dyssynchrony	MG	MG	all
41	Correlation of RV size and function with arrhythmias	To identify parameters measured by MRI and echo with presence of atrial and ventricular arrhythmias	MG	MG	all
42	Impact of pacemakers on RV size and function	Compare patients with and without PM regarding RV- and LV- size and function, AV regurgitation, paradoxical events	MG	MG	all
EXERCISE					
	Impact of ventricular size and function on exercise capacity	To analyse the impact on cardiac function (as measured by CMR and TTE) and biomarkers on exercise capacity	MG	MG	all
	Impact of baffle anatomy on exercise capacity	Analysis of baffle anatomy and properties and correlation of these characteristics with exercise capacity	MG	MG	all
	Exercise capacity in systemic RV: baffles vs. ventricular function	What impacts on exercise capacity in TGA patients: baffle conduit capacity or resting ventricular function	MS	MS	all
43	Predictors of exercise capacity in systemic RV patients	Impact of baffle anatomy, ventricular function and neurohumoral activation on exercise capacity	MS / MG	MS	all
MISCELLANEOUS					
44	Coronary artery anatomy and RV mass and function	To assess the impact on coronary artery pattern on systemic right ventricular muscle mass and function	MG	MG	all
45	Prediction score for adverse outcomes in systemic RV's	Prediction score based on cardiac function, biomarkers, QRS, previous arrhyth.- to be validated prospectively	MG	MG	all
46	Quality of life in patients with a systemic RV	Determinants of QoL in systemic RV's: Medical issues vs. Personality	MS	MS	all
47	Impact of daily activties and BP on RV function	Impact of BP, BMI, amount of cardiovascular exercise on parameters of systemic RV function	MG	MG	all
48	Sleep disorders in systemic RV patients	To define the presence and importance of breathing disorders on systemic RV function	MG	MG	all
49	Heart rate variability in systemic RV	Heart variability and its correlates with exercise performance, nt-proBNP, prior and after heart failure therapy	MG	MG	all

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