Statistical analysis plan EDITA

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

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1 Objectives

1.1 Trial objectives

Primary [Objectives/ Endpoints]

Determine whether mPAP of SSc patients with borderline-PAH (mPAP 21-24 mmHg, TPG ≥11 mmHg) can be reduced by 3 mmHg (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

1. 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
2. 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)
3. Assessment of tolerability and safety

1.2 Trial design

This is a monocentric, randomized, controlled, double-blind study. Male or female SSc patients with borderline PAH will be randomized into two groups: Ambrisentan group and Placebo group. The primary endpoint will be the change of mean pulmonary arterial pressure between baseline and after 6 months compared to placebo.

2 Analysis of data quality

This analysis will be performed before unblinding the therapy arms.

1. For all variables at baseline, after 3-months and 6-months descriptive statistics mean standard deviation, median, IQR, min max, boxplot inspections of outliers for continuous variables and frequencies for categorical variables. Validation/correction will be performed by queries.

2. Calculation of differences for the parameters mPAP and all secondary endpoints. Descriptive statistics as in 1. for the differences to evaluate plausibility of the data.

3. Control of inclusion and exclusion criteria and withdrawal criteria, definition of patients to be excluded if applicable.

4. Control of laboratory values (and comparison to normal values)

3 Closure of the database and unblinding of treatment groups

1. After all data quality and plausibility checks have been performed and queries haven been answered
2. Database lock will be signed by data management, statisticians, principal investigator and trial coordinator
3. Data Transfer from open clinica to SPSS
4. Unique labeling of all major variables for the statistical Evaluation
5. Data dictionary
6. Merging of the data with the randomization list/group allocation

4 Analysis sets

4.1 Definitions

All patients randomized and treated will be valid for the intention-to-treat analysis population. A randomized patient is valid for the intention-to-treat, if at least one dose of study medication was administered. A patient is valid for per-protocol analysis, if the patient has an adequate hemodynamic measurement at baseline and after 12 weeks or if withdrawn due to lack of efficacy, who has an adequate hemodynamic assessment at any time post-baseline up to 12 weeks, and shows no major protocol deviation.

Major protocol deviations are:

1. Patients who do not meet the inclusion criteria
2. Administration of study medication not according to protocol (e.g. compliance less than 80% or greater 120%)

The above specifications of the analysis populations are in accordance with the recommendations given in the ICH-E9 Guideline “Note for guidance on statistical principles for clinical trials”.

The safety set comprises all patients who have been included in the study.

4.2 Application

Efficacy analyses will be performed for the intention-to-treat analysis set. A sensitivity analysis for the primary endpoint will be performed with the per-protocol set.
Safety analyses will be performed with the safety set.

5 Trial centres

Zentrum für pulmonale Hypertonie, Thoraxklinik am Universitätsklinikum Heidelberg

6 Analysis variables

6.1 Demography and baseline characteristics

Age, height, weight, systemic sclerosis characteristics, duration of systemic sclerosis, concomitant disease, concomitant medication
And all efficacy variables at baseline

6.2 Primary variable

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

6.3 Secondary variables

6.3.1 Efficacy

(1) Analyze if in patients with SSc and borderline-PAP an improvement by treatment with ambrisentan 10 mg/die over 6 months is show in:
(2) 6-Minute-walking test
(3) Echocardiography: right atrial area (RA-area), right ventricular area (RV-area), Tei, Tricuspid Annular Plane Systolic Excursion (TAPSE), systolic pulmonary arterial pressure (sPAP), right ventricular pump function, left ventricular pump function,

(4) 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

(5) Borg Dyspnea Index

(6) WHO-functional class

(7) further invasively measured hemodynamic parameters evaluated by RHC: right atrial pressure, pulmonary vascular resistance, cardiac output (CO), cardiac index (CI), PAWP, venous oxygen saturation (SvO_2) at rest and during exercise

(8) Raynaud-syndrome and skin involvement, assessed by the modified Rodnan-Skin score and Symptoms of Scleroderma (descriptive)

(9) WHO functional class

(10) Laboratory parameters (NT-proBNP)

6.3.2 Safety/Tolerability

Adverse events, Laboratory: hemoglobin, hematocrit, AST, ALT, bilirubin, CRP, sodium, urea, creatinine, clearance, NT-proBNP

Vital signs, hospitalisations, time point from baseline and duration, Hemodynamics: Cardiac Output, venous oxygen saturation (during RHC)

6.3.3 Quality of life

Quality of life (QoL, SF-36); Two summation scores: Mental component score, Physical component score; 8 subscales: vitality, physical functioning, bodily pain, general health perceptions, physical role functioning, emotional role functioning, social role functioning, mental health.

7 Handling of missing values and outliers

7.1 Missing values

Variables with more than 20% missing values will be excluded. For all others, a complete case data analysis for each variable will be performed. No imputation method will be applied.

7.2 Outliers

Definition: outliers and extreme values (according to boxplots)

The primary and all secondary efficacy parameters and their difference between baseline and 6 month visit will be analysed whether there are outliers or extreme values in the respective medication group. Outliers are defined as values that are larger than Q75+1.5*IQR or lower than Q25-1.5*IQR; extreme Values are defined as values that are larger than Q75+3*IQR or lower than Q25-3*IQR.

8 Statistical analyses / methods

8.1 Subject disposition

Systemic sclerosis severity (modified Rodnan Skin score; disease duration; type of systemic sclerosis; systemic sclerosis characteristics including presence of digital ulcera, calcinosis, dysphagia, teleangiectasia, Raynaud phenomenon, joint pain), hemodynamics at baseline (mPAP at rest and during exercise, achieved workload, cardiac index and cardiac output) and WHO-FC will be analyzed descriptively within the therapy groups and compared. Changes during the study will be analysed descriptively.

8.2 Demography and baseline characteristics

All variables (demographic and other baseline characteristics, continuous data at each visit and their change to baseline) will be characterized by arithmetic mean, median, standard deviation, standard error, 95% confidence limits of mean, median, first and third quartiles, minimum, and maximum for quantitative variables. Frequency tables for qualitative data will be provided.

8.3 Prior or concomitant medication and diseases

Frequencies by organ system and duration, difference between therapy groups.

8.4 Exposition to treatment/Compliance

Frequencies and duration of intake or application, difference between treatment groups will be analysed. A compliance between 80-120% will be defined as target level.

8.5 Efficacy Analysis primary 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, if the assumptions for a covariance analysis are fulfilled. Otherwise the individual differences of baseline mPAP and 6 months mPAP will be compared between therapy groups by robust comparisons of means as implemented in JMP14.

8.6 Analysis secondary parameters

No subgroup analyses and interim analyses planned.

8.6.1 Efficacy

Secondary efficacy analysis comprises hemodynamics, vital signs, electrocardiogram, echocardiography, systemic sclerosis characteristics, laboratory parameters, pulmonary function, 6-minute walking distance, quality of life scales. For continuous variables the therapy groups will be compared with the same methods as for the primary parameter.

WHO functional class is supposed to either remain the same, improve by one or two categories, or deteriorate by one category in most cases. A change score (baseline minus end of study) will be calculated, which could go from -3 (class 4 at baseline and class 1 at end of study) to +1 (class 3 at baseline and class 4 at end of study). This will be analyzed using the Wilcoxon test.

For categorical variables Mc Nemar Tests will be applied.

8.6.2 Safety/Tolerability

The safety analysis will be performed in the population valid for safety. All tabulations will be descriptive only. Tables will be produced for drug-related treatment-emergent adverse events and serious adverse events.

Mortality in the 6 month period of the study will be summarized descriptively. Any deaths in the study period will be listed, with day of death relative to start and stop of study drug and cause of death. Vital signs will be summarized by visit and treatment group.

8.6.2.1 Adverse events

Frequency tables of adverse events with classification of system organ class according to MedDRA classification will be provided. Adverse events will be provided according to suspected and no suspected relation to the study medication. Serious adverse events will be listed separately.

Hospitalisations due to worsening or adverse events will be listed.

8.6.2.2 Laboratory parameters

For the clinical parameters Laboratory: hemoglobin, hematocrit, AST, ALT, bilirubin, CRP, sodium, urea, creatinine, clearance, NT-proBNP arithmetic mean, median, standard deviation, standard error, median, first and third quartiles, minimum, and maximum for quantitative variables) for baseline and 6 month time points for each therapy group separately as well as frequency tables with number of values outside their limits of normal (or 3 x upper limit of normal for hepatic transaminases) will be displayed.

8.6.2.3 Vital signs

For diastolic and systolic blood pressure, heart rate and weight we will list arithmetic mean, median, standard deviation, standard error, first and third quartiles, minimum, and maximum for quantitative variables for baseline and 6 month time point for each therapy group.

Furthermore, frequency tables of pathologic findings in the physical examination will be displayed.

8.6.3 Quality of life

Quality of life scales (QoL, SF-36) are secondary efficacy parameters. Their change from baseline to 6 months will be compared with the same methods as for the primary parameter.

9 Deviations from the protocol

Description and explanation of deviations regarding withdrawal criteria, in- and exclusion criteria, adherence to time window and treatment compliance will be provided.

Major protocol deviations are:

1. Patients who do not meet the inclusion criteria

2. Administration of study medication not according to protocol (e.g. compliance less than 80% or greater 120%); Discrepancies of study medication intake are noted as comments in the CRF.

10 Interpretation of results

Effect size estimation and description

Clinical worsening on the individual level is defined as 15% higher mPAP values at 6 months compared to baseline. Clinically significant improvement is defined as 15% lower mPAP values at 6 months compared to baseline.

Scatterplots of baseline versus 6-month measurements will be plotted with a linear fit for therapy. In case of outliers or extreme values robust fits will be used. Frequency tables with patients who have a clinically relevant worsening/improvement after 6 months of therapy will be displayed.

Descriptive analysis of differences of secondary parameters.

Secondary efficacy parameters will be screened whether they support the results of the primary endpoint or not.

11 Software

SPSS V24, SAS JMP 14

12 References

https://www.jmp.com/en_us/support/online-help.html
(last queried 17.7.2018)
https://www-01.ibm.com/support/docview.wss?uid=swg27047033
(last queried 17.7.2018)

13 Appendices

13.1 Reference ranges of laboratory parameters

	male	female
Hemoglobin	♂ 0-3 Day(s) 14.5 - 22.5 g/dl	♀ 0-3 Day(s) 14.5 - 22.5 g/dl
	♂ 4-7 Day(s) 13.5 - 21.5 g/dl	♀ 4-7 Day(s) 13.5 - 21.5 g/dl
	♂ 8-14 Day(s) 14 - 20 g/dl	♀ 8-14 Day(s) 14 - 20 g/dl

	♂ 15-30 Day(s) 15 - 20 g/dl	♀ 15-30 Day(s) 15 - 20 g/dl
	♂ 31-182 Day(s) 9.5 - 13.5 g/dl	♀ 31-182 Day(s) 9.5 - 13.5 g/dl
	♂ 183-365 Day(s) 11 - 16 g/dl	♀ 183-365 Day(s) 11.0 - 16 g/dl
	♂ 1-6 Year(s) 11 - 14.5 g/dl	♀ 1-6 Year(s) 11 - 14.5 g/dl
	♂ 7-12 Year(s) 11.5 - 15 g/dl	♀ 7-12 Year(s) 11.5 - 15 g/dl
	♂ 13-18 Year(s) 12 - 16 g/dl	♀ 13-18 Year(s) 12 - 16 g/dl
	♂ 19-99 Year(s) 13 - 17 g/dl	♀ 19-99 Year(s) 12 - 15 g/dl
	male	**female**
Hematocrite	♂ 0-3 Day(s) 0.45 - 0.67 l/l	♀ 0-3 Day(s) 0.45 - 0.67 l/l
	♂ 4-7 Day(s) 0.42 - 0.66 l/l	♀ 4-7 Day(s) 0.42 - 0.66 l/l
	♂ 8-14 Day(s) 0.39 - 0.63 l/l	♀ 8-14 Day(s) 0.39 - 0.63 l/l
	♂ 15-30 Day(s) 0.45 - 0.64 l/l	♀ 15-30 Day(s) 0.45 - 0.64 l/l
	♂ 31-60 Day(s) 0.28 - 0.42 l/l	♀ 31-60 Day(s) 0.28 - 0.42 l/l
	♂ 61-365 Day(s) 0.35 - 0.44 l/l	♀ 61-365 Day(s) 0.35 - 0.44 l/l
	♂ 1-2 Year(s) 0.33 - 0.39 l/l	♀ 1-2 Year(s) 0.33 - 0.39 l/l
	♂ 3-6 Year(s) 0.31 - 0.37 l/l	♀ 3-6 Year(s) 0.31 - 0.37 l/l
	♂ 7-12 Year(s) 0.33 - 0.40 l/l	♀ 7-12 Year(s) 0.33 - 0.40 l/l
	♂ 13-99 Year(s) 0.38 - 0.52 l/l	♀ 13-99 Year(s) 0.36 - 0.47 l/l
	male	**female**
Thrombocytes	♂ 0-10 Day(s) 140 - 320 /nl	♀ 0-10 Day(s) 140 - 320 /nl
	♂ 11-30 Day(s) 150 - 380 /nl	♀ 11-30 Day(s) 150 - 380 /nl
	♂ 31-365 Day(s) 200 - 480 /nl	♀ 31-365 Day(s) 200 - 480 /nl
	♂ 1-10 Year(s) 180 - 530 /nl	♀ 1-10 Year(s) 180 - 530 /nl
	♂ 11-199 Year(s) 150 - 440 /nl	♀ 11-199 Year(s) 150 - 440 /nl
	male	**female**
Creatinine	♂ 0-1 Day(s) 0.4 - 1.3 mg/dl	♀ 0-1 Day(s) 0.4 - 1.3 mg/dl
	♂ 2-7 Day(s) 0.16 - 1.0 mg/dl	♀ 2-7 Day(s) 0.16 - 1.0 mg/dl
	♂ 8-30 Day(s) 0.1 - 0.6 mg/dl	♀ 8-30 Day(s) 0.1 - 0.6 mg/dl
	♂ 31-365 Day(s) 0.1 - 0.65 mg/dl	♀ 31-365 Day(s) 0.1 - 0.65 mg/dl
	♂ 1-6 Year(s) 0.3 - 0.8 mg/dl	♀ 1-6 Year(s) 0.3 - 0.8 mg/dl
	♂ 7-13 Year(s) 0.3 - 1.0 mg/dl	♀ 7-13 Year(s) 0.3 - 1.0 mg/dl
	♂ 14-17 Year(s) 0.3 - 1.2 mg/dl	♀ 14-17 Year(s) 0.3 - 1.2 mg/dl
	♂ 18-60 Year(s) 0.6 - 1.2 mg/dl	♀ 18-60 Year(s) 0.5 - 0.9 mg/dl
	♂ 61-70 Year(s) 0.6 - 1.3 mg/dl	♀ 61-70 Year(s) 0.5 - 1.0 mg/dl
	♂ 71-80 Year(s) 0.6 - 1.4 mg/dl	♀ 71-80 Year(s) 0.5 - 1.1 mg/dl
	♂ 81-199 Year(s) 0.6 - 1.7 mg/dl	♀ 81-199 Year(s) 0.5 - 1.4 mg/dl
	male	**female**
Potassium	♂ 0-30 Day(s) 3.6 - 6.0 mmol/l	♀ 0-30 Day(s) 3.6 - 6.0 mmol/l
	♂ 31-365 Day(s) 3.5 - 5.7 mmol/l	♀ 31-365 Day(s) 3.5 - 5.7 mmol/l
	♂ 1-17 Year(s) 3.5 - 4.8 mmol/l	♀ 1-17 Year(s) 3.5 - 4.8 mmol/l
	♂ 18-40 Year(s) 3.4 - 4.6 mmol/l	♀ 18-40 Year(s) 3.4 - 4.6 mmol/l
	♂ 41-60 Year(s) 3.4 - 4.8 mmol/l	♀ 41-60 Year(s) 3.4 - 4.8 mmol/l
	♂ 61-199 Year(s) 3.4 - 5.0 mmol/l	♀ 61-199 Year(s) 3.4 - 5.0 mmol/l
	male	**female**
SGOT/ASAT	♂ 0-180 Day(s) <74 U/l	♀ 0-180 Day(s) <74 U/l

Serum-Glutamate-Oxalacetate-Transaminase	♂ 181-365 Day(s) <52 U/l	♀ 181-365 Day(s) <52 U/l
	♂ 1-5 Year(s) <43 U/l	♀ 1-5 Year(s) <43 U/l
	♂ 6-14 Year(s) <39 U/l	♀ 6-14 Year(s) <39 U/l
	♂ 15-17 Year(s) <50 U/l	♀ 15-17 Year(s) <35 U/l
	♂ 18-199 Year(s) <46 U/l	♀ 18-199 Year(s) <37 U/l
	male	**female**
SGPT/ALT Serum-Glutamate-Pyruvate-Transaminase	♂ 0-180 Day(s) <60 U/l	♀ 0-180 Day(s) <60 U/l
	♂ 181-365 Day(s) <43 U/l	♀ 181-365 Day(s) <43 U/l
	♂ 1-199 Year(s) <50 U/l	♀ 1-199 Year(s) <35 U/l
	male	**female**
LDH Lactate dehydrogenase	♂ 0-30 Day(s) <780 U/l	♀ 0-30 Day(s) <780 U/l
	♂ 31-365 Day(s) <416 U/l	♀ 31-365 Day(s) <416 U/l
	♂ 1-5 Year(s) <364 U/l	♀ 1-5 Year(s) <364 U/l
	♂ 6-14 Year(s) <312 U/l	♀ 6-14 Year(s) <312 U/l
	♂ 15-17 Year(s) <248 U/l	♀ 15-17 Year(s) <248 U/l
	♂ 18-40 Year(s) <316 U/l	♀ 18-40 Year(s) <264 U/l
	♂ 41-60 Year(s) <317 U/l	♀ 41-60 Year(s) <308 U/l
	♂ 61-199 Year(s) <342 U/l	♀ 61-199 Year(s) <301 U/l
	male	**female**
CK Creatinkinase	♂ 0-3 Day(s) <777 U/l	♀ 0-3 Day(s) <777 U/l
	♂ 4-10 Day(s) <420 U/l	♀ 4-10 Day(s) <420 U/l
	♂ 11-365 Day(s) <286 U/l	♀ 11-365 Day(s) <286 U/l
	♂ 1-199 Year(s) <190 U/l	♀ 1-199 Year(s) <170 U/l
	male	**female**
CRP	♂ 0- Year(s) <5 mg/l	♀ 0- Year(s) <5 mg/l
	male	**female**
NTproBNP	♂ 0-70 Year(s) <125 ng/l	♀ 0-70 Year(s) <125 ng/l
	♂ 71- Year(s) <450 ng/l	♀ 71- Year(s) <450 ng/l
ß-HCG		negative