EudraCT No.	**2016-004291-21**
Swissmedic No.	**2017DR3142**
Trial Name:	**SERVE**
Trial Title:	Effect of phosphodiesterase-5 inhibition with Tadalafil on SystEmic Right VEntricular size and function – a multi-center, double-blind, randomized, placebo-controlled clinical trial

1. Title Page

FINAL REPORT

According to ICH Guideline E3

Investigational product:	Tadalafil
Indication:	Systemic right ventricular size and function
Trial description:	International, multicentre, double-blind, randomised, placebo controlled study with 36 months of IMP/Placebo intake
Study period:	FPFV: 17/11/2017/ LPLV: 28/10/2021
Sponsor:	Insel Gruppe AG, Bern University Hospital, Inselspital Department of Cardiology, Freiburgstrasse, 3010 Bern, Switzerland Phone +41 31 632 50 00; Email: kardio.studien@insel.ch
Date of report:	18.10.2022
Identification Code:	SERVE
Phase:	Phase III
Coordinating Investigator & Sponsor-Investigator and Contact Person:	Prof. Markus Schwerzmann, Insel Gruppe AG, Bern University Hospital, Inselspital Department of Cardiology, Freiburgstrasse, 3010 Bern, Switzerland Phone +41 31 632 50 00; Email: kardio.studien@insel.ch and markus.schwerzmann@insel.ch

This study was performed in compliance with Good Clinical Practices (GCP), including the archiving of essential documents.

2. Synoposis

Name of Sponsor: Insel Gruppe AG	*(For National Autority Use only)*
Name of Finished Product: Tadalafil/ Placebo	
Name of active Ingredient: Tadalafil/ Phosphodiesterase-5-Inhibitor (PDE-5-Hemmer)	

Title of 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

Investigators:

See study center listing below

Study centre(s) and Investigators (local PI):

- Insel Gruppe AG, University Hospital Berne, Inselspital Berne, Berne, Switzerland
  Prof. Dr. med. Markus Schwerzmann (Sponsor-Investigator and local PI Inselspital Bern)
- Hôpitaux Universitaires de Genève, Genève, Switzerland
  PD Dr. Judith Bouchardy
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- University Hospital Basel, Basel, Switzerland
  Prof. Dr. med. Daniel Tobler
- University Hospital Zurich, Zurich, Switzerland
  Prof Dr. med. Matthias Greutmann
- Vienna General Hospital, AKH Wien, Wien, Austria
  Prof. Dr. med. Harald Gabriel
- Kantonsspital St. Gallen, St. Gallen, Switzerland
  Dr. med. Reto Engel

Main Publications:

- Manuscript is currently under review, see Appendix 16.1.1 for manuscript to be published

Studied period (years):	**Phase of development:**
FPFV: 17/11/2017 LPLV: 28/10/2021	Phase III

Objectives:

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

Methodology:

We conducted a double-blind, randomized, placebo-controlled, multi-center superiority trial comparing the PDE-5 inhibitor tadalafil 20mg once daily versus placebo (1:1-ratio) in adults with systemic RV. Primary endpoint was the change in RV endsystolic volume (RV-ESV) measured by cardiac magnetic resonance or computed tomography after three years of therapy or earlier in case of permanent discontinuation of study drug. Secondary endpoints were changes in RV ejection fraction, exercise capacity and NT-proBNP-concentration as quantitative markers of cardiac hemodynamic stress at study end compared to baseline.

Number of patients:

100

Diagnosis and main criteria for inclusion:

Inclusion criteria: Adults (≥18 years) with a systemic RV due to D-TGA repaired with an atrial switch procedure or due to ccTGA.

Exclusion criteria: No informed consent; myocardial infarction, stroke, or open heart surgery in the previous 3 months; expected heart transplant within the next 6 months; pregnant or nursing women; severe renal insufficiency; hypersensitivity to tadalafil; known allergy to iodinated or Gadolinium-based contrast agents.

Test product, dose and mode of administration:

Tadalafil 20 mg p.o. OD for 3 years vs. placebo p.o. OD (the study medication 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.

Duration of treatment: 36 month

Reference therapy, dose and mode of administration: see description above

Criteria for evaluation:

Efficacy

Safety

The study aimed to assess long-term safety of Tadalafil and its tolerability in terms of incidence of the following Adverse Events (AE):

- Headache (reported > 10%)

- Epipharyngitis (reported > 10%)

- Nausea and dyspepsia (reported > 10%)

- Symptomatic arterial hypotension (reported 1-10%)

Some AE did trigger a drug dose change (see SERVE_Clinical Investigation Plan 8.3, Appendix 16.1.2). As a safety objective, we wanted to achieve a study discontinuation rate due to AE lower than 20%. This figure appeared to be a reasonable threshold for this potential new therapy. In the landmark trial investigating the role of tadalafil in Pulmonary Arterial Hypertension (PAH), the discontinuation rate in the placebo group was 16% (13/82) and 11% (34/323) in the tadalafil group. We expect to observe similar or lower discontinuation rates in our patients, as they are less sick than patients with advanced PAH.

Statistical analysis:

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).

Summary of Results – Conclusions (see also manuscript Appendix 16.1.1)

A total of 100 adults (33 women, mean age: 40·7 years, SD 10·7) were enrolled. Primary endpoint assessment by intention to treat analysis at one and three years of follow up was possible in 91 and 83 patients respectively (45 and 42 patients in the tadalafil group and 46 and 41 patients in the placebo group). No significant changes over time in RV-ESV were observed in the tadalafil and the placebo-group, and no significant differences between treatment groups (3·4ml, CI -4·3 to 11·0,

p=0·39). No significant changes over time were observed for the pre-specified secondary endpoints for the entire study population, without differences between the tadalafil and the placebo-group.

Primary endpoint

Mean RV-ESV did not change during follow-up in the tadalafil group (145, SD: 57 versus 148, SD: 56, p = 0·27) or in the placebo-group (123, SD: 49 versus 121·2, SD 46, p = 0·67). There was no statistically significant difference between the tadalafil- and the placebo-group (3·37, confidence interval: -4·29 to 11·03, p = 0·39).

Secondary endpoints

There were no significant changes in end-diastolic volumes and right and left ventricular ejection fraction within the tadalafil and the placebo-group and no statistically significant differences between the tadalafil- and the placebo-group. A small change was observed for RV mass in the placebo-group but no statistically significant differences between the tadalafil- and the placebo-group.

Measures of exercise capacity remained stable over the three-year follow-up period, both within the tadalafil and the placebo-group, without differences between groups.

Among neurohormones, no significant change in NT-proBNP-levels were observed during the three-year follow-up period or between the tadalafil and the placebo-groups. In contrast, a significant increase of hs-Troponin T, was observed, both within the tadalafil- and the placebo-group (p <0·001 for both comparisons) without significant differences between the tadalafil- and the placebo-group (p = 0·57).

Measures of quality of life remained stable during follow-up, without differences between the tadalafil- and the placebo group.

Conclusion

In this prospective, multi-center, randomized, placebo-controlled trial with long-term follow-up, we investigated a novel pharmacologic treatment concept for improvement of ventricular function in adults with systemic RVs. Promising results from concepts in basic research and animal models did not translate into favourable clinical results. As compared to placebo, tadalafil, a phosphodiesterase-5 inhibitor, did not improve systemic right ventricular function and had no impact on other clinical endpoints, such as exercise capacity, neuro-hormonal activation or quality of life.

Date of report

18Oct2022