Clinical Trial protocol

FULL TITLE: THE EFFECT OF ADDITIVE ON-DEMAND SILDENAFIL VS. DEXTROSE CANDY ON MAXIMUM EXERCISE CAPACITY IN PULMONARY ARTERIAL HYPERTENSION: A RANDOMIZED, CROSS-OVER TRIAL.

SHORT TITLE: THE POCKET-PH TRIAL.

Study Type:	Clinical trial with Investigational Medicinal Product (IMP)
Study Categorisation:	Risk category A: In-Label Trial
Study Registration:	Intended Registry after approval: • Clinicaltrials.gov • Swiss National Clinical Trials Portal (HumRes)
Study Identifier / Study ID:	The Pocket-PH Trial
Sponsor and Principal Investigator:	**Prof. Dr. med. Silvia Ulrich** Director of Department, Department of Pulmonology Head of Pulmonary Hypertension University Hospital Zurich Rämistrasse 100 CH-8091 Zürich Switzerland Phone: +41 44 255 2220 Fax: +41 44 255 4451 E-mail: silvia.ulrich@usz.ch
Investigational medicinal product:	Sildenafil 20mg (Revatio 20mg)
Protocol Version and Date:	Version 1.1, 10.03.2026

CONFIDENTIAL

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Signature Page(s)

Study number	Not yet available. The trial will be registered on www.clinicaltrials.gov and on the Swiss National Clinical Trials Portal (HumRes) after acceptance.
Study Title	The Effect of Additive On-Demand Sildenafil vs. Dextrose Candy on Maximum Exercise Capacity in Pulmonary Arterial Hypertension: A Randomized, Cross-Over Trial.

The Sponsor/Investigator have approved the protocol version 1.1, 10.03.2026, and confirm hereby to conduct the study according to the protocol, current version of the World Medical Association Declaration of Helsinki, the ICH-GCP guidelines and the local legally applicable requirements.

The Sponsor-Investigator has received the ICF and consider it appropriate for use.

Sponsor/Principal Investigator: **Prof. Dr. med. Silvia Ulrich**

Zurich, March 10th, 2026 _____ _____

Place/Date Signature

Co-Investigator: **Dr. med. Arcangelo Friedrich Carta**

Zurich, March 10th, 2026 _____ _____

Place/Date Signature

Local Principal Investigator at study site*:

I have read and understood this trial protocol and agree to conduct the trial as set out in this study protocol, the current version of the World Medical Association Declaration of Helsinki, ICH-GCP guidelines and the local legally applicable requirements.

I have received the ICF and consider it appropriate for use.

Site	UniversitätsSpital Zürich, Klinik für Pneumologie
Principal investigator	**Prof. Dr. med. Silvia Ulrich**

Zurich, March 10th, 2026 _____ _____

Place/Date Signature

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STUDY SYNOPSIS

Sponsor	**Prof. Dr. med. Silvia Ulrich** Director of Department, Department of Pulmonology Head of Pulmonary Hypertension University Hospital Zurich Rämistrasse 100 CH-8091 Zürich Switzerland Phone: +41 44 255 2220 Fax: +41 44 255 4451 Email: silvia.ulrich@usz.ch
Study Title:	The Effect of Additive On-Demand Sildenafil vs. Dextrose Candy on Maximum Exercise Capacity in Pulmonary Arterial Hypertension: A Randomized, Cross-Over Trial
Short Title / Study ID:	The Pocket-PH Trial
Protocol Version and Date:	Version 1.1, 10.03.2026
Trial registration:	Intended Registration after Acceptance - www.clinicaltrials.gov - The Swiss National Clinical Trials Portal (HumRes)
Study category and Rationale	Risk Category A: In-label trial
Clinical Phase:	Phase II (focus on timing of dosage).
Background and Rationale:	Pulmonary arterial hypertension (PAH) is a progressive and debilitating disease characterised by increased mean pulmonary arterial pressure (mPAP) and pulmonary vascular resistance (PVR), leading to right ventricular overload, and ultimately right heart failure. Despite advancements in pharmacological therapy, treatment options remain limited, and optimising individualised approaches to improve exercise capacity and symptom burden remains a challenge. Phosphodiesterase type 5 (PDE-5) inhibitors, such as sildenafil, are cornerstones of PAH treatment, enhancing pulmonary vasodilation and improving haemodynamics. While three times daily dosing is standard, on-demand sildenafil use timed before exercise has not been studied. Given sildenafil's rapid onset of action with peak effects after 30–60 minutes, it may offer acute benefits regarding exercise capacity. This study aims to evaluate the efficacy and safety of additional, timed, on-demand sildenafil 20mg intake 45 minutes before maximum exercise capacity, administered to PAH patients in addition to their standard medical therapy, compared to a food item sham comparator, dextrose candy (Dextroenergy).

Objective(s):	We aim to demonstrate that in PAH patients, on-demand ("pill-in-the-pocket") 20 mg sildenafil (Revatio 20mg) versus dextrose candy (Dextroenergy) taken 45 min before incremental exercise testing (IET) increases maximum workload (Wmax) and constant work rate exercise test (CWRET) time (Tmax) at 75% of Wmax measured by cycle spiroergometry. We further aim to demonstrate favourable changes in cardiometabolic parameters, in right heart function, assessed by stress echocardiography and will assess safety by incidence and severity of adverse events (AEs).
Outcome(s):	<u>Primary outcome</u> - Difference in Wmax attained during IET after treatment with sildenafil 20mg (Revatio 20mg) versus dextrose candy (Dextroenergy) <u>Secondary outcomes</u> - Difference in Tmax attained during CWRET after treatment with sildenafil 20mg (Revatio 20mg) versus dextrose candy (Dextroenergy) - Changes in cardiometabolic parameters (SpO_2, BP, HR, RPP, $V'O2max$, $V'CO_2max$, $V'Emax$, $V'E/VO_2$, $V'E/VCO_2$, BF, BR, $P_{ET}O_2$, $P_{ET}CO_2$, F_IO_2, F_ICO_2, $F_{ET}O_2$, $F_{ET}CO_2$) - Changes in arterial blood gases (PaO_2, $PaCO_2$, HCO^{3-}, SaO_2, BE, lactate, Hb, Hct, glucose) - Changes in Borg CR10 questionnaire - Changes in stress-echocardiographic markers of right heart function (TRV, TRPG, TRV, RAP, sPAP, mPAP, FAC, TAPSE, TRPG/CO, CO, PVR, SV) - Safety and AEs of sildenafil 20mg (Revatio 20mg)
Study design:	Randomized, Cross-Over Trial
Inclusion / Exclusion criteria:	<u>Inclusion Criteria</u> - Signed Informed consent - Age 18 - 80 years (both sexes) - Pulmonary hypertension (PH) class I (PAH) previously diagnosed according to ESC/ERS 2022/2019 guidelines (mPAP ≥ 20 mmHg, PVR ≥ 2 WU, PAWP ≤ 15 mmHg) during diagnostic right-heart catheterization. - Stable condition, on the same PH-medication for >4 weeks <u>Exclusion Criteria</u> - Severe resting hypoxia (PaO_2 <7.3 kPa) - Moderate-to-severe chronic obstructive or restrictive pulmonary disease (FEV1 ≤ 60% predicted, FVC ≤ 60% predicted) - Women with known pregnancy or breast feeding - Other clinically significant concomitant disease states (e.g., severe renal or hepatic disease, unstable cardiovascular disease, etc.) - Concurrent medication with: o Nitric oxide donors (molsidomine, nicrorandil, etc.) o Soluble guanylate cyclase stimulators (riociguat) o Potent CYP3A4 inhibitors (azoles, clarithromycin, protease inhibitors) - History of anterior ischemic optic neuropathy or hereditary retinal disease - Participation in another study with investigational drug with potential influence the study data within the 30 days preceding and during the present study. - Known allergies or hypersensitivity to sildenafil 20mg (Revatio 20mg) or dextrose candy (Dextroenergy) including any of its components.

Measurements and procedures:	Screening & Baseline Baseline assessments include patient information and informed consent, assessment of inclusion & exclusion criteria, randomization, medical history, NYHA functional class, baseline demographic data, concomitant medication, physical examination, vital signs, resting ECG, arterial blood gases at rest, and assessment of preexisting symptoms by questionnaire. Study visits 1 & 2 (Intervention) Subjects will be randomly assigned to receive either 20 mg sildenafil (Revatio 20mg) or dextrose candy (Dextroenergy) orally. 45 minutes after the intervention, they will undergo identical exercise assessments, including IET until exhaustion. After a further rest phase of 30 minutes, subjects will perform CWRET until exhaustion. Right heart focused stress-echocardiography will be performed during IET. Further measurements include resting ECG, arterial blood gas analysis at rest and at end-exercise, Borg CR10 questionnaires and recording of AEs by questionnaire. After a washout phase of minimum 24 hours up to 12 weeks, the same assessments will be repeated, with each subject receiving the opposite treatment, according to the cross-over design.
Study Product / Intervention:	Sildenafil 20mg (Revatio 20mg)
Control Intervention (if applicable):	Dextrose candy (Dextroenergy)
Number of Participants with Rationale:	Sample size estimation for cross-over and a desired power of 0.8 and two-sided significance level of 0.05 calculated that 18 subjects will be needed to detect a minimal clinical important difference in Wmax. Accounting for a 10% dropout rate, we aim to include 20 subjects, which is within a realistic scope for the suggested timeframe of the study and rarity of the disease in question.
Study Duration:	Anticipated total trial duration: 24 months
Study Schedule:	April 2026: First-Participant-In March 2028: Last-Participant-Out

Investigator(s):	Principal Investigator Prof. Dr. med. Silvia Ulrich Director of Department, Department of Pulmonology Head of Pulmonary Hypertension University Hospital Zurich Rämistrasse 100 CH-8091 Zürich Switzerland Phone: +41 44 255 2220 Fax: +41 44 255 4451 E-mail: silvia.ulrich@usz.ch Co-Investigator Dr. med. Arcangelo Friedrich Carta Resident Physician, Department of Pulmonology University Hospital Zurich Rämistrasse 100 CH-8091 Zürich Switzerland E-mail: arcangelo.carta@usz.ch A full list of investigators and study personnel is provided in the annex.
Study Centre(s):	Single Center: Department of Pulmonology, University Hospital of Zurich
Statistical Considerations:	Statistical Analysis Mixed linear model regressions will be conducted in the intention-to-treat population for the specified outcome variables. Models will be adjusted for treatment (sildenafil 20mg vs. dextrose candy), order of administration, and the interaction between treatment and order to account for potential carry-over effects. Individual subjects will be modelled as random effects. In a secondary analysis, regressions will be further adjusted for relevant baseline values as additional fixed effects. Regression results will be reported as the average marginal effects of each predictor. Continuous variables will be presented as means ± standard deviation. Single missing data points will neither be replaced nor imputed, and implausible outliers will be omitted. Statistical significance will be assumed if the 95% confidence interval does not overlap 0, with a corresponding p-value < 0.05. All statistical analyses will be performed using R Studio.
GCP Statement:	This study will be conducted in compliance with the protocol, the current version of the Declaration of Helsinki, ICH-GCP, as well as all national legal and regulatory requirements.

ABBREVIATIONS

6MWD	six-minute walking distance
AE	Adverse Event
BASEC	Business Administration System for Ethical Committees, (https://submissions.swissethics.ch/en/)
BE	Base excess
BF	Breathing frequency
BP	Blood pressure
BR	Breathing reserve
CA	Competent Authority
CEC	Competent Ethics Committee
CRF	Case Report Form
ClinO	Ordinance on Clinical Trials in Human Research *(in German: KlinV, in French: OClin, in Italian: OSRUm)*
CO	Cardiac Output
CTCAE	Common terminology criteria for adverse events
CWRET	Constant work-load exercise test
CYP3A4	Cytochrome P450 isoenzyme 3A4
ECG	Electrocardiogram
ERA	Endothelin receptor antagonist
ERS	European Respiratory Society
ESC	European Society of Cardiology
FAC	Fractional area change
$F_{ET}CO_2$	Fraction of end-tidal carbon dioxide
$F_{ET}O_2$	Fraction of end-tidal oxygen
FEV_1	Forced expiratory volume in 1 second
F_ICO_2	Inspiratory fraction of carbon dioxide
F_IO_2	Inspiratory fraction of oxygen
FVC	Forced vital capacity
GCP	Good Clinical Practice
Ho	Null hypothesis
H_1	Alternative hypothesis
HCO^{3-}	Bicarbonate
Hb	Hemoglobin
Hct	Hematocrit
HR	Heart rate
HRA	Federal Act on Research involving Human Beings *(in German: HFG, in French: LRH, in Italian: LRUm)*
IMP	Investigational Medicinal Product
IET	Incremental exercise testing
mPAP	Mean pulmonary arterial pressure
$PaCO_2$	Arterial partial pressure of carbon dioxide
PAH	Pulmonary arterial hypertension

PaO_2	Arterial partial pressure of oxygen
PAP	Pulmonary arterial pressure
PAWP	Pulmonary arterial wedge pressure
PDE-5	Phosphodiesterase type 5
$P_{ET}CO$	End-tidal partial pressure of carbon dioxide
$P_{ET}O_2$	End-tidal partial pressure of oxygen
PFT	Pulmonary function test
PH	Pulmonary hypertension
PI	Principal Investigator
PVR	Pulmonary vascular resistance
QD	*Quaque die,* i.e. once daily
RAP	Right atrial pressure
RPP	Rate-pressure product
SaO_2	Arterial saturation of oxygen
SAE	Serious Adverse Event
SOP	Standard Operating Procedure
sPAP	Systolic pulmonary arterial pressure
SpO_2	Peripheral saturation of oxygen
SUSAR	Suspected Unexpected Serious Adverse Reaction
SV	Stroke Volume
TAPSE	Tricuspid anular plane systolic excursion
TID	*Ter in die*, i.e. three times daily
TMF	Trial Master File
TRPG	Tricuspid regurgitation pressure gradient
TRPG/CO	Tricuspid regurgitation pressure gradient divided by cardiac output
TRV	Tricuspid regurgitation velocity
Tmax	Maximum endurance time
$V'CO_2max$	Maximum carbon dioxide exhaustion
V'Emax	Maximum exercise ventilation
$V'E/VCO_2$	Ventilatory equivalent for carbon dioxide
$V'E/VO_2$	Ventilatory equivalent for oxygen
V'O2max	Maximum oxygen uptake
Wmax	Maximal workload
WU	Woods Unit

SUMMARY OF THE REVISION HISTORY IN CASE OF AMENDMENTS

Version Nr, Version Date	Chapter	Description of change	Reason for the change
Version 1.1, 10.03.2026	Study Synopsis + Chapters 6.1 and 9.3.2 + Table 1	Change of washout period to 24 hours	Requested by the CEC.
	Study Synopsis + Chapters 5.1, 9.2.1, 11	Specified primary outcome (Wmax) and clarified secondary outcomes.	Requested by the CEC.
	Chapter 12	Specified data storage	Requested by the CEC.
	Various	Corrected various typographical errors	For improved reading purposes.

STUDY SCHEDULE

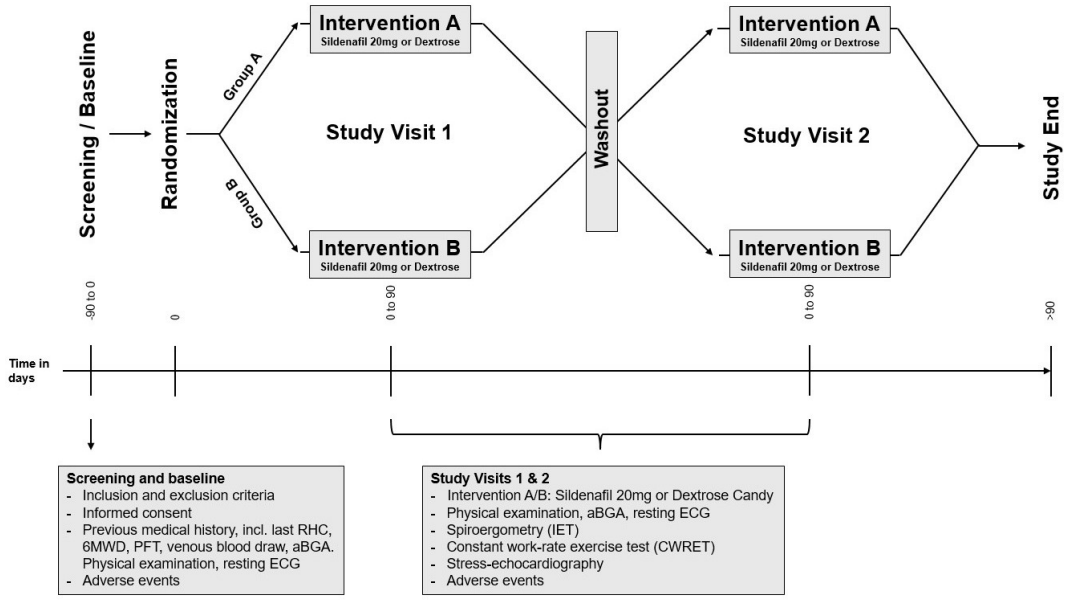


Figure 1: Study Flow Chart: *6MWD: 6-minute walking distance, aBGA: arterial blood gas analysis, CWRET: constant work-rate exercise test, ECG: electrocardiogram, IET: incremental exercise testing, incl.: including, RHC: right heart catheterization, PFT: pulmonary function test.*

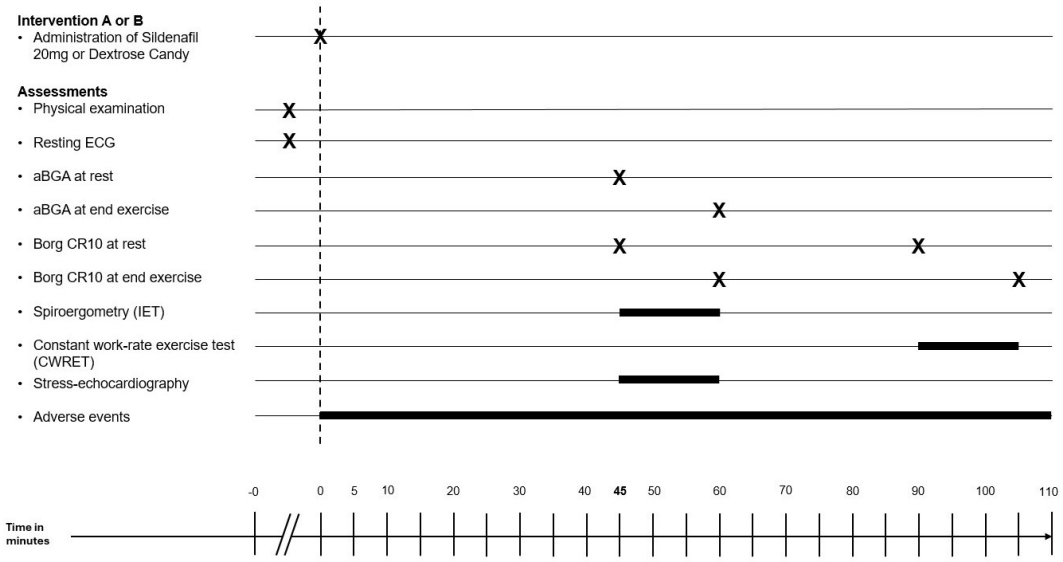


Figure 2: Study Visits 1 & 2 Timeline: *aBGA: arterial blood gas analysis, CWRET: constant work-rate exercise test, ECG: electrocardiogram, IET: incremental exercise testing, "**X**": indicates an assessment at a specific point in time, "—": indicates a continuous assessment across the indicated period of time.*

Table 1: Study Schedule

	Screening & Baseline	Study Visit 1 Can be on the same day as Screening & Baseline	Study Visit 2
Study Visit	0	1	2
Time (weeks)	0	0 - 12	0 – 12
Informed consent	x		
Inclusion & Exclusion Criteria	x		
Randomization	x		
Baseline demographic data	x		
Medical History	x		
Physical Examination	x	x	x
Intervention Administration of sildenafil 20mg or dextrose candy		x	x
Resting ECG	x	x	x
Spiroergometry (IET)		x	x
Stress Echocardiography (IET)		x	x
aBGA at Rest (IET)	x[2]	x[2]	x
aBGA at End Exercise (IET)			x
Spiroergometry (CWRET)		x	x
Borg CR10 Questionnaires		x	x
Assessment of Adverse Effects		x	x

[1]If applicable/necessary

[2]If not obtained within the last 90 days.

1. STUDY ADMINISTRATIVE STRUCTURE

1.1 Sponsor

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1.3 Statistician ("Biostatistician")

N/A

1.4 Laboratory

N/A

1.5 Monitoring institution

N/A

1.6 Data Safety Monitoring Committee

N/A

1.7 Any other relevant Committee, Person, Organisation, Institution

N/A

2. ETHICAL AND REGULATORY ASPECTS

Approval of the study will be requested from the CEC and the decision of the CEC concerning the conduct of the study will be made in writing to the Sponsor-Investigator before commencement of this study. The clinical study will only begin once approval from all required authorities has been received. Any additional requirements imposed by the authorities shall be implemented.

2.1 Study registration

The trial will be registered on www.clinicaltrials.gov, on the Swiss National Clinical Trials Portal (HumRes) after acceptance by the CEC.

2.2 Categorisation of study

Risk category A:

- The medication Sildenafil 20mg (Revatio 20mg) is already authorised in this dosage for treatment of PAH, the disease of interest, and thus falls under in-label use.
- The sham comparator, dextrose candy (Dextroenergy), is a widely distributed food item and does not fall under the placebo category.

2.3 Competent Ethics Committee (CEC)

The responsible investigator ensures that approval from an appropriately constituted CEC is sought for the clinical study.

Reporting duties and changes in protocol are not made without prior approval of the sponsor and the CEC, except where necessary to eliminate apparent immediate hazards to study participants.

The investigator will report the premature termination, interruption or resumption of the study, including reasons thereof, to the CEC within 15 days. An interruption lasting more than two years is considered a premature termination.

The investigator will report the first visit of the first participant in Switzerland and the end of the study in Switzerland to the CEC within 30 days. The final study report will be submitted within one year after the completion of the study or premature termination. Amendments are reported according to chapter 2.10.

2.4 Competent Authorities (CA)

N/A. CA approval is not necessary since the study risk category is neither B nor C.

2.5 Ethical Conduct of the Study

The study will be carried out in accordance with the protocol and with principles enunciated in the current version of the Declaration of Helsinki, the guidelines of Good Clinical Practice (GCP) issued by ICH, and Swiss Law and Swiss regulatory authority's requirements. The CEC and regulatory authorities will receive annually a safety report and interim reports and be informed about study stop/end in agreement with local requirements. The CEC will also be informed annually about the general progress of the clinical trial.

2.6 Declaration of interest

None of the authors declare any conflicts of interest.

2.7 Patient Information and Informed Consent

The investigators will explain to each subject the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits and any discomfort it may entail. Each subject is informed that the participation in the study is voluntary and that he/she may withdraw from the study at any time and that withdrawal of consent will not affect his/her subsequent medical assistance and treatment.

The subjects are informed that he/she/they can ask any question, and consult with family members, friends, their treating physicians or other experts before deciding about their participation in the study. Enough time shall be given to the subjects for consideration.

The subjects must be informed that authorised individuals other than their treating physician may

examine his/her medical records.

All subjects are given a subject information sheet and a consent form describing the study and providing sufficient information for the subjects to make an informed decision about their participation in the study.

The formal consent of a subject, using the approved consent form, is obtained before the subject is submitted to any investigation procedure.

The subject should read, understand, and voluntarily agree before signing and dating the informed consent form, and is given a copy of the signed document. The consent form is signed and dated by the subject and the PI (or her/his designee). The signed consent form is retained as part of the investigation records.

2.8 Participant privacy and confidentiality

The investigator affirms and upholds the principle of the participant's right to privacy and that they shall comply with applicable privacy laws. Especially, anonymity of the participants shall be guaranteed when presenting the data at scientific meetings or publishing them in scientific journals.

The investigator has appropriate knowledge and skills in the areas of data security and data protection or is able to ensure compliance by calling in appropriate expertise (Art. 6, ClinO)

Individual subject medical information obtained as a result of this study is considered confidential and disclosure to third parties is prohibited.

Confidentiality will be further ensured by utilizing subjects' identification code numbers to correspond to treatment data in the computer files.

For data verification purposes, authorised representatives of the Sponsor (-Investigator), or CEC may require direct access to parts of the medical records relevant to the study, including participants' medical history.

2.9 Premature termination of the study

The Sponsor-Investigator may terminate the study prematurely according to certain circumstances, for example:

- ethical concerns,
- when the safety of the participants is doubtful or at risk, respectively,
- alterations in accepted clinical practice that make the continuation of a clinical trial unwise,
- early evidence of benefit or harm of the experimental intervention

If the study is terminated earlier than planned, the investigator notifies the CEC according to the provisions of ClinO Article 38.

2.10 Protocol amendments

The sponsor-investigator is authorized to amend the study protocol or to approve amendments after having delegate them to his/her designee and reviewed them.

Substantial amendments are only implemented after approval of the CEC.

Under emergency circumstances, deviations from the protocol to protect the rights, safety and well-being of human subjects may proceed without prior approval of the sponsor and the CEC. Such deviations shall be documented and reported to the sponsor and the CEC as soon as possible.

All non-substantial amendments once a year to the CEC with the safety report / general study progress report of the clinical trial.

3. BACKGROUND AND RATIONALE

3.1 Background and Rationale

Pulmonary arterial hypertension (PAH) is a progressive disease characterised by increased mean pulmonary arterial pressure (mPAP), pulmonary vascular resistance (PVR), leading to right ventricular overload and, ultimately, right heart failure. (1, 2) PAH falls under Group 1 of the World Health Organization (WHO) classification of pulmonary hypertension (PH) and is defined by mPAP >20 mmHg, PVR ≥ 2 Wood units, and pulmonary artery wedge pressure (PAWP) ≤15 mmHg in the absence of left heart disease or chronic lung pathology. (1, 2) The underlying pathology includes endothelial dysfunction, excessive vasoconstriction, and vascular remodelling, contributing to the disease's chronic progression. (1-3)

Phosphodiesterase type 5 (PDE-5) inhibitors are a cornerstone of PAH treatment and function by enhancing the nitric oxide-cyclic guanosine monophosphate pathway, promoting pulmonary vasodilation and reducing vascular remodelling. (4) They are frequently prescribed in combination with endothelin receptor antagonists (ERAs), such as ambrisentan or bosentan, as recommended by major guidelines to optimise treatment efficacy and delay disease progression. (1, 2) The key benefits of PDE-5 inhibitors in PAH include long-term improved exercise capacity, symptom relief, and favourable pulmonary hemodynamic effects in form of reduction in mPAP and PVR. (5-7) These effects translate into an increase in the six-minute walk distance (6MWD) by approximately 30–50 meters and a delayed time to clinical worsening in randomised controlled trials. (4, 8) Among the available PDE-5 inhibitors, tadalafil is preferred due to its longer half-life (~17.5 hours), which allows for once-daily (QD) dosing and greater patient adherence. (6) Sildenafil remains an effective alternative, requiring three daily doses (TID) due to its shorter duration of action (with peak effects occurring within 30-120 min). (3, 5) The recommended doses for PAH include tadalafil 40 mg QD and sildenafil 20 mg TID. (5, 6) Higher doses of sildenafil (e.g., 40–80 mg TID) were initially thought not to confer additional benefit in most patients and are not standard practice. (4, 5) A recent randomised-controlled trial however revealed that 80mg sildenafil TID was as safe as 5mg TID and potentially revealed better efficacy in terms of improved time-to-clinical worsening and 6MWD and thus, dose escalation should be considered in treatment-resistant patients. (1, 9) In summary, PDE-5-Inhibitor therapies, particularly when combined with ERA, form the foundation of modern PAH management, and are recommended in the current guidelines to improve patient outcomes. (1, 2, 10-14)

Overall, given sildenafil's relatively rapid onset of action, there is there is a rationale for the use of on-demand sildenafil in PAH patients, particularly for administration timed shortly before exercise which may enhance pulmonary vasodilation and oxygen delivery during exertion and may acutely enhance exercise performance (4, 5) (14). This approach has been hypothesised to provide acute improvements in exercise capacity and reducing exertional dyspnea more effectively than continuous dosing alone. However, while some preliminary studies suggest benefits of increased doses of sildenafil, (15) no study ever looked at the safety of on-demand sildenafil use in PAH in a "pill-in-the pocket" concept aiming at tailoring medication to exercise demands during daily activities when patients need it.

We aim to investigate whether the timed intake of on-demand sildenafil vs. dextrose candy 45 minutes before incremental exercise testing (IET) has a beneficial effect on maximum workload (Wmax) in PAH, as well as improving right-heart focused stress-echocardiography parameters, cardiometabolic parameters, maximum endurance time (Tmax), maximum oxygen uptake (V'O2max) and right heart function.

Sex-related considerations

PAH exhibits notable sex-based differences in incidence, clinical presentation, haemodynamics, and prognosis, suggesting that biological factors may influence disease development and progression. PAH has a strong female predominance, with a female-to-male ratio of approximately 3-4:1. (16) Women are more likely to have connective tissue disease-associated PAH, whereas men more often present with idiopathic PAH. (17, 18) Despite similar mean ages at diagnosis, women are often diagnosed earlier, with a better baseline functional status and less severe hemodynamic impairment. (17, 18) In contrast, men present with worse haemodynamics, particularly higher mPAP and greater right ventricular strain, leading to faster disease progression and worse survival outcomes. (18, 19) Male sex is an independent risk factor for higher mortality, as seen in registries and risk prediction models (e.g., REVEAL). (17, 20) In cardiopulmonary exercise testing different patterns of exercise intolerance have been suggested. (17, 21)

Current PAH guidelines do not differentiate treatment strategies based on sex, (1, 2) but emerging evidence suggests sex may influence drug efficacy. (22) Regarding PDE-5-Inhibitors there is no clear

evidence pointing to any sex-related treatment difference. (23) PDE-5-Inhibitors, notably, are safe to use in women during pregnancy - however, out of an abundance of precaution, known pregnant patients will be excluded in this trial to avoid any potential adverse events (AE) in a vulnerable population already facing altered physiological demands.

In line with the above-mentioned considerations, we plan to include both sexes and will conduct stratified subgroup analyses, adjusting for key baseline characteristics (most importantly sex, age, and baseline medication) within our mixed regression models to explore potential differences in treatment response. Correct interpretation of the results will be critical, as baseline characteristic distribution within smaller sample sizes can potentially show discrepancies with broader epidemiological data. (24)

3.2 Investigational Medicinal Product (treatment) and Indication

The IMP under investigation in this study is Sildenafil 20mg (Revatio 20mg), which is a PDE-5 Inhibitor indicated for treatment of PAH functional classes II and III.

Phosphodiesterase type 5 (PDE-5) inhibitors are a cornerstone of PAH treatment and function by enhancing the nitric oxide-cyclic guanosine monophosphate pathway. Comprehensive details on mechanism of action, side effects, pharmacokinetics are found in the adjunct professional information on sildenafil 20mg and elaborated briefly below.

In vitro studies have shown that sildenafil is a selective PDE-5 inhibitor with a stronger effect on PDE-5 than on other known phosphodiesterases (10 to 8000-fold), although certain side-effects can be attributed to non-selective cross-inhibition (i.e. visual disturbances, back pain and myalgias, flushing, systemic hypotension, etc.). Sildenafil causes a transient, mild reduction in systemic blood pressure (BP) in healthy patients, which is less extensive in patients with PAH, presumably due to increases in cardiac output (CO), secondary to improved pulmonary hemodynamics. Relevant electrocardiogram (ECG) changes haven't been documented in either healthy subjects or PAH patients.

Maximum plasma levels are reached within 30 to 120 minutes (median: 60 minutes) after oral administration on an empty stomach. Overall, the terminal half-life of sildenafil is 3 to 5 hours. Sildenafil is metabolized predominantly by the liver via the microsomal isoenzymes CYP3A4 and its metabolites are excreted, approximately 80% in the feces and approximately 13% renally. Concomitant intake of CYP3A4-inhibiting enzymes is contraindicated due to altered metabolization. In subjects with mild to moderate hepatic impairment (Child-Pugh A and B), the clearance of sildenafil is reduced 47% higher maximum concentrations. In subjects with severe renal impairment (creatinine clearance <30 mL/min), the clearance of sildenafil and its main metabolites was reduced, resulting in increases in maximum concentration by 88%. Therefore, intake in patients with severe hepatic or renal disease should be monitored, and these patients will not be included in this trial.

3.3 Preclinical Evidence

Preclinical data do not indicate any particular risk to humans. This conclusion is based on the usual tests to determine safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenicity, and reproductive toxicity.

3.4 Clinical Evidence to Date

Current evidence is elucidated in more detail in the introductory chapter 3.1. Phosphodiesterase type 5 (PDE-5) inhibitors are a cornerstone of PAH treatment by increasing pulmonary vasodilation and reducing vascular remodelling, (4) and are recommended by the ESC/ERS 2022/2019 guidelines to optimise treatment efficacy and delay disease progression. (1, 2) The key benefits of PDE-5 inhibitors in PAH include long-term improved exercise capacity, symptom relief, and favourable hemodynamic effects, such as reductions in mPAP and PVR. (5-7) These effects translate into an increase in the 6MWD, an important marker of disease progression, by approximately 30–50 meters and a delayed time to clinical worsening in randomised controlled trials. (4, 8) A randomised-controlled trial revealed that 80mg potentially revealed better efficacy in terms of improved time-to-clinical worsening and 6MWD and thus, dose escalation should be considered in treatment-resistant patients. (1, 9) In summary, PDE-5-Inhibitor therapies, particularly when combined with ERA, form the foundation of PAH treatment, and are recommended in the current leading guidelines to improve patient outcomes. (1, 2, 10-14)

3.5 Rationale for the dosage, route, regimen

Sildenafil 20mg (Revatio 20mg) will be administered orally. This is a well-studied standard dosage and administration route for patients with PAH (20mg TID). Hence, we expect 20mg to be sufficient to induce

a significant a clinically important effect on our primary and secondary outcomes, with the pertinent aspect of this study being the timing of the dosage 45 minutes before exercise

A randomised-controlled trial revealed that up to 80mg sildenafil TID was as safe as 5mg TID, with similar AE and mortality rates. Treatment with higher dosages potentially revealed better efficacy in terms of improved time-to-clinical worsening and 6MWD) and provides a rationale for dose escalation, at least in treatment-resistant patients. (1, 9) Therefore, we expect that the additional intake of 20mg should not result in any significant AEs.

3.6 Explanation for choice of comparator

For this study, we will utilise dextrose candy (Dextroenergy, a widely distributed food item commonly marketed for and used during exercise) as a sham comparator.

The use of this sham comparator is intended to minimize any bias which could result from the patients' knowledge of any treatment vs. no treatment, which could result in their (sub-)consciously applying different levels of effort during the assessments.

We considered and decided against the manufacturing of a placebo specifically for this trial, as it would not result in significantly improved information compared to an already approved in-label treatment specifically for PAH. Moreover, the resulting change in risk category would lead to unreasonable costs, expenditure and use of human resources compared to the scope of this small-scale and low-risk trial with a concise study question (fehlende Wirtschaftlichkeit).

3.7 Risks / Benefits

We aim to investigate whether on-demand sildenafil 20mg has a beneficial effect on exercise capacity in PAH, including maximum workload (Wmax) and endurance (Tmax), maximum oxygen uptake (V'O2max) and right heart function. The knowledge of these outcomes would benefit our patient collective by allowing to tailor their treatment according to their physical demands in form of a "pill-in-the-pocket" concept for usage shortly before exercise. This could in turn alleviate symptoms during exercise (such as dyspnea, dizziness, fatigue) and improve quality of treatment and lessen the burden of disease as well as providing patients agency for adapting their therapy on demand.

Patients at our clinic will most likely already be on PAH-specific treatment, including PDE-5-Inhibitors (usually sildenafil or tadalafil), and are thus expected to tolerate the medication well. The occurrence of any prohibitive side-effects prior to study inclusion will be evaluated at screening/baseline.

Side-effects of Sildenafil 20mg have been previously documented (a comprehensive list is detailed in the adjunct professional information) and include systemic hypotension, flushing, nasal congestion and gastrointestinal upset, as well as rarely syncope, loss or decrease of hearing and/or vision.

Thus, we anticipate a low occurrence of side effects / AEs, and we will systematically monitor these symptoms with questionnaires at baseline/screening and during each study visit. In addition, patients will be monitored for any clinical signs which could indicate worsening of PAH (dyspnea, leg edema, weight gain, increased need for diuretics or syncope) at the same points in time.

Dextrose candy carries a minimal risk of hyperglycaemia in vulnerable patients (primarily with known diabetes). However, the dose given is small and glucose levels will be obtained as part of the aBGA analysis and if necessary, baseline treatment can be adapted accordingly.

The assessments and measurements (most notably: IET with spiroergometry, CWRET, aBGA, resting ECG and stress-echocardiography), are non- or minimally invasive procedures and form part of routine clinical care for patients with PAH, who will be familiar with them. Each assessment carries a low to very low risk of adverse event and is well justifiable compared to the information gained through each assessment.

Currently, we aren't aware of any other competing trials investigating the same research question, so we have no concerns of redundancy.

3.8 Justification of choice of study population

Inclusion and exclusion criteria of the study population are referred to in Chapter 7.1.

PAH is a rare disease, and patients are typically referred to a tertiary level care centre, such as our PH clinic for expert treatment. Patients will be recruited from this collective during routine clinical visits. Therefore, we expect the results from our study population to be internally and externally valid.

Given the rarity of the disease and the aimed inclusion number of 20 subjects, balanced distribution of sexes cannot be guaranteed. Adjustment for sex will be performed during statistical analysis to account for any distribution imbalance and any demonstrable effects will be discussed and reported.

Vulnerable subjects (minors, subjects incapable of judgment or subjects under tutelage) and patients with known pregnancy are **not** foreseen for recruitment.

3.9 Patient and public involvement

N/A

4. STUDY OBJECTIVES

4.1 Overall Objective

We aim to demonstrate that on-demand “pill-in-the-pocket” intake of 20mg sildenafil (Revatio 20mg) compared to dextrose candy (Dextroenergy) increases exercise capacity in patients with Pulmonary Arterial Hypertension.

4.2 Primary Objective

The primary objective of this study is to evaluate:

- Difference in Wmax attained during IET after treatment with sildenafil 20mg (Revatio 20mg) versus dextrose candy
- Difference in Tmax attained during CWRET after treatment with sildenafil 20mg (Revatio 20mg) versus dextrose candy

4.3 Secondary Objectives

Secondary objectives of this study include to evaluate changes in

- Cardiometabolic parameters (SpO_2, BP, HR, RPP, V’O2max, $V'CO_2max$, V’Emax, $V'E/VO_2$, $V'E/VCO_2$, BF, BR, $P_{ET}O_2$, $P_{ET}CO_2$, F_IO_2, F_ICO_2, $F_{ET}O_2$, $F_{ET}CO_2$)
- Arterial blood gases (PaO_2, $PaCO_2$, HCO^{3-}, SaO_2, BE, lactate, Hb, Hct, glucose)
- Borg CR10 questionnaire
- Stress echocardiographic markers of right heart function IET (TRPG, TRV, RAP, sPAP, mPAP, FAC, TAPSE, TRPG/CO, CO, PVR, SV)

4.4 Safety Objectives

This study will evaluate the safety and tolerability of sildenafil 20mg (Revatio 20mg) by systematically monitoring the incidence and severity of AEs.

Moreover, clinical signs potentially indicating worsening of PAH will be monitored.

5. STUDY OUTCOMES

5.1 Primary Outcome

The primary outcome of this study is:

- The difference in Wmax attained during maximum spiroergometry 45 minutes after treatment with Sildenafil 20mg (Revatio 20mg) versus dextrose candy (Dextroenergy).

5.2 Secondary Outcomes

Secondary outcomes of this study include:

- Difference in Tmax attained during CWRET after treatment with Sildenafil 20mg (Revatio 20mg) versus dextrose candy (Dextroenergy)
- Changes in cardiometabolic parameters (SpO_2, BP, HR, RPP, V'O2max, $V'CO_2max$, V'Emax, $V'E/VO_2$, $V'E/VCO_2$, BF, BR, $P_{ET}O_2$, $P_{ET}CO_2$, F_IO_2, F_ICO_2, $F_{ET}O_2$, $F_{ET}CO_2$) during maximum spiroergometry 45 minutes after treatment with 20mg sildenafil versus dextrose candy and during CWRET, respectively.
- Changes in arterial blood gases (PaO_2, $PaCO_2$, HCO^{3-}, SaO_2, BE, lactate, Hb, Hct, glucose) before and after spiroergometry, 45 minutes after treatment with 20mg sildenafil versus dextrose candy.
- Changes in Borg CR10 questionnaire after spiroergometry 45 minutes after treatment with 20mg sildenafil versus dextrose candy and after CWRET, respectively.
- Changes in stress-echocardiographic markers of right heart function (TRPG, TRV, RAP, sPAP, mPAP, FAC, TAPSE, TRPG/CO, CO, PVR, SV) during spiroergometry (IET) 45 minutes after treatment with sildenafil versus.
- Safety and AEs of sildenafil 20mg (Revatio 20mg).

5.3 Other Outcomes of Interest

N/A.

5.4 Safety Outcomes

This study will evaluate the safety and tolerability of the additional intake of the IMP Sildenafil 20mg (Revatio 20mg) and dextrose candy (Dextroenergy) by systematically monitoring for AEs (incidence and severity) which may be associated with their intake, including specifically the following (not exclusively, a comprehensive list is provided in the adjunct professional information):

Dyspnea, leg edema, weight gain, increased need for diuretics, syncope, systemic hypotension, flushing, nasal congestion, gastrointestinal upset, loss or decrease of hearing, loss or decrease of vision.

6. STUDY DESIGN

6.1 General study design and justification of design

In a first randomized, cross-over trial, the effects of additive on-demand intake of sildenafil 20mg vs. dextrose candy on maximum exercise capacity in patients with PAH, timed 45 minutes before IET will be studied.

Patients will be recruited and screened for eligibility at screening / baseline. Patient information will be provided, inclusion & exclusion criteria assessed and signed informed consent obtained. Patients will be randomized to an intervention sequence (Sildenafil 20mg (Revatio 20mg) or dextrose candy (Dextroenergy) first). Baseline assessments will be performed.

In study visit 1, participants will perform spiroergometry (IET) on a cycle ergometer to exhaustion 45 minutes after intervention (administration of sildenafil 20mg or dextrose candy) according to a randomized, cross-over protocol. After a 30 minutes rest phase, CWRET will be performed until exhaustion.

During IET / spiroergometry, focused right-heart stress-echocardiography will be performed, and further assessments, such as aBGA at rest and end-exercise, and Borg CR10 questionnaires will be obtained. Incidence and severity of AEs will be monitored by questionnaires.

Then, in study visit 2, after a washout period of minimum 24 hours up to 12 weeks, participants will cross over to the opposite intervention, repeating the same sequence of assessments.

Maximum Workload (Wmax), cardiometabolic parameters, echocardiographical markers of right heart strain, maximum endurance time (Tmax), Borg CR 10 questionnaires, and AEs will be compared between the two interventions.

The content of one study visit is in accordance with daily clinical practice. The envisioned duration per study visit is 120 minutes up to maximum a day. The maximum duration of the trial per patient is up to maximum 12 weeks starting from study inclusion. Preferably, study visits 1 and 2 will be performed on separate days, although a minimum washout of 24 hours is allowed according to protocol. The maximum washout of 90 days is designed to avoid any significant disease progression between assessments.

The study design and timeline is visually depicted in **Figure 1.** The timeline of study visits 1 and 2 are depicted in **Figure 2**. Details of assessments per study visit are provided in chapter 9.3 and in **Table 1**.

6.2 Methods of minimising bias

6.2.1 Randomisation

The patients taking part in this study will be randomly assigned and equally distributed to the order of intervention in a cross-over design (Sildenafil 20mg or dextrose candy first). Randomization will be performed with a computer program allocating blocks of 4 participants.

6.2.2 Blinding procedures

Efforts to conceal the intervention will be applied though neither patients nor investigators will not be formally blinded. The sildenafil 20mg tablets or dextrose candy (both white, flat tablets) will be placed in small, opaque plastic dispenser cups with lids and patients will be instructed to take them swiftly.

6.2.3 Other methods of minimising bias

The randomized-controlled, cross-over design allows each subject to be its own comparator, thus reducing the intra-individual variability of the results and therefore allowing for a smaller sample size, as well as accounting for any order effects.

6.3 Unblinding Procedures (Code break)

N/A

7. STUDY POPULATION

7.1 Eligibility criteria

Participants fulfilling all of the following **inclusion** criteria are eligible for the study:

- Signed Informed consent
- Age 18 - 80 years (both sexes)
- Pulmonary hypertension (PH) class I (PAH) previously diagnosed according to ESC/ERS 2022/2019 guidelines (mPAP ≥ 20 mmHg, PVR ≥ 2 WU, PAWP ≤ 15 mmHg) during diagnostic right-heart catheterization.
- Stable condition, on the same PH-medication for >4 weeks

The presence of any one of the following **exclusion** criteria will lead to exclusion of the participant:

- Severe resting hypoxia (PaO_2 <7.3 kPa)
- Moderate-to-severe chronic obstructive or restrictive pulmonary disease (FEV1 ≤ 60% predicted, FVC ≤ 60% predicted)
- Women with known pregnancy or breast feeding
- Other clinically significant concomitant disease states (e.g., severe renal or hepatic disease, unstable cardiovascular disease, etc.)
- Concurrent medication with:
    - Nitric oxide donors (molsidomine, nicrorandil, etc.)
    - Soluble guanylate cyclase stimulators (riociguat)
    - Potent CYP3A4 inhibitors (azoles, clarithromycin, protease inhibitors)
- History of anterior ischemic optic neuropathy or hereditary retinal disease
- Participation in another study with investigational drug with potential influence the study data within the 30 days preceding and during the present study.
- Known allergies or hypersensitivity to sildenafil 20mg (Revatio) or dextrose candy including any of its components.

7.2 Recruitment and screening

Patients with PAH who present themselves in our PH Clinic for routine clinical follow-up who potentially fulfil the inclusion criteria will be screened and invited for participation in this clinical trial.

The trial will be announced though mouth-to-mouth propaganda.

Patients will not receive any payment or compensation except for coverage of travel costs to the second study visit upon request. Costs of any additional examinations will be paid for by the sponsor.

Patients can participate without obligation and will be given enough time to consider whether they want to participate in the study or not.

The investigator or the sponsor will notify the CEC of the first study participant, in accordance to Art 23a ClinO. If the first participating person is not included in the trial within two years following the issuance of the last authorization, the trial is considered interrupted. The clinical trial may not be commenced until an application for an extension of the time limit has been approved. The application for the extension is submitted to the CEC as a substantial amendment.

7.3 Assignment to study groups

Randomization will take place at the end of the screening/baseline visit by computer program. The study groups differ by order of the intervention (sildenafil 20mg or dextrose candy first) and each participant will go through both interventions according to the cross-over model.

7.4 Criteria for withdrawal / discontinuation of participants

Patients will be withdrawn from the study if:

- They fulfill any exclusion criteria section 7.1.
- They express their wish for withdrawal for any reasons
- They do not comply the study procedure for any reasons
- In case of an occurred AE that is not acceptable in the opinion of the investigator and / or participating patient

Participants will be withdrawn from the study if they cannot comply with the therapy and the study protocol for personal reasons or due to deterioration of their underlying illness or emergence of new illnesses or health hazards (accidents, new diseases etc.).

8. STUDY INTERVENTION

8.1 Identity of Investigational Medicinal Products

8.1.1 Experimental Intervention

The experimental intervention consists of the administration of the IMP Sildenafil 20mg (Revatio 20mg (*Viatris Pharma GmbH)*).

Revatio 20mg is a white, round, biconvex film tablet with the inscriptions “VLE” on one and “RVT 20” on the other side.

Full details of the IMP are supplied in the adjunct professional information.

8.1.2 Control Intervention

The control intervention will be dextrose candy (Dextroenergy), a widely distributed food item.

Dextroenergy is a white, quadrangular, flat candy tablet, weighing ~5.75g, containing 89% dextrose.

Nutrient values are provided separately.

8.1.3 Packaging, Labelling and Supply (re-supply)

Packaging and labelling

The IMP sildenafil 20mg (Revatio 20mg) will be kept in its original package with additional labelling according to standard medicine management.

The label will contain the following: a statement “for clinical trial use only”, the study number, the sponsor’s name, the number of tablets in the box, the instruction how to take the tablets, and a warning that all drugs should be stored out of the reach from children and at room temperature.

Before application, the medication will be placed in an opaque plastic dispenser cup with a lid. The dispensers will likewise be labelled, including the patient ID number and intervention identifier.

The dextrose candy will be kept in its original package. Before application, one unit of Dextroenergy will likewise be placed in an opaque plastic dispenser cup with a lid. The dispensers will be labelled, including specifically the patient ID number and intervention identifier.

8.1.4 Storage Conditions

The IMP and dextrose candy will be stored in a secure, limited access storage area within our Department of Pulmonology at the University Hospital of Zurich. Storage of the IMP sildenafil 20mg and dextrose candy will comply with the recommendations given to us by the professional information (kept in a dry storage unit, temperatures not above 30°C, out of reach of children).

8.2 Administration of experimental and control interventions

8.2.1 Experimental Intervention

See chapter 8.1.1.

8.2.2 Control Intervention

See Chapter 8.1.2.

8.3 Dose modifications

Rationale for dose selection is given in chapter 3.5. No dose modifications are planned during the study.

8.4 Compliance with study intervention

As patients will only receive each intervention once (1x sildenafil 20mg or 1x dextrose candy) under supervision, there are no concerns regarding long-term adherence. If the patient refuses to take the medication or the dextrose candy, the act will be considered as a wish to withdraw from the study and

the patient will be excluded.

8.5 Data Collection and Follow-up for withdrawn participants

In case of any withdrawals, the reason for dropout will be recorded.

Patients with any AE will be followed by our team until we are sure it has resolved to the pre-study level and/or will have been addressed according to best clinical practice.

Data obtained during the last study visit will be considered as end of study visit. If a patient withdraws his/her informed consent the data collected during study participation will be used for analysis and any collected blood samples will be destroyed after analysis.

Further treatment in our pulmonary hypertension clinic will not be influenced in any way in case of withdrawal from the trial.

8.6 Trial specific preventive measures

As per the trial's exclusion criteria, patients will be screened for any co-medications which are contraindicated during intake of sildenafil 20mg. These include:

- Nitric oxide donors (molsidomine, nicrorandil, etc.)
- Soluble guanylate cyclase stimulators (riociguat)
- Potent CYP3A4 inhibitors (azoles, clarithromycin, protease inhibitors)

Any intake of these medications will be recorded in the CRF and will automatically lead to exclusion from the trial.

As patients with PAH are sometimes [concomitantly] treated with the above-mentioned medication, this may impact the number of patients needed to be screened to achieve the target inclusion goal.

Our clinic provides the necessary infrastructure and emergency medication for managing any emergency situations which might arise from a serious AE. Treatment will be tailored to the clinical needs of the patient, respectively. As such, no specific rescue medication is foreseen.

8.7 Concomitant Interventions (treatments)

Pre-existing concomitant medication will be continued according to clinical standard and will be recorded in the CRF. This specifically includes any PAH therapy, such as sildenafil, other PDE-5 Inhibitors, endothelin-receptor antagonists, diuretics, anticoagulants, etc.

In case of any doubts concerning any additional medication or ongoing treatments, participation will be evaluated on an individual basis.

8.8 Study Drug Accountability

A drug inventory will be established and a drug receipt log filled out and signed by the investigator / study staff responsible for the acquisition. Designated investigator / study staff will count and verify that the medication batch is complete. Any damaged or unusable study drug (active drug or comparator) will be documented in the study files. Dates of receipt, expiry, use of lot/batch numbers and quantities will be noted.

Regular study drug reconciliation will be performed to document drug assigned, drug consumed, and drug remaining. This reconciliation will be logged on the drug reconciliation form and signed and dated by the study team.

As a standard packaging of Revatio 20mg contains 90 tablets a single batch acquisition should suffice (20 tablets are required, one each for 20 patients). In case of expiry or any unexpected loss of Revatio 20mg before the completion of the study additional supplies will be repurchased.

8.9 Return or Destruction of Study Drug

At the completion of the study, there will be a final reconciliation of medication acquired, consumed and remaining. This reconciliation will be logged on the drug reconciliation form, signed and dated. Any discrepancies noted will be investigated, resolved, and documented prior to return or destruction of unused study drug. Any remaining IMPs will be disposed of according to standard clinical practice. Drug destroyed on site will be documented in the study files.

9. STUDY ASSESSMENTS

9.1 Study flow chart(s) / table of study procedures and assessments

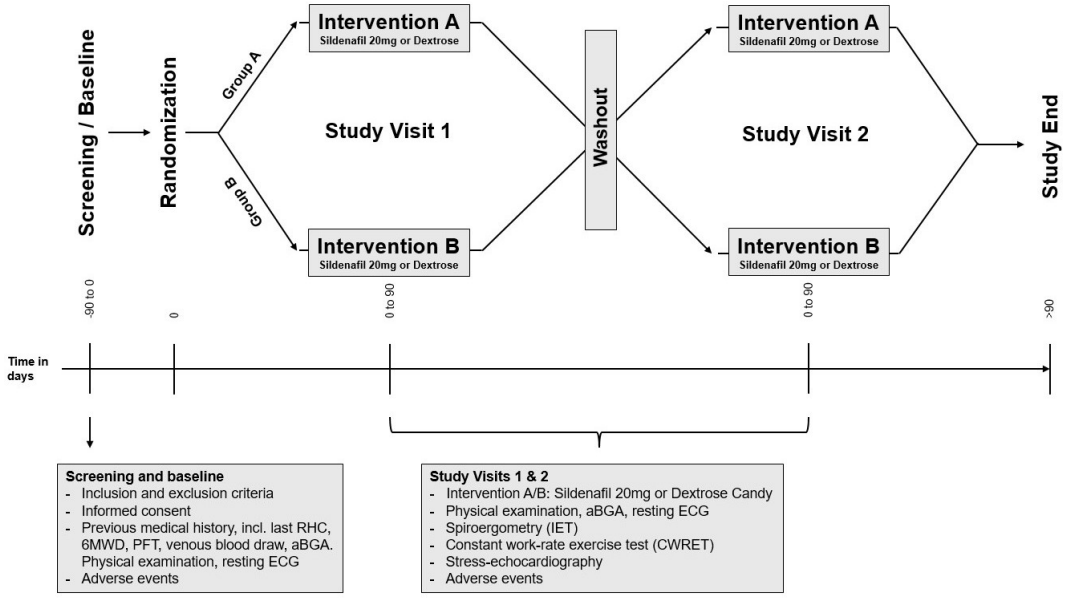


Figure 1: Study Flow Chart: *6MWD: 6-minute walking distance, aBGA: arterial blood gas analysis, CWRET: constant work-rate exercise test, ECG: electrocardiogram, IET: Incremental exercise testing, incl.: including, RHC: right heart catheterization, PFT: pulmonary function test.*

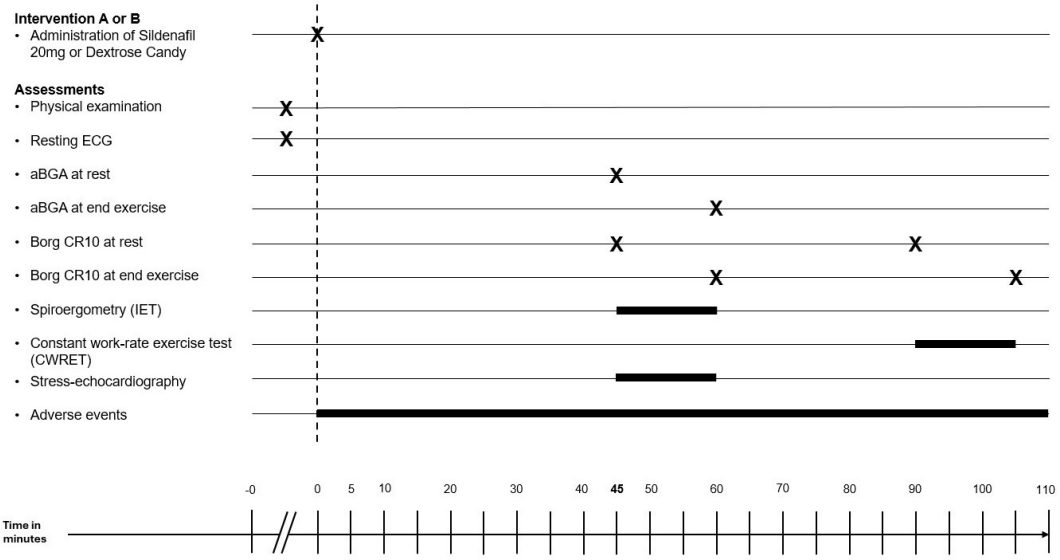


Figure 2: Study Visits 1 & 2 Timeline: *aBGA: arterial blood gas analysis, CWRET: constant work-rate exercise test, ECG: electrocardiogram, IET: incremental exercise testing, "**X**": indicates an assessment at a specific point in time, "—": indicates a continuous assessment across the indicated period of time.*

Table 1: Study Schedule

	Screening & Baseline	Study Visit 1 Can be on the same day as Screening & Baseline	Study Visit 2
Study Visit	0	1	2
Time (weeks)	0	0 - 12	0 – 12
Informed consent	x		
Inclusion & Exclusion Criteria	x		
Randomization	x		
Baseline demographic data	x		
Medical History	x		
Physical Examination	x	x	x
Intervention Administration of sildenafil 20mg or dextrose candy		x	x
Resting ECG	x	x	x
Spiroergometry (IET)		x	x
Stress Echocardiography (IET)		x	x
aBGA at Rest (IET)	x[2]	x[2]	x
aBGA at End Exercise (IET)			x
Spiroergometry (CWRET)		x	x
Borg CR10 Questionnaires		x	x
Assessment of Adverse Effects		x	x

[1]If applicable/necessary

[2]If not obtained within the last 90 days.

9.2 Assessments of outcomes

The following assessments and measurements are all part of routine clinical care for patients with PAH, who will be well familiar with them. All measurements will be obtained by trained study personnel and recorded in the dedicated section of the CRF with corresponding identifiers of each investigator.

9.2.1 Assessment of primary outcome

Spiroergometry (Incremental Exercise Testing)

During study visits 1 and 2, patients will perform spiroergometry in a seated position on a cycle ergometer to exhaustion, 45 minutes after receiving sildenafil 20mg or dextrose candy according to a randomized, cross-over design. The primary outcome, the predicted maximal workload (Wmax), will be automatically calculated based on age, sex, and weight, with the ramp adjusted to achieve an expected test duration of 8–12 minutes. Following two minutes of rest, patients will be instructed to maintain a pedalling rate of 50-60 revolutions per minute. The first two minutes will be unloaded, followed by incremental increases of 10–20 W per minute until exhaustion. End-exercise variables will be defined as the mean values from the final 30 seconds before termination, indicated by a decrease in pedalling rate to <50 revolutions per minute. The testing will be followed by a recovery phase of at least 2–3 min.

9.2.2 Assessment of secondary outcomes

Cardiometabolic measurements

During spiroergometry respiratory gas exchange parameters will be measured using a flow sensor connected to a cardiometabolic unit via a mouthpiece, calibrated before each test. Gas exchange parameters, including tidal volume (VT), minute ventilation (V′E), oxygen uptake (V′O2), carbon dioxide production (V′CO2), respiratory exchange ratio (RER), and derived variables, recorded breath-by-breath. SpO_2 will be continuously monitored via finger clip pulse oximetry, while heart rate will be derived from a 12-lead ECG and blood pressure measured using an automated arm cuff. Maximal voluntary ventilation (MVV) will be calculated as forced expiratory volume in 1 second × 40. The gas exchange threshold will be defined as the first RER >1.0. At rest and at peak exercise, arterial blood samples from the radial artery will be drawn and immediately analysed. Arterial oxygen content (CaO_2) will be calculated as SaO_2 × Hb × 1.34 + PaO_2 × 0.0031 (where SaO_2 is arterial oxygen saturation, and Hb is haemoglobin concentration). Dead space fraction (VD/VT) will be calculated as ($PaCO_2$ − $PETCO_2$)/$PaCO_2$ (where $PaCO_2$ is arterial carbon dioxide tension and $PETCO_2$ is end-tidal carbon dioxide tension).

Spiroergometry and CWRET will be conducted according to standard clinical practice, supervised by a physician, and stopped in case of clinical signs warranting discontinuation. (25) If a patient is on long-term oxygen therapy only ergometry will be performed without respiratory gas exchange parameter measurements.

Constant Work-Rate Exercise Testing

Following a rest phase of 30 minutes after completion of the spiroergometry (IET), patients will perform CWRET on the cycling ergometer in an upright position at 75% of achieved Wmax until exhaustion, providing Tmax. Cardiometabolic measurements during CWRET will be performed analogously to IET, as described above.

Borg CR10 Scale

During study visits 1 and 2, after each spiroergometry and CWRET test, patients will report leg fatigue and dyspnea using the Borg CR10 scale.

Arterial blood gas analysis

During study visits 1 and 2, before each IET, resting aBGA sampling will be performed by puncture of the radial artery and immediately analysed. The resting aBGA result at study visit 1 may be substituted for the baseline/screening values, if obtained within 90 days under equal conditions. At end-exercise, aBGA will be repeated using the same techniques.

Focused Stress-echocardiography

Right heart focused stress-echocardiographic recordings will be obtained in a seated position during IET. A real-time, phased-array sector scanner with an integrated colour Doppler system and a transducer containing crystal sets for imaging (1–5 MHz), continuous-wave (CW), and pulsed-wave (PW) Doppler will be used, as previously described. (26) Right heart parameters and function will be recorded and analysed in accordance with the guidelines of the American Society of Echocardiography and as previously applied by our group. (27-29) Maximal tricuspid regurgitation pressure gradient

(TRPG) will be derived from the maximal tricuspid regurgitation velocity (TRV) using CW Doppler and calculated via the modified Bernoulli equation: ΔPressure = 4 × TRVmax². Right atrial pressure (RAP) will be estimated based on inferior vena cava diameter and its inspiratory variation. Systolic pulmonary artery pressure (sPAP) will be determined as TRPG + RAP, while mPAP will be estimated using the formula mPAP = 0.61 × sPAP + 2 mmHg. (30) Right ventricular (RV) area will be manually traced, and fractional area change (FAC) will be calculated as (end-diastolic RV area − end-systolic RV area) / end-diastolic RV area. Tricuspid annular plane systolic excursion (TAPSE) will be measured in M-mode. Cardiac output (CO) will be estimated using the Doppler velocity-time integral method at the left ventricular outflow tract. (31) The pressure-flow relationship will be assessed as TRPG/CO, while PAWP will be estimated using the formula PAWP = 1.24 × (E/e′) + 1.9. (32) PVR will be calculated as (mPAP − PAWP) / CO, and right ventricular-arterial coupling will be assessed using TAPSE/TRPG. (33) Stroke volume (SV) will be derived as SV = CO/HR.

9.2.3 Assessment of other outcomes of interest

Base Assessments

At screening/baseline, a detailed medical history, physical examination, and current medication list and allergies will be collected or updated if already available from previous visits. Recorded parameters will include age, height, weight, body mass index, body surface area (BSA, calculated using the Dubois formula, $BSA = 0.007184 \times W^{0.425} \times H^{0.725}$), functional class (NYHA), ethnicity, as well as current medication, allergies, and use and duration of domiciliary or long-term oxygen treatment.

Last 6MWD, last RHC and last PFTs results will be collected from the medical history including the date of assessment. Last aBGA parameters (at rest) and NT-proBNP value from venous blood draw will be taken form the medical records.

Pregnancy testing

We will not include known pregnant or breast-feeding patients. However, as the study would not be a risk for women with early occult pregnancy (as spiroergometry is done in everyday practise without prior pregnancy tests in this patient collective and sildenafil is not contraindicated in pregnancy), we will not perform routine pregnancy tests before the study.

9.2.4 Assessment of safety outcomes

9.2.4.1 Adverse events

Patients will be systematically monitored at each study visit for AEs and symptoms which might indicate deterioration of PAH using standardised questionnaires.

Any medication side effects or AEs will be monitored during the study visits. At the end of study visits 1 & 2, questionnaires assessing symptoms or AEs during the respective study visit will be completed. Date and hour of onset will be recorded, as well as severity according to CTCAE.

Assessed symptoms include (non-exclusively) dyspnea, leg edema, weight gain, increased need for diuretics, systemic hypotension, syncope, flushing, nasal congestion, gastrointestinal upset, loss or decrease of hearing and/or vision. Any other symptoms or AEs will be recorded individually.

In case of any AEs, the continuation or termination of the study will be evaluated individually by the local physician staff/investigator and will be noted. Any criteria requiring interruption of the study, medical surveillance and/or treatment will be explicitly stated.

In case of any symptoms or AEs in between study visits (or any other wish for discontinuation), the patients will be able to contact us via the provided with the telephone numbers of our PH clinic or via the department's on-duty physician (available 24/7).

9.2.4.2 Laboratory parameters

Markers of disease severity will be assessed and handled as done in daily clinical practice.

9.2.4.3 Vital signs and physical examination

Vital signs including blood pressure (standard upper arm automated arm cuff), heart rate and SpO_2 (by standard finger clip pulse oximeter), and respiratory rate will be recorded at the beginning of each study visit. A 12-lead resting ECG will be electronically recorded in a supine position. Physical examination will be performed, including assessment of the heart, lungs, volume status and any other relevant abnormalities.

In case of any significant or unexpected abnormalities (hyper- or hypotension, brady- or tachycardia,

brady- or tachypnea, deoxygenation, significant ECG changes, or any other signs), continuation or termination of the study will be evaluated individually by the investigator/physician staff.

9.2.5 Assessments in participants who prematurely stop the study

If patients are withdrawn prematurely from our study due to AEs, we will offer follow-up and standard care management on an individual basis until resolution of the AEs including, if necessary, additional visits to our PH clinic.

Patients who withdraw informed consent will receive standard care according to our clinical follow-up (if no study-related medical care is required).

9.3 Procedures at each visit

The procedures at each visit are additionally depicted in **Table 1** and **Figures 1** and **2**.

9.3.1 Screening and baseline

At screening/baseline, patient information and informed consent, inclusion & exclusion criteria, randomization, medical history including last 6MWD, last RHC & last PFTs, NYHA functional class, baseline demographic data, concomitant medication, physical examination, vital signs, resting ECG, arterial blood gases at rest are obtained.

9.3.2 Study visits 1 & 2

At study visit 1, Physical examination, vital signs, resting ECG, study intervention (administration of sildenafil 20mg or dextrose candy), spiroergometry (IET), arterial blood gases at and at end-exercise (IET), stress echocardiography (IET), CWRET, Borg CR10 questionnaires (IET and CWRET), assessment of AEs by questionnaire are obtained.

On study visit 2, after a washout phase of minimum 24 hours up to 12 weeks, the same assessments will be repeated, with each subject receiving the opposite treatment in a cross-over design.

10. SAFETY

10.1 Drug studies

The Sponsor's SOPs provide more detail on safety reporting.

During the entire duration of the study, all AEs and all serious adverse events (SAEs) are 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.

10.1.1 Definition and assessment of (serious) adverse events and other safety related events

An **Adverse Event (AE)** is any untoward medical occurrence in a patient, or a clinical investigation participant administered a pharmaceutical product, and which does not necessarily have a causal relationship with the study procedure. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational medicinal product, whether or not related to the investigational medicinal product.

A **Serious Adverse Event (SAE)** is classified as any untoward medical occurrence that:

- results in death,
- is life-threatening,
- requires in-patient hospitalization or prolongation of existing hospitalisation,
- results in persistent or significant disability/incapacity, or
- is a congenital anomaly/birth defect.

In addition, important medical events that may not be immediately life-threatening or result in death, or require hospitalisation, but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed above should also usually be considered serious. [ICH E2A]

SAEs should be followed until resolution or stabilisation. Participants with ongoing SAEs at study termination (including safety follow-up visit) will be further followed up until recovery or until stabilisation of the disease after termination.

Assessment of Causality

Both Investigator and Sponsor make a causality assessment of the event to the study investigational medicine product, based on the criteria listed in the ICH E2A guidelines:

Relationship	Description
Definitely	Temporal relationship Improvement after dechallenge* Recurrence after rechallenge (or other proof of drug cause)
Probably	Temporal relationship Improvement after dechallenge No other cause evident
Possibly	Temporal relationship Other cause possible
Unlikely	Any assessable reaction that does not fulfil the above conditions
Not related	Causal relationship can be ruled out
*Improvement after dechallenge only taken into consideration, if applicable to reaction	

Unexpected Adverse Drug Reaction

An "unexpected" adverse drug reaction is an adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g. Investigator's Brochure for drugs that are not yet approved and Product Information for approved drugs, respectively). [ICH E2A]

Suspected Unexpected Serious Adverse Reactions (SUSARs)

The Sponsor evaluates the SAE that has been reported regarding seriousness, causality and expectedness. If the event is related to the investigational medicinal product and is both serious and unexpected, it is classified as a SUSAR.

Assessment of Severity

Severity grading of AE will be applied according to the Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0. The specifics of AE grading according to each system organ class are detailed in the original reference.

- Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental Activities of Daily Life.
- Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care Activities of Daily Life.
- Grade 4: Life-threatening consequences; urgent intervention indicated.
- Grade 5: Death related to AE.

10.1.2 Reporting of serious adverse events (SAE) and other safety related events

Reporting of SAEs

All SAEs must be reported immediately and within a maximum of 24 hours to the Sponsor-Investigator of the study. The Sponsor-Investigator will re-evaluate the SAE and return the form to the site.

Reporting of SUSARs

A SUSAR needs to be reported to the Ethics Committee (local event via local Investigator) via BASEC within 7 days, if the event is life-threatening or fatal, or within 15 days (all other events).

The reporting obligations of SUSAR also apply if the investigator or the sponsor becomes aware of a suspected case that has arisen in Switzerland after termination of the clinical trial, or if the investigator or the sponsor only becomes aware of such a suspected case after termination of the clinical trial.

Reporting of immediate safety and protective measures

All suspected new risks and relevant new aspects of known adverse reactions that require immediate safety-related measures, must be reported to the Sponsor-Investigator within 24 hours. The Sponsor-Investigator must report these measures within 7 days to the Ethics Committee (local event via local Investigator) via BASEC and to Swissmedic (applicable in case of a category B or C study.

Reporting and Handling of Pregnancies

Sildenafil is not contraindicated in pregnancy but pregnancy per se is contraindicated in PAH-patients. If pregnancy would be detected between the two study visits, we would not perform the second visit in order to avoid a maximal exercise test during pregnancy. Thus, patients with known pregnancy will not be included or withdrawn immediately from the clinical study as soon as pregnancy would be reported. As these are two single study visits, pregnancy cannot occur during the treatment phase of the study. The course and outcome of the pregnancy will be followed up carefully (patients are routinely followed up closely at our PH clinic by default in case of pregnancy due to the nature of their disease), and any abnormal outcome regarding the mother or the child should be documented and reported.

Periodic reporting of safety and general progress of the clinical trial.

Once a year, the investigator submits to the CEC a list of the safety events including the severity of the events, their causality to the intervention and the safety of the study participants. The investigator also informs the CEC about the general progress of the clinical trial.

The safety report / general study progress report is submitted once a year to the CEC via Investigator.

The safety report / general study progress report is submitted to the CEC throughout the duration of the clinical trial in Switzerland, and the last submission of the safety report will cover the Last Patient Last Visit in Switzerland.

10.1.3 Follow up of (Serious) Adverse Events

Data obtained during the last study visit will be considered as end of study visit. Patients with any AE will be followed by our team, including, if necessary, additional visits to our PH-clinic, until we are sure that any (serious) AE has resolved to the pre-study level and/or will have been addressed according to best clinical practice.

10.2 Assessment, notification and reporting on the use of radiation sources

N/A

10.3 Exemption from the documentation requirements of AE

N/A

10.3.1 Exemption from the documentation requirements of AE due to pharmacological arguments

N/A

10.3.2 Exemption from the documentation requirements of AE due to clinical arguments

N/A

11. STATISTICAL METHODS

11.1 Hypothesis

H_0: Treatment with sildenafil 20mg does not induce any significant and minimally clinical important difference in Wmax compared to treatment with dextrose candy.

H_1: Treatment with sildenafil 20mg induces a significant and minimally clinical important difference in Wmax compared to treatment with dextrose candy.

11.2 Determination of Sample Size

According to the current literature on patients with respiratory disorders, the minimal clinical important difference of Wmax (primary outcome) is 4±1 W. (34) We propose a conservative assumption that the standard deviation of Wmax within each patient is equal to the minimal clinical difference.

Sample size estimation for cross-over with above assumptions and a desired power of 0.8 and two-sided significance level of 0.05 calculated that 18 subjects will be needed to detect a minimal clinical important difference in Wmax.

Accounting for a 10% dropout rate, we aim to include 20 subjects, which is within a realistic scope for the suggested timeframe of the study and rarity of the disease in question.

11.3 Statistical criteria of termination of trial

Analysis before termination of the data collection is not intended. Thus, no statistical criteria of premature termination have been determined.

11.4 Planned Analyses

11.4.1 Datasets to be analysed, analysis populations

Statistical analysis will be performed in in the intention-to-treat population for the specified outcome variables. All statistical analyses will be performed using R Studio after completion of the clinical phase of the trial.

11.4.2 Primary Analysis

Mixed linear model regressions will be performed for the specified primary (Wmax/) and secondary outcome variables (see chapter 5.2). The models will be adjusted for intervention (sildenafil 20mg vs. dextrose candy), order of administration, and the interaction between treatment and order to account for potential carry-over effects. Individual subjects will be modelled as random effects.

Regression results will be reported as the average marginal effects of each predictor. Continuous variables will be presented as means ± standard deviation. Statistical significance will be assumed if the 95% confidence interval does not overlap 0, with a corresponding p-value < 0.05.

11.4.3 Secondary Analyses

In a secondary analysis, mixed linear model regressions will be further adjusted for relevant, predefined clinical baseline values (i.e. sex, age, baseline medication, etc.) as additional fixed effects.

H_0: Clinical baseline values (sex, age, baseline medication) do not significantly influence any significant and minimally clinical important difference in Wmax (and secondary outcome variables) after treatment with sildenafil 20mg compared to treatment with dextrose candy.

H_1: Clinical baseline values (sex, age, baseline medication) significantly influence any significant and minimally clinical important difference in Wmax (and secondary outcome variables) after treatment with sildenafil 20mg compared to treatment with dextrose candy.

Statistical will be performed *after* analysis of the primary outcome by the above-mentioned methods.

11.4.4 Interim analyses

An interim analysis is not planned.

11.4.5 Safety analysis

A safety analysis includes a scan of all collected data regarding potential medication side effects, vital signs and ECGs.

Potential medication side effects and AEs will be graded according to severity (according to CTCAE version 5.0., see chapter 10.1.1.) and presented in table and graphical formats. The incidence rates of side effects / AEs will be compared between the interventions using two-sided McNemar's tests (assuming low incidence rates and for paired data in our cross-over study model), whereby statistical significance will be assumed if the p-value < 0.05.

11.4.6 Deviation(s) from the original statistical plan

If any analysis deviates from the initial analysis plan, it will be reported and justified in the final report.

11.5 Handling of missing data and drop-outs

Data will be analysed in an intention to treat population. Dropouts will be reported, and their data until time of dropout will remain in the analysis. Single missing data points will neither be replaced nor imputed, and implausible outliers will be omitted. In case of missing data for random reasons, an additional analysis per protocol will be taken into consideration.

12. QUALITY ASSURANCE AND CONTROL

12.1 Data handling and record keeping / archiving

12.1.1 Case Report Forms

CRFs are always kept up to date and will be anonymous. To allocate the CRF to the study subject, the study ID in combination with the year of birth will be noted in the CRF.

The data entry will be legible and done with black or blue ball-point pens to ensure legibility of reproduced copies. Any inserted or changed data must be traceable to the investigator by its initials and the date of entry. A list of the investigators' signatures and initials will be prepared and stored in a study related folder.

Data that could not be assessed, should be clearly declared by adding N/A or ND in the CRF.

The investigator ensures by signing the CRF, that the entered data are accurate and correct. All entered data except source data, which were entered in the CRF must be available in the subject study folder either as printouts or as a note taken by the investigator.

In addition, one collective screening log, where all the subjects who were tested for eligibility are listed, an enrolment log, where all enrolled participants are captured and a master subject list, where all the subject for analysis are listed, will be available.

12.1.2 Specification of source documents

A non-exclusive list of source data documents is listed below:

- Collective screening log (electronic, in dedicated file)
- Enrolment log (electronic, in dedicated file)
- Master subject list (electronic, in dedicated file)
- Case Report Form (CRF, in study folder)
- Signed Study participation and Informed Consent Form (including ID, in study folder)
- Randomization master list (electronic, in dedicated file)
- IMP/Drug reconciliation list (electronic, in dedicated file).
- Records of SAE & AE (in CRF and electronic).
- Records of reason(s) for withdrawal
- Demographic data (electronic, in clinical information system)
- Details of medical history (electronic) and physical examinations (in CRF)
- Records of current medication (electronic in clinical information system)
- Medical records from our Department of Pulmonology and Pulmonary Hypertension Clinic (electronic, in clinical information system)
- Medical records from other department(s), or other institution(s) including discharge letters or correspondence between institutions that were developed during the study period (electronic, in clinical information system).
- Laboratory/aBGA data (electronic, in clinical information system, and/or printouts)
- Results of obtained examinations and assessments (spiroergometry, echocardiography, etc.), (electronic, in respective programs and devices)
- Study visit dates (in CRF).
- Any additional records made by clinical coordinators or nurses (electronic and/or on paper).
- List of investigators, including initials (electronic and in study folder).

Source data will be available at the study site to prove the integrity of the data collected throughout this study.

12.1.3 Record keeping / archiving

The sponsor retains all data relating to the clinical trial for at least 20 years after completion or premature termination of the clinical trial. The investigator retains all documents necessary for the identification and follow-up of the trial participants and all other original data for at least 20 years after completion or discontinuation of the clinical trial.

12.2 Data management

12.2.1 Data Management System

The data will be collected with the paper-based CRFs and will then be transferred to electronic

datasheets for statistical analysis. The CRFs will be stored in appropriate folders according to the storing rules of all the other essential documents.

12.2.2 Data security, access and back-up

The Access to clinical data of these studies is exclusively limited to the staff of the PH Clinic of the Department of Pulmonology at the University Hospital of Zurich.

The CRFs will be locked away whenever they are not in use and will only be accessible by electronic badge and/or key. Electronically saved data will be stored on external hard drives (e.g. echocardiography data). These data will likewise be stored in a secure location and transferred to the access-limited (access granted only upon authorization by the department) and password-secured network servers at the University Hospital in Zurich, which provide automated periodical backups.

Any data in relation to these studies are strictly confidential and any disclosure to third parties is prohibited. By coding the subjects with their study ID, confidentiality will be warranted.

12.2.3 Analysis and archiving

Once the data are entered, they can directly be extracted from the network of the University Hospital in Zurich. Storage of both on-site physical and electronical data is guaranteed for at least 20 years in secure locations or network servers provided by the University Hospital of Zurich.

12.2.4 Electronic and central data validation

Data will be cross-checked after transfer by a second investigator and thereby validated. Furthermore, graphical and statistical plausibility checks (i.e. range-checking, screening for outliers, etc.) will be implemented to confirm the integrity of the data.

12.3 Monitoring

External monitoring is not required for the risk category A study. Instead, comparable quality control will be organised internally by the sponsor and performed periodically (at a minimum annually) by a designated candidate.

Quality control will encompass:

Project Initiation (prior to study launch: January – March 2026)

- Review of study organisation
- Confirmation of patient information procedures
- Verification of safety management
- Verification of proof of GCP of study staff
- Review of SOPs

Routine Monitoring Visits (Annually: April 2026 – March 2028; *can selectively be performed on a random sample basis*)

- Assessment of study progress
- Source data verification and documentation review
- Process optimisation
- Safety management verification

Close-out Procedures (After end of study: March 2028 (latest))

- Final project and documentation review
- Study drug accountability
- Reporting and archiving.

Insights to any documents related to the study will be provided to the quality control and study related questions will be answered. The participants' data will be kept strictly confidential at any time. In the event of any external monitoring, insight will likewise be provided.

12.4 Audits and Inspections

In case of an audit or an inspection by certified authorities, insight to any documents related to the study will be guaranteed and study related questions would be answered. The participants' data will be kept strictly confidential at any time.

12.5 Confidentiality, Data Protection

Patient data will be kept confidential at any time and permission for insight will be given for monitoring/quality control (12.3.), audits and inspections (12.4). Otherwise, access to the protocol and datasets will solely be given to the investigators, who are able to identify the patients.

12.6 Storage of biological material and related health data

No biological samples will be stored. Any health or study related data will be secured according to clinical standard in the hospital patient database including study-specific data.

13. PUBLICATION AND DISSEMINATION POLICY

The investigators will make an effort to publish the results of the clinical trial in peer-reviewed journals. Sex and gender results will naturally be included. Authorship will be defined by standard authorship criteria. The authority over publication lies with the sponsor-investigator.

The sponsor will enter and publish a summary of the trial results in a public register in accordance with ClinO Art. 65a within one year of completion or premature termination of the trial.

For the purpose of publication in the public register, the sponsor also ensures that a lay summary of the trial results is entered in BASEC within one year of completion or premature termination of the trial. The entry is made at least in the national languages of Switzerland in which the study participants were recruited.

The investigators will provide each study participant with the lay summary of the trial results at the end of the study, directly. The results will be diffused via the PAH patient organization and our website.

14. FUNDING AND SUPPORT

14.1 Funding

All costs of the study will be covered by the sponsor.

14.2 Other Support

This project was submitted to the University of Zurich's career development program "Filling the Gap in March 2025 for funding support of the co-investigator but was declined in November 2025.

15. INSURANCE

The University Hospital of Zurich ensures that insurance is provided (current insurance: Baloise Versicherungen AG, Policy Number 30/4.204.572) to cover any damage (up to a maximum sum of CHF 10'000'000.--) caused throughout this clinical trial including up to 20 years after conclusion/termination of the trial (coverage details are supplied in the dedicated document). The University Hospital of Zurich pledges to renew insurance coverage annually, thus policy Numbers and Insurance Companies may differ and will be updated accordingly. A copy of the certificate is filed in each investigator site file and the trial master file.

Participants are strictly obliged to follow the instructions of the study staff in order to avert any distorted incentives of this insurance coverage. The investigators will be instantly informed in the event of any health problems or other damages during these projects.

Delegates from the insurance can have permission to source data if necessary to judge a damage related to study participation. Confidentiality will be fulfilled at any time within these projects.

16. REFERENCES

ICH: References to literature and data that are relevant to the trial, and that provide background for the trial.

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c. International Conference on Harmonization ICH E8 Guideline: General Considerations for Clinical Trials (https://www.ich.org/page/efficacy-guidelines)
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17. APPENDICES

17.1.1 Documents provided separately

- 1 Cover Letter
- 2 Protocol Synopsis
- 3 Patient Information and Informed Consent Form
- 4a Quality Control Plan
- 5 Case Report Form (CRF)
- 6 Sponsor / Principal Investigator's CV
- 7 Sponsor / Principal Investigator's proof of GCP training
- 8 Details on Infrastructure Suitability and Availability
- 10 Current Insurance Policy Excerpt
- 12 Details of Nature and Scope of Compensation for Participants
- 13 Staff List
- 14 Information on Secure Handling of Material and Data
- 16 Professional Information approved by Swissmedic (Professionelle Fachinformation) for Revatio 20mg
- 16b Product information for dextrose candy (Dextroenergy).
- 18 Proof of Proper Labelling of the Therapeutic Products