CLINICAL TRIAL PROTOCOL

SYNOPSIS

Early Treatment of Borderline Pulmonary Arterial Hypertension Associated with Systemic Sclerosis (SSc-APAH)

A randomized, controlled, double-blind, parallel group, proof-of-concept trial

EDITA

Local Project ID: 2014-05ED

Clinical Trial Code:	*EDITA*
EudraCT No.:	2014-001882-28
Clinical Phase:	IIA (proof of concept)
Version:	3.1 Version, Amendment 2 29.04.2016

1 Protocol Outline

Title

Early Treatment of Borderline Pulmonary Arterial Hypertension Associated with Systemic Sclerosis (SSc-APAH)

Short title: EDITA

Local Project ID: 2014-05ED

Phase

IIA (proof of concept)

Sponsor

Thoraxclinic at the University Hospital Heidelberg represented by its commercial director Roland Fank

Principal Investigator/ Coordinating Investigator

Prof. Dr. med. Ekkehard Grünig
Thoraxclinic at the University of Heidelberg
Centre for pulmonary hypertension
Röntgenstraße 1
69126 Heidelberg

Financing/ Status of the Sponsor

Co-financing by pharmaceutical industry GlaxoSmithKline GmbH

Indication

Clinical phenotype systemic sclerosis-patients with borderline-PAH: mean pulmonary arterial pressure (mPAP) values at rest (between 21-24 mmHg) and/or elevated mPAP during exercise (>30 mmHg, with transpulmonary gradient (TPG) >11 mmHg and pulmonary artery wedge pressure (PAWP) < 15 mmHg at rest and <18 mmHg at exercise).

I27.0 Primary pulmonary hypertension

M34.9 Systemic sclerosis, unspecified, or

M35.8 Other specified systemic involvement of connective tissue

MedDRA (V. 12.0)

Systemic Sclerosis ID 10042953, Level 4

Pulmonary Hypertension 10037400, Level 4

Trial Population

Inclusion Criteria

Male or female SSc patients with borderline - PAH and

1. mPAP 21-24 mmHg, TPG > 11 mmHg, PAWP <15 mmHg and/or
2. Exercise induced elevated mPAP-values >30 mmHg, PAWP <18 mmHg; TPG >15 mmHg, as defined in Saggar et al. (2012) without left heart or severe lung disease or systemic arterial hypertension
3. Adult patients having completed his/her 18th birthday
4. Patients with definite diagnosis of Systemic Sclerosis using the scleroderma criteria of the American Rheumatism Association
5. SSc-disease duration >3 years
6. Able to understand and willing to sign the Informed Consent Form
7. Negative pregnancy test at the start of the trial and appropriate contraception throughout the study for women with child-bearing potential.

Exclusion Criteria

1. Any connective tissue diseases (CTD) other than SSc
2. Pulmonary hypertension (PH) confirmed by right heart catheter (RHC) before enrolment, i.e. mPAP ≥25 mmHg at rest
3. Patients presenting normal mPAP values, i.e. mPAP<21 mmHg at rest, and ≤30 mmHg during exercise, and/or PAWP ≥15 mmHg at rest or ≥18 mmHg during exercise
4. Ongoing or a history of >2 weeks of continued use of therapies that are considered definitive PH treatment: endothelin receptor antagonists (ERA; e.g. bosentan, ambrisentan), phosphodiesterase type 5 inhibitors (PDE5; e.g. sildenafil, tadalafil, vardenafil), prostanoids (e.g. epoprostenol, treprostinil, iloprost, beraprost) and soluble guanylate cyclase stimulator (e.g. Riociguat). Intermittent use of PDE5 inhibitors for male erectile dysfunction is permitted.
5. Except for diuretics and corticosteroids medical treatment should not be expected to change 4 weeks prior inclusion into the study and during the entire 12-week study period.
6. Known intolerance to ambrisentan or one of its excipients
7. Clinically significant anemia (hemoglobin concentration of less than 75% of the lower limit of normal, LLN)
8. Forced vital capacity (FVC) <60%, forced expiratory volume in first second (FEV_1)

<65%

9. Severe interstitial lung disease, idiopathic pulmonary fibrosis
10. Renal insufficiency (glomerular filtration rate [GFR] <60 mL/min/1.73m^2 at least for the last 3 months before inclusion)
11. Baseline values of hepatic aminotransferases (ALT and/or AST) >3 x upper limit of normal (ULN)
12. Systolic blood pressure <85 mmHg;
13. evidence of inadequately treated blood pressure >160/90 mmHg and/or blood pressure during exercise >220/120 mmHg
14. Patients referred with clinically significant overt heart failure
15. Clinically significant fluid retention
16. Previous evidence or diagnosis of clinically relevant left heart disease, i.e. at least one of the following: Previous echocardiography with estimated left ventricular (LV) ejection fraction <50%, previous history of cardiogenic pulmonary edema, increased size of left atrium (>50 mm)
17. Known significant diastolic dysfunction associated with clinical heart failure
18. Known coronary disease or significant valvular heart disease
19. Known congenital heart defects such as single ventricle, transposition, Eisenmenger
20. Known hypertrophic cardiomyopathy or left ventricular hypertrophy (interventricular septum thickness (IVS) or posterior wall thickness (PWD) >1.2 cm)
21. Participation in any clinical drug trial within 4 weeks prior to screening of this study and/or who is scheduled to receive another investigational medicinal product (IMP) during the course of this study
22. Pregnancy or lactation

Objectives

Primary [Objectives/ Endpoints]

1. Determine whether mPAP of SSc patients with borderline-PAH (mPAP 21-24 mmHg, TPG ≥11 mmHg) can be reduced by 3 mm Hg (absolute change baseline vs. 6 months; equals 15%) by treatment with ambrisentan 10 mg/die (may be initiated with 5 mg/die and escalated to 10 mg/die) over 6 months (primary endpoint) compared to baseline and placebo.

Secondary Objectives

2. Determine whether exercise induced elevated mPAP-values (>30 mmHg without left

heart or severe lung disease or systemic arterial hypertension) and further measures of exercise capacity, symptoms and quality of life can be reduced by ambrisentan 10 mg/die over 6 months

3. Analyze if the progression (adverse events, hospitalization, initiation of pulmonary hypertension treatment) of borderline-PAH to manifest PH can be avoided by ambrisentan-treatment (descriptive, observational)
4. Assessment of tolerability and safety

Secondary Endpoints

Analyze if in patients with SSc and borderline-PAP show an improvement by treatment with ambrisentan 10 mg/die over 6 months in:

- 6-Minute-walking test
- Quality of life (QoL, SF-36)
- Echocardiography: right atrial area (RA-area), right ventricular area (RV-area), Tei, Tricuspid Annular Plane Systolic Excursion (TAPSE), systolic pulmonary arterial pressure (sPAP)
- Lung function tests: forced expiratory flow (FEV_1), total lung capacity (TLC), diffusion-limited carbon monoxide (DLCo), DLCo/alveolar volume (VA), forced vital capacity (FVC), forced expiratory volume in one second (FEV_1), residual volume
- Borg Dyspnea Index
- WHO-functional class
- further invasively measured hemodynamic parameters evaluated by RHC: right atrial pressure, pulmonary vascular resistance, cardiac output (CO), cardiac index (CI), PAWP, venous oxygen saturation (SvO2)
- Raynaud-syndrome and skin involvement, assessed by the modified Rodnan-Skin score and Symptoms of Scleroderma (descriptive)

Trial Design

Patients with borderline PAH indicated by borderline mPAP values will be included in this single centre study. This clinical investigation is performed as a Proof-of-Concept (PoC) investigator initiated trial (IIT) using a prospective, randomized, double-blind, parallel group, placebo-controlled, phase IIA clinical study design. On their first visit their medical history will be obtained and physical examination will be conducted. Moreover, an electrocardiogram (ECG), laboratory testing (NT-proBNP, uric acid and other laboratory tests), echocardiography

at rest and right heart catheterization will be carried out. If patients have been identified within the last 6 months before screening investigations by right heart catheterization, the measurements are considered valid as baseline investigations and will not be repeated. If patients fulfill the inclusion criteria and still suffer from borderline mPAP values they will be invited to join the study. The clinical investigations will begin within 28 days. The prospective study will comprise a 6 months study period (180 ±2 weeks) plus the screening phase up to 28 days and a follow-up phase of 30 ±7 days.

Investigational Medicinal Product(s) (IMPs)

IMP: Test treatment

Ambrisentan [Volibris®] once daily starting at 5 mg/die in the beginning of the study. Dosage will be up-titrated to 10 mg/die after 1-4 weeks according to the physician's and the patient's estimation.

Study medication will be provided orally with or without food. Treatment effect will be controlled at each study visit and the dose will be adapted. The patient will take one or two tablets of ambrisentan 5 mg once daily.

IMP: Placebo

Placebo tablets with the same treatment regimen (once daily) as the verum therapy will be provided. One pill a day will be given. Treatment effect will be controlled at each study visit and the sham dose will be adapted. The patient will take one or two tablets once daily.

Sample Size

In this randomized, controlled, double-blind study patients with borderline PAH will be randomized into two groups: one group receiving ambrisentan and one Placebo. The main comparison will be the difference in treatment effect between ambrisentan arm and placebo. The primary endpoint will be the change of mean pulmonary arterial pressure between baseline and after 6 months compared to placebo.

Based on previous data and the inclusion criteria we expect a baseline mPAP of 20 mmHg, a mean reduction of 3 mmHg (equals 15%) with standard deviation of the difference of 2.5 mmHg. To reject the null hypothesis with 90 percent probability if the means of the mPAP differ by at least 3 mmHg (17 vs. 20 mmHg, 15%) a sample of 15 patients in each group is required, according to the two-tailed Student's t-test, with a type I error of 0.05 (two-sided) and equal standard deviations of 2.5 mmHg in both patient groups.

Due to the fact that the borderline–PAP-group is defined by an mPAP of 21-24 mmHg the sample will have a small standard-deviation. The effect of lowering the mPAP in SSc-APAH-patients by 15% has been reached in several studies as in Klinger et al. (2011). In order to cover a possible 20% drop-out rate, we will include 19 patients in each group = 38 patients in total.

The sample size was calculated by means of a two-sided two-sample t-test. Primary efficacy analysis will be performed by an analysis of covariance (ANCOVA) model including baseline scores as covariate, thereby yielding a power advantage over the standard t-test used for sample size calculation. The calculated sample size will thus provide 90% power or more.

Statistical Analysis

General

Descriptive statistics:

All data (demographic and other baseline characteristics, continuous data at each visit and their change to baseline) will be listed and trial summary tables will be provided.

Descriptive statistics will be displayed by treatment and placebo corrected for the active treatment group (arithmetic mean, median, standard deviation, standard error, 95% confidence limits of mean and median, first and third quartiles, minimum, and maximum for quantitative variables). Frequency tables for qualitative data will be provided.

Primary efficacy parameter:

The main parameter is the mPAP after 6 months compared to baseline. The differences will be compared between treatment and placebo group along with baseline mPAP as covariate using a covariance analysis.

Secondary efficacy parameters:

Secondary efficacy analysis comprises hemodynamics, vital signs, electrocardiogram, echocardiography, systemic sclerosis characteristics, laboratory parameters, pulmonary function, 6-minute walking distance, quality of life questionnaire, safety parameters adverse events and concomitant medication.

1.1 Flow Chart/ Trial Schedule

	Randomized; double-blind controlled study including 38 patients with "borderline-PAH"				
Assessment	Screening "borderline-PAH" day –28/-1 Visit 1*	Baseline° day 1* Visit 2	After 3 months/ 90 days ± 2weeks Visit 3	After 6 months/ 180 days ± 2weeks Visit 4*	30±7 days Follow-up by phone
Written Informed Consent, obtained before any study procedure	X				
Check of eligibility criteria	X	X			
Demographics (height)	X				
Medical History	X				
Randomization		X			
Physical Examination	X	X	X	X	
SSc characteristics		X		X	
Modified Rodnan Skin Score and Symptoms of Scleroderma		X		X	
Vital Signs (blood pressure, heart rate, oxygen saturation, body weight)	X	X	X	X	
WHO functional class	X	X	X	X	
Electrocardiogram		X	X	X	
Pulmonary function tests: DLCo, DLCo/VA, FVC, FEV1, TLC, residual volume; blood gas analysis		X		X	
Local lab assessment #	X	X	X	X	
Pregnancy test (serum or urine)	X	X	X	X	
Echocardiography	X	X		X	
Right heart catheterization** (RHC), at rest, during exercise	X			X	
Quality of life Questionnaire SF-36		X		X	
6MWD, Borg Dyspnea Index		X	X	X	
Adverse events (AE)		X	X	X	X
Concomitant medication	X	X	X	X	
Concomitant disease	X	X	X	X	X
Study medication and Diary hand out or check		X	X	X	

° In borderline-PH-patients the screening assessment of PH screening (screening study, accepted by the Ethics committee University of Heidelberg) may be used as baseline examination for the randomized, double-blind part of the study when the screening assessment is not older than 28 days.

* according to hospital practice possible in-hospital stay

** Baseline-RHC may be up to 6 months old at inclusion, continuous ECG, CO and SvO_2 recording during haemodynamic investigations

additional lab assessments for hepatic aminotransferases and haemoglobin will be performed at the patient's general physician for safety reasons, reports will be faxed to the clinical site on a monthly basis