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CONFIDENTIAL

STATISTICAL ANALYSIS PLAN

A multi-center, prospective, randomized, double-blind study to assess the impact of sacubitril/valsartan vs. enalapril on daily physical activity using a wrist worn actigraphy device in adult chronic heart failure patients

Sponsor Study Code: CLCZ696B3301 / NCT02900378

[redacted]

Sponsor	Novartis
Product/Compound	Sacubitril/valsartan (LCZ696)
Phase of the study	IIIB
Author	[redacted], BSc, [redacted]
Company	[redacted]
Address	[redacted]
Telephone number	[redacted]
Version	Final 4
Date	12 DEC 2018

SIGNATURES

Sponsor Study code: CLCZ696B3301

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Add time to all dates if on the same day as unblinding.

Reviewing Statistician
Name, academic level, title: [redacted], BSc, [redacted]
Company [redacted]

Signature: _____ Date/time (xxxx-xxx-xx): _____

Sponsor Approval

Name, academic level, title: Dr. [redacted]
Company Novartis

Signature: _____ Date/time (xxxx-xxx-xx): _____

Name, academic level, title: [redacted]
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ABBREVIATIONS

AE	Adverse Event
CI	Confidence Interval
CRF	Case Report Form
CSR	Clinical study report
ECG	Electrocardiogram
EMA	European Medicines Agency
FAS	Full Analysis Set
H_0	Null hyphotesis
H_1	Alternative hyphotesis
HF	Heart failure
HFrEF	Heart failure with reduced ejection fraction
HFpEF	HF with preserved ejection fraction
HFmrEF	HF with mid-range ejection fraction
ITT	Intention to Treat
IS	Interdaily Stability
IV	Interdaily Variability
LOCF	Last observation carried forward
LPLV	Last patient last visit
M6min	Actigraphy-based measure of the peak six minutes of daytime physical activity
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple Imputation
MSE	Mean square error
NYHA	New York Heart Association
NCPRA	Non Parametric Circadian Rhythm Analysis
PP	Per Protocol
PSW	Premature Study Withdrawal
Q1	Percentile of 25%
Q3	Percentile of 75%
QoL	Quality of Life
RS	Randomized Set
SAP	Statistical Analysis Plan
SAE	Serious adverse events
SD	Standard deviation
SE	Standard error

SMQs	Standard MedDRA Queries
SOC	System Organ Class
TEAE	Treatment-emergent adverse events
WHO	World Health Organization
6MWT	6-Minutes walking test

1 INTRODUCTION

This Statistical Analysis Plan (SAP) is based on Clinical Study Protocol (CLCZ696B3301) Version 04, dated September 11, 2018.

This document describes the planned statistical methods for all safety and efficacy analyses which will be used in the phase IIIb clinical trial CLCZ696B3301.

The purpose of this randomized, actively controlled, double-blind study with prospective data collection is to assess differences between sacubitril/valsartan versus enalapril in distance walked in a 6 minute walk test (6MWT) and increasing non-sedentary daytime physical activity in HFrEF patients. To this end, the 6MWT will be performed before the patients are randomized to any of the treatments and at 12 weeks of randomized treatment whereas physical activity will be continuously measured by means of a wrist-worn accelerometry device from 2 weeks before until 12 weeks after start of study therapy (sacubitril/valsartan or enalapril).

The statistical analyses to be performed in this study were originally specified in the clinical study protocol. Further details of the planned statistical analysis are provided in this statistical analysis plan (SAP) that will be finalised prior to closing the data base. A summary of the contents will also be presented in the clinical study report (CSR).

Please refer to the following document:

Clinical Trial Protocol CLCZ696B3301 Version 04, dated September 11, 2018

2 STUDY OBJECTIVES

Primary objectives

- To elucidate the change in physical activity as assessed by the distance walked in meters during the 6-minute walking test between baseline and 12 weeks of study drug treatment in sacubitril/valsartan vs. enalapril patients.
- To assess changes in daily non-sedentary daytime activity between baseline and after 12 weeks of treatment in sacubitril/valsartan vs. enalapril treated patients.

Secondary objectives

- To compare the proportion of patients with improved performance (≥30m) in the 6-minute walking test at week 12 between sacubitril/valsartan vs. enalapril treated patients.
- To demonstrate that sacubitril/valsartan is superior in improving exercise capacity as assessed by the six-minute walk test (6MWT) at week 12 in a subset of patients with baseline six-minute walk distance equal to or less than 300 meters
- To demonstrate that sacubitril/valsartan is superior in improving exercise capacity as assessed by the six-minute walk test (6MWT) at week 12 in the patients with baseline six-minute walk distance between 100-450 meters.
- To assess changes from baseline (week 0) in exercise capacity assessed by means of the 6-minute walking test at weeks 4, 8 and 12

- To compare the effects of sacubitril/valsartan vs. enalapril on patients' symptom progression by means of the Patient Global Assessment (PGA) questionnaire at week 4, week 8 and week 12.
- To assess dynamics of changes from baseline in daily non-sedentary daytime physical activity in sacubitril/valsartan vs. enalapril treated patients in weekly and two-weekly intervals.
- To assess changes from baseline in mean daily non-sedentary daytime physical activity classified by its intensity for sacubitril/valsartan vs. enalapril treated patients after week 4, week 8 and week12.
- To assess the difference in non-sedentary daytime physical activity between sacubitril/valsartan vs. enalapril treated patients during the treatment period (weeks 0 to 12).
- To assess changes from baseline on M6min (an actigraphy-based measure of the peak six minutes of daytime physical activity) in sacubitril/valsartan vs. enalapril treated patients after week 4; week 8 and week 12.

3 EFFICACY AND SAFETY ENDPOINTS

3.1 Primary Efficacy Endpoint

Change in distance walked in meters during the 6-minute walking test between baseline and 'end of study'.

Change in mean daily non-sedentary daytime activity between baseline and 'end of study'.

3.2 Secondary Efficacy Endpoints

The secondary efficacy variables are the following:

- 6-minute walking test, proportion of patients with improved performance (≥ 30 m) from baseline (week 0) at week 12
- 6-minute walking test, proportion of patients with improved performance (≥ 30 m) from baseline (week 0) at week 12 in a subset of patients with baseline six-minute walk distance equal to or less than 300 meters
- 6-minute walking test, proportion of patients with improved performance (≥ 30 m) from baseline (week 0) at week 12 in a subset of patients with baseline six-minute walk distance between 100-450 meters.
- 6-minute walking test, changes from baseline (week 0) at weeks 4, 8 and 12
- Proportion of patients who show increased levels (≥ 10% increase) of non-sedentary daytime physical activity at week 12 compared to baseline
- PGA score at week 4, week 8 and week 12.
- Proportion of patients with improved symptoms of HF as assessed by PGA
- Change from baseline in mean daily non-sedentary daytime activity in weekly and two-weekly intervals
- Proportion of patients at weekly and two-weekly intervals who show increased levels (≥ 10% increase) of mean daily non-sedentary daytime physical activity compared to baseline
- Change from baseline in mean daily light and moderate-to-vigorous non-sedentary daytime physical activity between baseline and different time points under treatment.
- Total weekly time spent in non-sedentary daytime physical activity.
- Total weekly time spent in light non-sedentary daytime physical activity.
- Total weekly time spent in moderate-to-vigorous non-sedentary daytime physical activity
- Change from baseline in M6min (actigraphy-based measure of the peak six minutes of daytime physical activity).
- Proportion of patients with increased M6min compared to baseline at week 4, week 8 and week 12.

[redacted]

3.4 Safety Endpoints

The following safety variables will be measured:

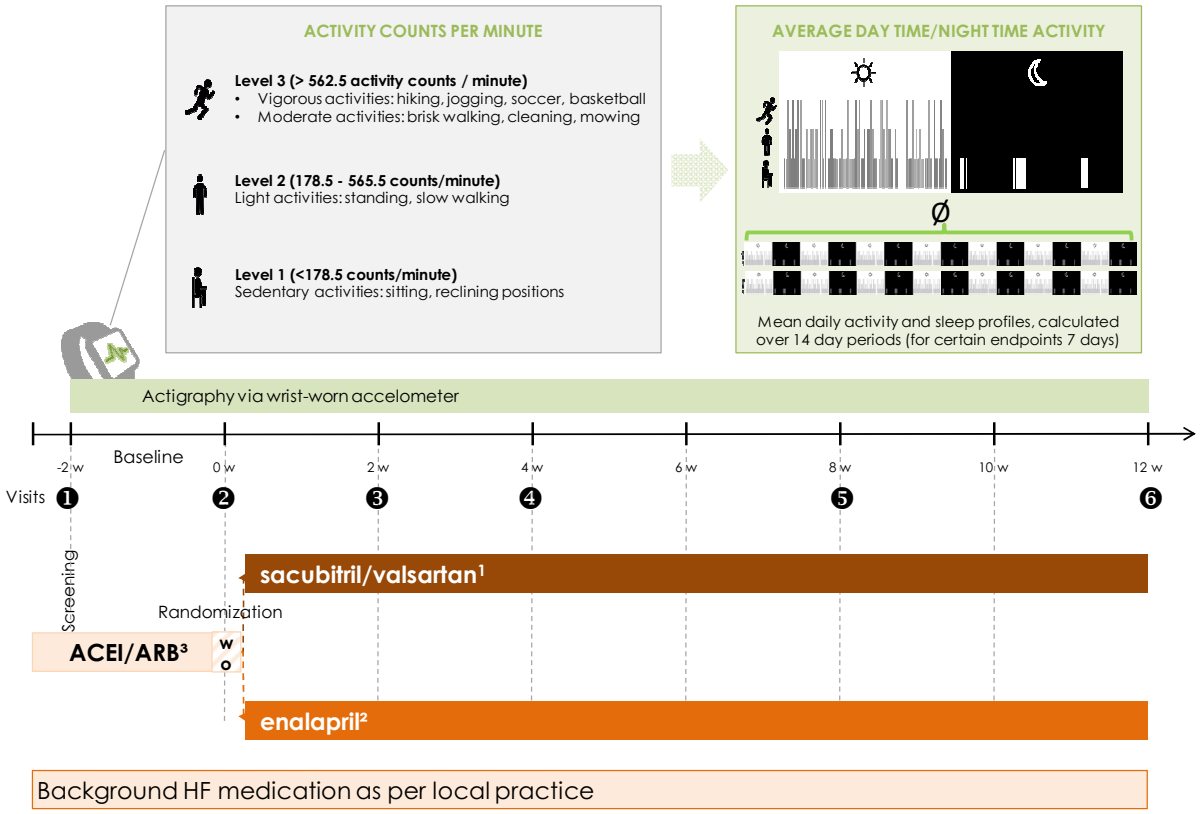
- All AEs, including treatment-emergent adverse events (TEAEs)
- Laboratory data
- Vital Signs
- Treatment exposure and treatment compliance
- Prior and concomittant drug/non-drug therapies
- Physical examination
- Diagnostic evaluations
- Pregnancy and assessment fertility

4 OVERALL STUDY DESIGN

4.1 Overview of Study Design

This is an international (European), randomized, actively controlled, double-blind, double-dummy, interventional study with prospective data collection. The study comprises 6 visits over 14 weeks. Adult patients with symptomatic HFrEF (NYHA classes II or III/IV at a 1:1 ratio) managed in an ambulatory setting (i.e. by primary care physicians, office based cardiologists, HF outpatient clinics) will be randomized in a 1:1 allocation to receive sacubitril/valsartan or enalapril during the double-blind period. Actigraphy will be performed during the entire duration of the study by means of a wrist-worn accelerometry device; the device will be worn continuously for two weeks prior to randomization in order to obtain an individual baseline for each patient, and throughout the treatment period of the study (12 weeks). Figure 4-1 depicts the study design along with the treatment and visit schedule.

Figure 4-1 Study design



[1-2] sacubitril/valsartan or enalapril (double-blind study drugs) will be given at dose levels (up-titration) depending on pre-study ACEI/ARB doses.

[3]Pre-study ACEI and/or ARB are replaced by study medication after Visit 2. Therefore washout period (WO) of 36 hours is required; it should start 12 hours before Visit 2 (randomization); the first study treatment intake should be 24 hours after Visit 2. All other HF background and CV medications (e.g. beta blockers, MRAs etc.) and symptomatic treatment (e.g. diuretics) the patient has been taking should remain unchanged throughout the study, if possible and medically justified in the judgement of the investigator.

"Background HF medication per local practice": patients must be on stable HF treatment regimen for at least 4 weeks prior Visit 1. After Visit 1, patients shall retain their pre-study HF treatment for another 2 weeks (week -2 to week 0) for baseline actigraphy recording.

4.2 Determination of Sample Size

There are no published data on a possible effect of a drug intervention on physical activity as measured by accelerometer in HFrEF patients. However, Alosco and colleagues observed patients with HF over a period of 12 weeks and reported activity levels at baseline and after 12 months using a similar accelerometry device (Alosco, Spitznagel et al. 2015). The mean activity time in light intensity was 188 min/day (SD = 56) at baseline and 183 min/day (SD = 58) after 12 weeks. The corresponding values for activity in moderate to vigorous intensity were 46 min/day (SD = 35) at baseline and 41 min/day (SD = 30) after 12 weeks. From these data an average of 234 min/day at baseline and 224 min/day after 12 weeks can be concluded for the non-sedentary daily activity time. The observed standard deviations for sedentary daily activity time were 76 min/day (baseline) and 63 min/day (month 12), respectively. From these values the standard deviation for non-sedentary activity time (which is approximately the same as for sedentary activity time) is estimated as SD = 70 min/day for both time points.

For the present study we assume a mean baseline value of 200 to 230 min/day for both treatment groups. If treatment with sacubitril/valsartan leads to an improvement which is at least 20 min/day higher than the changes under enalapril, this is considered as clinically relevant.

The standard deviation for the changes from baseline is expected not to be larger than the standard deviations at the two respective visits (corresponding to a correlation coefficient of 0.5 between the values at baseline and at week 12 to 14). Accordingly, the standard deviation for the primary endpoint is estimated as SD = 70 min/day for both treatment groups.

Planning a two-sided test (using the t-test model with α = 5% and 90% power at Δ = 20 min/day) results in 259 patients per treatment group (nQuery Advisor® 7.0). In order to account for non-eligible patients, it is planned to recruit 300 patients per treatment arm, i.e. 600 patients in total.

With respect to other primary endpoint "change in 6-minute walk test between baseline and weeks 4, 8 and 12week 12", the following sample size considerations apply: From Täger et al. we deduce a minimal important difference of 35 meters at week 12 and a standard deviation of 114 meters (Tager, Hanholz et al. 2014). Planning a two-sided test with α = 0.05 and 90% power for a group difference of 35 meters leads to a sample size of 224 patients per group, which is covered by the planned patient numbers.

After defining the primary hypotheses H1 and H2, to control the familywise error rate at level 5%, the Hochberg procedure will be used to test the primary hypotheses. It will reject both H1 and H2, if both of them are significant at level 5% simultaneously. Otherwise, it will reject H1 if it is significant at level α/2, or reject H2 if it is significant at level α/2.

Table 9-1 Power of the study considering both the end-points – Considering 259 subjects in each arm

Correlation between the two end-points	Power to reject H1	Power to reject H2	Power to reject any of H1 and H2	Power to reject both of H1 and H2
0	89.7%	93%	98.5%	84.4%
0.2	89.5%	93%	97.6%	85%
0.4	89.4%	93%	96.5%	85.7%
0.5	89.3%	93%	96%	86%
For power calculations, H1 is based on accelerometry data end-point while H2 is based on the 6 minutes walking test end-point.				

Table** Error! No text of specified style in document.**-2 Power of the study considering both the end-points – Considering 300 subjects in each arm

Correlation between the two end-points	Power to reject H1	Power to reject H2	Power to reject any of H1 and H2	Power to reject both of H1 and H2
0	93.6%	96.2%	99.4%	90.4%
0.2	93.5%	96%	99%	90.6%

5 DATA SETS TO BE ANALYSED

The following analysis sets will be used for the statistical analysis and presentation of data:

The screen set (SCR) comprises all patients who have signed the informed consent.

The Randomized Set (RS) consist of all patients who had been randomized in the study.

The safety data set (SAF) consists of all patients who have received the study medication at least once. Safety analyses will be performed based on the SAF set, and according to the treatment received.

The full analysis set (FAS) comprises all patients of the safety data set who provide the baseline value and any post-baseline value of at least one primary endpoint (6-minute walking test or daily non-sedentary daytime activity).

The per-protocol (PP) data set includes all patients of the FAS who do not have any major deviations from the protocol. Such deviations will be defined in the Data Validation Plan or similar document and in the protocol of the blind data review without knowledge of the treatment group assignment. Patients with more than 12 days between last dose administration date and 6MWT date at visit 6 will be excluded from the per-protocol (PP).

Efficacy analyses will be conducted based on FAS and PP, and according to the treatment patients were randomized to.

6 STATISTICAL AND ANALYTICAL PLANS

The planned tables and listings are presented in Appendix 1.

6.1 Changes in the Planned Analyses

Following sleep parameters are not possible to be collected as defined in protocol

- Mean daily sleep efficiency
- Mean daily time in bed
- Actual sleep time
- Actual wake time
- Sleep latency.
- Mean daily sleep fragmentation, defined as the sum percent mobile time and percent immobile bouts of ≤ 1 min duration

In order to give more information about the actigraphy data and the evolution of the patients during the study, new variables (Non Parametric Circadian Rhythm Analysis (NPCRA)) will be add to the analysis.

Non Parametric Circadian Rhythm Analysis (NPCRA): Long-term recordings of activity levels show a rhythmic pattern with alternating high levels of activity during the day and low levels of activity during the night. Such alternating patterns are known as circadian rhythms, from the Latin words 'circa' (approximately) and 'dies' (day). These rhythms are not only present in activity levels but also in hormone levels, body temperature and virtually all measurable biological events, including molecular, physiological, behavioral and cognitive phenomena.

The specific characteristics of circadian rhythms may be of interest to researchers and clinicians, and thus need to be quantified. Many circadian rhythms resemble a cosine wave, and indeed there is a long tradition in circadian rhythm research to fit a cosine curve to the data, and to use the mesor (mean), amplitude and phase of the fitted curve as variables of interest. One may for example be interested whether a patient group differs from a control group on their average mesor, amplitude or phase. The method is known as Cosinor-analysis.

Activity data, however, seldom resemble a cosine wave, and it is consequently not appropriate to apply Cosinor-analysis in order to obtain valid parameters describing the rhythms. Therefore, a number of alternative quantification methods have been developed. These methods do not suppose the rhythm to have a cosine-like shape. Details on the mathematics and usefulness of the measures can be found in e.g. (Van Someren et al., 1996; Van Someren et al., 1997a; Van Someren et al., 1997b; Van Someren et al., 1998; Van Someren et al., 1999).

NPCRA Variables – Interdaily Stability (IS)

A first nonparametric variable is the Interdaily Stability (IS). This variable quantifies the degree of resemblance between the activity patterns on individual days. If, for example, a subject has a very rigid schedule of getting up in the morning every day at the same time, and shows activity and rest periods every day at the same time, this will result in a high Interdaily Stability. The measure theoretically ranges from 0 to 1, and may typically be about 0.6. A higher value indicates a more stable rhythm. The variable has shown to be sensitive to rhythm changes in Alzheimer's dementia: whereas normal human aging is associated with rather regular or even rigid daily activity schedules, demented elderly may show very different profiles from day to day.

NPCRA Variables – Intradaily Variability (IV)

Another nonparametric variable is the Intradaily Variability (IV). This variable quantifies the fragmentation of periods of rest (or sleep) and activity (or wakefulness). Healthy subjects usually show one prolonged activity period and one prolonged rest period in every 24-hour cycle. Under certain conditions, as high age and Alzheimer's dementia, the periods of rest and activity may become shorter, or fragmented, for example due to naps during the day and periods of nocturnal restlessness. The measure theoretically ranges from 0 to 2, with higher values indicating a more fragmented rhythm, and typically is below 1.

NPCRA Variables – L5 and M10

As mentioned before, it is not appropriate to fit a cosine wave to activity data. However, one may still want to have an indication of the trough level, peak level, amplitude, and phase of the rhythm. Useful nonparametric variables have been developed in order to quantify these rhythm phenomena. They are all based on an average 24-hour curve, calculated by overlaying all available 24-hour periods. In this 24-hour average curve, the sequence of the five least active hours is denoted 'L5'. The average activity during these five hours gives an indication of the trough or nadir of the rhythm, i.e. how restful and regular the rest (sleep) periods are. The time of onset of the sequence marks the phase of the onset of the most restful five hours.

In a similar way, the sequence of the ten most active hours is denoted 'M10'. The average activity during these ten hours gives an indication the peak of the rhythm, i.e. of how active and regular the activity (wake) periods are. The time of onset of the sequence marks the phase of the onset of the most active ten hours.

NPCRA Variables – Amplitude

The difference between the average activity level during M10 and the average activity level during L5 gives an indication of the amplitude of the rhythm, and is denoted as 'AMP'. This measure is sensitive to the overall level of activity, which is not always wanted. For example, if one measures activity on the trunk instead of the wrist, the activity level will drop both during the day and during the night, resulting in a 'smaller' amplitude.

As a correction for the offset in sensitivity to movements, one may prefer to use the relative amplitude (RA), which is calculated by dividing AMP by the sum of L5 and M10. The measure theoretically ranges from 0 to 1, with higher values indicating a rhythm of higher amplitude.

6.2 Blind Review

The blind review meeting will be held before database closure and before breaking the blind to make final assessments of which patients should be included in the analysis sets and other decisions regarding the statistical analysis.

Protocol deviations observed and documented during the study (Protocol deviation log from the study site and observed during the data validation) will be listed in Section 16 of the CSR. Patients with major protocol deviations will be excluded from the PP population.

All relevant listings and tables prepared for the data review meeting will be verified for consistency and correctness by the study data manager and the statistician [redacted] and the Sponsor before the database is locked.

Apart from the data review meeting after LPLV, other data review meetings during the study may be done if appropriate to review protocol deviations and identify trends or recurrent queries within or across sites/countries.

6.3 Hypotheses and Statistical Methods

6.3.1 Definitions

Study baseline

For all objectives/endpoints assessed by means of actigraphy, the baseline value is obtained over a period of two weeks prior to randomization, i.e. week -2 to week 0.

Parameters collected in both Visit 1 and Visit 2: for assessments (Vital signs, NYHA class, [redacted] and laboratory evaluations) the last non-missing assessment prior to the first dose will be considered as the baseline value in order to calculate the changes between baseline visit and following visits.

Actigraphy

Actigraphy is a non-invasive method of monitoring human physical activity patterns. Actigraphy will be performed in this study by means of a wrist-worn device that collects data on activity (by means of tri-axial accelerometry). The device (MotionWatch8®, CamNtech, Cambridge, UK) collects the data on movement continuously in 30-second bins. The device is lightweight and waterproof and worn on the wrist of the non-dominant arm continuously (24 hours/day) for the entire study duration. Based on accelerometry for each 30-second bin, activity counts for each minute of each day are generated. Higher counts reflect a higher level of activity. For an elderly population, cut-off values for activity counts per minute defining the intensity of physical activity have previously been defined (Landry, Falck et al. 2015) . These cut-off values will be used to define sedentary, light and moderate to vigorous activity counts for each minute the device is worn. Sedentary activity is defined as < 178.5 activity counts per minute; light activity as 178.5 – 565.5 activity counts/minute and > 565.5 activity counts/minute define moderate to vigorous physical activity (see also Figure 3-1). The time patients spend in a given activity intensity category will be recorded and represents the basis for all endpoints that are derived from actigraphy. Where appropriate, activity data will be integrated over 2-week intervals (i.e. baseline non-sedentary physical daytime activity is the mean time per day the patient spent in non-sedentary activity during the daytime during the 14 days of baseline recording (week -2 to week 0).

M6min
M6min is a parameter derived by validated algorithms of the software that will be used to pre-process actigraphy data. The parameter reflects the peak 6 minutes of physical activity. The mean daily M6min will be calculated over 14 day epochs.

Actigraphy measurements

All variables needed for actigraphy objectives will be calculated using CamNtech Motionware 1.2.18 software or latest version.

- Mean daily non-sedentary daytime activity
- Mean daily light and moderate-to-vigorous non-sedentary daytime physical activity
- Total weekly time spent in non-sedentary daytime physical activity.
- Total weekly time spent in light non-sedentary daytime physical activity.
- Total weekly time spent in moderate-to-vigorous non-sedentary daytime physical activity
- M6min
- Interdaily Stability (IS)
- Intradaily Variability (IV)
- L5 average
- M10 average
- Relative Amplitude

Six minute walking test

The distance covered by the patient walking during 6 minutes will be determined and recorded at Visit 2, Visit 4, Visit 5 and Visit 6.

The assessment is performed according to the current standards (Tager, Hanholz et al. 2014) and will be provided as a separate manual to all sites. In brief – patients are instructed

to walk down a long corridor at their own pace, attempting to cover as much distance as possible within 6 minutes. At the end of the 6 minute duration, the walked distance is calculated and recorded along with the symptoms experienced by the patient. It is crucial that patients are allowed to rest, before the test is performed – therefore the 6-minute walking test should be done as the last assessment at the respective visits.

Patient Global Assessment (PGA)

The Patient Global Assessment (PGA) is a self-reported tool to assess the patients' subjective rating of their disease activity widely used in HF research and other indications. It has been shown that the PGA responses of CHF patients correlate the patients' functional capacity assessed by means of the 6-minute walk test (Cooper, Anker et al. 2016).

The patients are asked to report functioning or response to an intervention by rating their current condition compared to their pre-intervention condition on a numerical scale:

1) much improved 2) moderately improved 3) a little improved 4) unchanged 5) a little worse 6) moderately worse or 7) much worse.

This self-assessment will be completed by the patients in a quiet environment, before any study assessment or drug dispensing at Visit 4, Visit 5 and Visit 6.

6.3.2 Summary Statistics

In general, categorical data will be summarized with number of missing values, frequencies and percentages, while continuous data will be reported using number of patients, number of missing values, mean, standard deviation (SD), median, Q1, Q3, minimum and maximum. Minimum and maximum values will be provided with the same level of accuracy as raw data; means and medians will be provided with an additional decimal place and SD with 2 additional decimal places.

For secundary objectives and continuous variables, the 95% CI will be added to the statistics.

Comparing continuous variables between groups, if the variable has a normally distributed data a two sample (independent group) t-test will be used, but if the variable has a non-Normally distributed data then the non-parametric Mann–Whitney–Wilcoxon (Wilcoxon rank sum) test will be applied.

Comparing proportions of a categorical outcome between groups of treatment: ussually chi-square test will be used, but when more than 20% of cells have expected frequencies < 5 the Fisher's exact test will be applied.

6.3.3 Patient/Subject Data Listings

Data collected in the CRF will generally be listed in Appendix 16.2 (see section 8.3). CRF check questions [e.g. lab samples taken (Yes/No)] and reminders will not be listed.

In CRF modules where a date is recorded, the date and also the relative day may be printed in the corresponding listing. In modules where both a start date and stop date is recorded, also a duration may be included in the listing.

6.3.4 Demographic and other Baseline Characteristics

Subject disposition i.e. number and percentage of patients randomized, screening failures i.e. patients who discontinued at screening, patients who discontinued the study and discontinued the treatment and the reasons for premature discontinuation will be presented for all consented patients. Number of patients enrolled by country and number of patients with at least one major protocol deviation will be listed.

Patients included in the analysis populations and reasons for exclusion and inclusion/ exclusion criteria will also be tabulated for all consented patients.

All background data such as patient demographics (sex, age, age groups (<65 years vs ≥ 65 years), race, ethnicity, source of patients' referral, living conditions, smoking status, relevant medical history/conditions at baseline by body system, previous drug/non-drug therapy of HF and pregnancy test) will be described by presenting absolute and relative frequency and/or summary statistics for continuous data.

Besides, weight, height, body mass index (BMI), NYHA class and actigraphy variables (Mean daily non-sedentary daytime activity, Mean daily light and moderate-to-vigorous non-sedentary daytime physical activity, Total weekly time spent in non-sedentary daytime physical activity, Total weekly time spent in light non-sedentary daytime physical activity, Total weekly time spent in moderate-to-vigorous non-sedentary daytime physical activity, M6min, Interdaily Stability (IS), Intradaily Variability (IV), L5 average, M10 average, Relative Amplitude will be summarized. BMI will be calculated as weight (kg) / height² (m²) from the collected height and weight at the screening Visit.

6.3.5 Primary Efficacy analysis

One of the primary end-points is the change from baseline to 'end of study' in the 6-minute walking test.

The aim of the primary analysis of this study is to assess differences between sacubitril/valsartan and enalapril patients with respect to the primary endpoint in the FAS population excluding the patients who have an AE/SAE (non-HF related) during/around the 6-minute walking test which directly is causally linked to the 6-minute walking test performance.

Change from baseline values will be summarized. The comparison of treatment groups will be carried out using an ANCOVA model adjusting for treatment and baseline NYHA class (NYHA II vs. III/IV) and the baseline value as covariates.

The following hypothesis will be tested:

H0: $\mu 0 = \mu 1$ vs. H1: $\mu 0 \neq \mu 1$

Where 0 corresponds to treatment with sacubitril/valsartan and 1 corresponds to treatment with enalapril.

$6MWT_0$ = 6-minute walking test at baseline (week 0).

$6MWT_1$ = 6-minute walking test EOS (week 12).

$6MWT_{ch}$ = change in 6-minute walking test from baseline ($6MWT_1$ - $6MWT_0$).

$GROUP_k$ = treatment group.

$NYHA_{0i}$ = baseline NYHA class

ANCOVA model:

$$6MWT_{chi} = \mu + GROUP_k + 6MWT_{0i} + NYHA_{0i} + e_{ik}$$

where:

$6MWT_{chi}$: change in 6-minute walking test for each subject i.

μ: global mean

$GROUP_k$: treatment group

$6MWT_{0i}$ = 6-minute walking test baseline (week 0) value for each subject i.

$NYHA_{0i}$ = NYHA class baseline value for each subject i.

e_{ik}: associated unobserved error term.

Other primary endpoint is the change from baseline to 'end of study' in mean daily non-sedentary daytime activity (defined as ≥178.50 activity counts per minute) as calculated by the MotionWatch 8 accelerometer device. Baseline is defined as the average minutes per day in non-sedentary daytime activity over 2 weeks (week -2 to week 0) prior to randomization and 'end of study' is defined as the average minutes per day in non-sedentary daytime activity between week 10 to week 12.

The aim of the primary analysis of this study is to assess differences between sacubitril/valsartan and enalapril patients with respect to the primary endpoint in the FAS with MI .

Change from baseline values will be summarized. The comparison of treatment groups will be carried out using an ANCOVA model adjusting for treatment and baseline NYHA class (NYHA II vs. III/IV) and the baseline value as covariates.

The following hypothesis will be tested:

H0: $\mu 0 = \mu 1$ vs. H1: $\mu 0 \neq \mu 1$

Where 0 corresponds to treatment with sacubitril/valsartan and 1 corresponds to treatment with enalapril.

$DNSDA_0$ = daily non- sedentary daytime activity baseline (week -2 to week 0).

$DNSDA_1$ = daily non- sedentary daytime activity EOS (week 10 to week 12).

DNSDAch = change in daily non-sedentary daytime activity from baseline ($DNSDA_1$ - $DNSDA_0$).

$GROUP_k$ = treatment group.

$NYHA_{0i}$ = baseline NYHA class

ANCOVA model:

$$DNSDAch_i = \mu + GROUP_k + DNSDA_{0i} + NYHA_{0i} + e_{ik}$$

where:

$DNSDAch_i$: change in daily non- sedentary daytime activity for each subject i.

μ: global mean

$GROUP_k$: treatment group

$DNSDA_{0i}$ = daily non- sedentary daytime activity baseline (week -2 to week 0) value for each subject i.

$NYHA_{0i}$ = NYHA class baseline value for each subject i.

e_{ik}: associated unobserved error term.

6.3.6 Secondary Efficacy Analyses

Proportion of patients with improved performance (≥ 30 m) in 6-minute walking test at week 12 compared to baseline. The comparison of patient groups will be carried out using logistic regression model with factors treatment and baseline NYHA class (NYHA II vs. III/IV) and the baseline value as further covariate. The Odds Ratio for the factor treatment and its 95%-confidence interval will be given.

Proportion of patients with improved performance (≥ 30 m) in 6-minute walking test at week 12 compared to baseline in a subset of patients with baseline 6-minute walk distance equal to or less than 300 meters. The comparison of patient groups will be carried out using logistic regression model with factors treatment and baseline NYHA class (NYHA II vs. III/IV) and the baseline value as further covariate. The Odds Ratio for the factor treatment and its 95%-confidence interval will be given.

Proportion of patients with improved performance (≥ 30 m) in 6-minute walking test at week 12 compared to baseline in a subset of patients with baseline 6-minute walk distance between 100-450 meters. The comparison of patient groups will be carried out using logistic regression model with factors treatment and baseline NYHA class (NYHA II vs. III/IV) and the baseline value as further covariate. The Odds Ratio for the factor treatment and its 95%-confidence interval will be given.

Score of 6-minute walking test will be summarised at baseline, week 4, week 8 and week 12. Change from baseline values will be presented. The comparison of patient groups at week 12 compared to baseline will be analyzed using a two sample (independent group) t-test or a non-parametric Mann–Whitney–Wilcoxon (Wilcoxon rank sum) test, where applicable.

Proportion of patients who show increased levels (≥ 10% increase) of non-sedentary daytime physical activity at week 12 compared to baseline. The comparison of patient groups will be carried out using logistic regression model with factors treatment and baseline NYHA class (NYHA II vs. III/IV) and the baseline value as further covariate. The Odds Ratio for the factor treatment and its 95%-confidence interval will be given.

PGA scores will be tabulated at week 4, week 8 and week 12. The comparison of patient groups at week 4, week 8 and week 12 will be analyzed using a chi-square test or Fisher's exact test, where applicable.

Proportion of patients with improved symptoms of HF as assessed by PGA, number and proportion will be tabulated at week 4, week 8 and week 12. The comparison of patient groups will be presented and analyzed using a chi-square test or Fisher's exact test, where applicable.

Change from baseline in mean daily non-sedentary daytime activity in weekly and two-weekly intervals will be summarised. The comparison of patient groups will be analyzed using a two sample (independent group) t-test or a non-parametric Mann–Whitney–Wilcoxon (Wilcoxon rank sum) test, where applicable.

Proportion of patients at weekly and two-weekly intervals who show increased levels (≥ 10% increase) of mean daily non-sedentary daytime physical activity compared to baseline will be tabulated. The comparison of patient groups will be presented and analyzed using a chi-square test or Fisher's exact test, where applicable.

Change from baseline in mean daily light and moderate-to-vigorous non-sedentary daytime physical activity between baseline and different time points under treatment (weekly or two-weekly from week 0 to week 12) will be summarised. The comparison of patient groups will be analyzed using a two sample (independent group) t-test or a non-parametric Mann–Whitney–Wilcoxon (Wilcoxon rank sum) test, where applicable.

Total weekly time spent in non-sedentary daytime physical activity will be summarised by week, from week 0 to week 12. The comparison of patient groups will be analyzed using a two sample (independent group) t-test or a non-parametric Mann–Whitney–Wilcoxon (Wilcoxon rank sum) test, where applicable.

Total weekly time spent in light non-sedentary daytime physical activity will be summarised by week, from week 0 to week 12. The comparison of patient groups will be analyzed using a

two sample (independent group) t-test or a non-parametric Mann–Whitney–Wilcoxon (Wilcoxon rank sum) test, where applicable.

Total weekly time spent in moderate-to-vigorous non-sedentary daytime physical activity will be summarised by week, from week 0 to week 12. The comparison of patient groups will be analyzed using a two sample (independent group) t-test or a non-parametric Mann–Whitney–Wilcoxon (Wilcoxon rank sum) test, where applicable.

M6min (an actigraphy-based measure of the peak six minutes of daytime physical activity) will be summarised at baseline, week 2, week 4, week 6, week 8, week 10 and week 12. Change from baseline values will be presented. The comparison of patient groups at week 12 compared to baseline will be analyzed using a two sample (independent group) t-test or a non-parametric Mann–Whitney–Wilcoxon (Wilcoxon rank sum) test, where applicable.

Proportion of patients with increased M6min (an actigraphy-based measure of the peak six minutes of daytime physical activity) compared to baseline at week 4, week 8 and week 12 will be tabulated. The comparison of patient groups will be presented and analyzed using a chi-square test or Fisher's exact test, where applicable.

6.3.7 Sensitivity analyses

6-minute walking test:

For the main analysis the patients who have an AE/SAE (non-HF related) during/around the 6-minute walking test which directly is causally linked to the 6-minute walking test performance will be remove. A sensitivity analysis will be performed including all patients for each population.

Main analysis for 6-minute walking test primary variable:

FAS population subset patients without AE/SAE (non-HF related) during/around the test

Sensitivity analyses for 6-minute walking test primary variable:

FAS population

PP population

PP population subset patients without AE/SAE (non-HF related) during/around the test

Mean daily non-sedentary daytime activity:

In addition to the primary analysis, the primary efficacy variables will also be analyzed using the same analysis model in the PP population as supportive. Furthermore, the analysis of the

primary variable (mean daily non-sedentary daytime activity) will be repeated in the FAS population without MI of missing values.

Besides, the last-observation-carried-forward principle (LOCF) imputation method will be performed as a sensitivity analysis (Section 6.6).

Main analysis for mean daily non-sedentary daytime activity primary variable:

FAS population with MI

Sensitivity analyses for mean daily non-sedentary daytime activity primary variable:

PP population with MI

PP population with LOCF

PP population without MI

FAS population without MI/LOCF

FAS population with LOCF

6.3.8 Exposure to Treatment

The duration of exposure (in weeks) to the study treatment i.e. number of weeks study drug was taken as per protocol will be summarized by treatment for the safety population (SAF).

The number and percentage of patients will be tabulated by treatment group for duration (categorized by weeks), defined as

(Last dose date – First dose date* + 1) / 7

*First dose date is not collected in the eCRF, we wil use the visit 2 date as a first dose date because it is the administration date.

Study drug compliance will be summarized for all patients in the SAF by visit, separately by treatment group. The study drug compliance is assessed at each visit by the investigator.

Additionally, the number and percentage of patients will be tabulated by visit and treatment group for compliance category (categorized in <80% and 80-100%).

6.3.9 Concomitant Medication

Concomitant medications will be summarized by the preferred term as coded by the World Health Organization Drug (WHODRUG) dictionary for the SAF population.

6.3.10 Adverse Events

Treatment emergent adverse events TEAEs (events started on or after the first dose date of study treatment or events present prior to the first dose of study treatment but increased in severity based on preferred term) will be summarized. Only primary paths within MedDRA will be considered for TEAEs reporting.

TEAEs will be summarized by presenting, for each treatment group, the number and percentage of subjects

- having any TEAEs,
- having a TEAEs in each primary system organ class and

- having each individual TEAEs (preferred term).

Summaries will also be presented for TEAEs by severity and for study treatment related TEAEs. If a subject reported more than one adverse event with the same preferred term, the adverse event with the greatest severity will be presented. If a subject reported more than one adverse event within the same primary system organ class, the subject will be counted only once with the greatest severity at the system organ class level, where applicable.

Separate summaries will be provided for death, serious adverse event, adverse events leading to discontinuation and adverse events leading to dose adjustment (including study treatment discontinuation).

A listing of all AEs will be presented, whether treatment emergent or not.

6.3.11 Liver Events

Number and percentage of patients with liver events and information related with the events will be tabulated

A listing of all liver events will be presented.

6.3.12 Renal Events

Number and percentage of patients with renal events and information related with them will be tabulated

A listing of all renal events will be presented.

6.3.13 Other Safety Assessments

Vital Signs

Analysis of the vital sign (blood pressure and pulse) measurements using summary statistics for the change from baseline for each post-baseline visit will be performed. These descriptive summaries will be presented by vital sign and treatment group. Change from baseline will only be summarized for subjects with both baseline and post-baseline values. All information collected will be listed by subject and abnormal values be flagged.

Clinical Laboratory Measurements

Laboratory data will be summarized by presenting shift tables using extended normal ranges (baseline to most extreme post-baseline value), by presenting summary statistics of raw data and change from baseline values (mean, medians, standard deviations, ranges) and by the flagging of notable values in data listings.

Clinically notable laboratory abnormalities for selected tests based on a percent change from baseline.

Hemoglobin	> 50 % increase, > 20 % decrease
ALT	> 150 % increase
AST	> 150 % increase
Creatinine	> 50 % increase

Potassium > 20 % increase, > 20 % decrease

6.4 Level of Significance, Multiple Comparisons and Multiplicity

All statistical hypotheses will be two-sided and will be performed using a 5% significance level.

No adjustment for multiple comparisons or corrections for multiplicity are planned.

6.5 Adjustment for Covariates

Statistical analyses for efficacy endpoints including ANCOVA model with covariates are detailed in Sections 6.3.4 and 6.3.5 of this document.

6.6 Handling of Dropouts and Missing Data

For patients who do not have the baseline values or patients who drop out prematurely and/or do not have a valid measurement in mean daily non-sedentary daytime activity between weeks 10-12, a Multiple Imputation (MI) method will be used for the primary analysis. For the key secondary variable the same imputation strategy will be used.

Multiple imputation (MI)

The MI procedure in the SAS Software is a multiple imputation procedure that creates multiply imputed data sets for incomplete p-dimensional multivariate data. It uses methods that incorporate appropriate variability across the m imputations. Once the m complete data sets are analyzed by using standard procedures, the MIANALYZE procedure can be used to generate valid statistical inferences about these parameters by combining results from the m complete data sets:

- The missing data are filled in m times to generate m complete data sets.
- The m complete data sets are analyzed by using standard procedures.
- The results from the m complete data sets are combined for the inference.

The MI process through SAS software:

1. To explore missing data patterns

```
PROC MI DATA=example NIMPUTE=0;
VAR [list of variables];
RUN;
```

2. To select the most appropiate MI method (see appendix 8.5)
3. Process of imputation with PROC MI. Imputation step
4. SAS statistical procedure to analyze each MI repetition (MIXED,MEANS, GENMOD…). Analysis step
5. Finally, the MIANALYZE procedure combines the results and provides valid statistical inferences. Pooled step.

Sensitivity analysis LOCF. For patients who drop out prematurely and/or do not have a valid measurement in mean daily non-sedentary daytime activity between weeks 10-12, the last

available value of non- sedentary daytime activity over two weeks under treatment will be used for the primary analysis (last-observation-carried-forward principle, LOCF). Patients with major protocol violations, but with a valid assessment of the primary variable will be included in the primary analysis with their observed value. For the key secondary variable the same imputation strategy will be used.

For the analyses of further secondary and of the exploratory endpoints referring to data at 'end of study' the same algorithm will be applied to create an extra LOCF visit next to the usual Week 12 visit. This additional 'end of study' measure constitutes a conservative approach in handling of missing data and ensures much as possible unbiased and comparable efficacy results.

In case of qualitative (e.g., increased level of non-sedentary daytime physical activity) or semi-quantitative (e.g., PGA) efficacy variables, missing Week 12 values of patients previously dropped out due to hospitalization or death will be substituted by the worst value possible for the respective variable (e.g., increased level of non-sedentary daytime physical activity="No", PGA="much worse").

In the event that any date for Adverse Events is incomplete after Data Management processing and this date needs to be used for a calculation, the following will be assigned for the missing date:

- if no field is available: no imputation will be performed

- if only the year is available:

  - Onset date: day "01" and month of "January" or first dose administration date, whatever occurs after will be imputed
  - End date: day "31" and month of "December" or EOS date, whatever occurs before will be imputed

- if the month and year are available:

  - Onset date: day "01" will be imputed
  - End date: "last day of the month" will be imputed

6.7 Multicentre Studies

No analysis stratified by center will be performed in this study

6.8 Examination of Subgroups

Post-hoc analysis on specific subgroups e.g. by NYHA, country, etc. may be considered once the study data has been published.

6.9 Interim Analysis

No interim analysis are planned for the study.

6.10 Data Monitoring

There will be no independent data monitoning committee reviewing the data

7 REFERENCES

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Van Someren EJW, Swaab DF, Colenda CC, Cohen W, McCall WV and Rosenquist PB (1999) Bright light therapy: improved sensitivity to its effects on rest-activity rhythms in Alzheimer patients by application of nonparametric methods. Chronobiol Int 16:505-518.

8 APPENDIX 1

Data from subjects screened but not included in the study will not be presented in any listings or tables.

8.1 Tables to be Produced for the Clinical Study Report (Section 14 according to ICH E3)

14.1 DEMOGRAPHIC DATA

Subject disposition

Table 14.1-1. Subject disposition in analysis sets and reason for exclusions

SCR population

Table 14.1-2. Study populations

SCR population

Table 14.1-3. Inclusion and exclusion criteria

FAS population

Demographic and baseline characteristics

Table 14.1-4. Demographic data

SAF population / FAS population

Table 14.1-5. Cardiovascular medical history at baseline

SAF population / FAS population

Table 14.1-6. Relevant medical history/concurrent medical conditions at baseline

SAF population / FAS population

Table 14.1-7. Previous drug/non-drug therapy of HF

SAF population / FAS population

Table 14.1-8. Height, weight, body mass index (BMI) and NYHA class

SAF population / FAS population

Table 14.1-9. Actigraphy variables (Mean daily non-sedentary daytime activity, Mean daily light and moderate-to-vigorous non-sedentary daytime physical activity) at baseline

SAF population

Table 14.1-10. Actigraphy variables (Total weekly time spent in non-sedentary daytime physical activity, Total weekly time spent in light non-sedentary daytime physical activity, Total weekly time spent in moderate-to-vigorous non-sedentary daytime physical activity) at baseline

SAF population

Table 14.1-11. Actigraphy variables (M6min, Interdaily Stability (IS), Intradaily Variability (IV), L5 average, M10 average, Relative Amplitude) at baseline

SAF population

Table 14.1-12. Hospitalizations and medical visits 12 months previous to baseline

SAF population / FAS population

Table 14.1-13. Etiology of heart failure

SAF population / FAS population

Table 14.1-14. 12 Lead ECG Evaluation at baseline

SAF population / FAS population

14.2 EFFICACY DATA

Primary efficacy analysis

Table 14.2-1 6-minute walking test: absolute and change between baseline and end of study by treatment group.

FAS population/PP population/FAS population subset patients without AE/SAE/PP population subset patients without AE/SAE

Descriptive statistics

Table 14.2-2 6-minute walking test: ANCOVA comparison of change between baseline and end of study.

FAS population/PP population/FAS population subset patients without AE/SAE/PP population subset patients without AE/SAE

Statistical (mixed model) by treatment group

Table 14.2-3 Mean daily non-sedentary daytime activity: absolute and change between baseline and end of study by treatment group.
FAS population with MI/FAS population with LOCF/FAS population without MI/LOCF/PP population with MI/ PP population with LOCF/PP population without MI

Descriptive statistics

Table 14.2-4 Mean daily non-sedentary daytime activity: ANCOVA comparison of change between baseline and end of study.

FAS population with MI/FAS population with LOCF/FAS population without MI/LOCF/PP population with MI/ PP population with LOCF/PP population without MI

Statistical (mixed model) by treatment group

Secondary efficacy analysis

Table 14.2-5 Improved performance (≥ 30 m) in 6MWT: proportion of patients at the end of study by treatment group.

FAS population/FAS population subset patients without AE/SAE

Descriptive statistics

Table 14.2-6 Improved performance (≥ 30 m) in 6MWT: logistic regression model.

FAS population/FAS population subset patients without AE/SAE

Statistical (logistic model) by treatment group

Table 14.2-7 Improved performance (≥ 30 m) in 6MWT for patients with baseline 6MWT equal to or less than 300 meters: proportion of patients at the end of study by treatment group.

FAS population/FAS population subset patients without AE/SAE

Descriptive statistics

Table 14.2-8 Improved performance (≥ 30 m) in 6MWT for patients with baseline 6MWT equal to or less than 300 meters: logistic regression model.

FAS population/FAS population subset patients without AE/SAE

Statistical (logistic model) by treatment group

Table 14.2-9	Improved performance (≥ 30 m) in 6MWT for patients with baseline 6MWT between 100-450 meters: proportion of patients at the end of study by treatment group. FAS population/FAS population subset patients without AE/SAE Descriptive statistics
Table 14.2-10	Improved performance (≥ 30 m) in 6MWT for patients with baseline 6MWT between 100-450 meters: logistic regression model. FAS population/FAS population subset patients without AE/SAE Statistical (logistic model) by treatment group
Table 14.2-11	6-minute walking test: absolute and change between baseline at week 4, week 8 and week 12 by treatment group. FAS population/FAS population subset patients without AE/SAE *Descriptive statistics and statistical analysis by treatment group*
Table 14.2-12	Increased levels (≥ 10% increase) of non-sedentary daytime physical activity: proportion of patients at the end of study by treatment group. FAS population *Descriptive statistics*
Table 14.2-13	Increased levels (≥ 10% increase) of non-sedentary daytime physical activity: logistic regression model. FAS population *Statistical (logistic model) by treatment group*
Table 14.2-14	PGA score at week 4, week 8 and week 12 by treatment group. FAS population *Descriptive statistics and statistical analysis by treatment group*
Table 14.2-15	Patients who improved symptoms of HF as assessed by PGA: proportion of patients at week 4, week 8 and week 12 by treatment group. FAS population *Descriptive statistics and statistical analysis by treatment group*
Table 14.2-16	Mean daily non-sedentary daytime activity: absolute and change in weekly and two-weekly intervals by treatment group. FAS population *Descriptive statistics and statistical analysis by treatment group*
Table 14.2-17	Mean daily non-sedentary daytime activity: Proportion of patients at weekly and two-weekly intervals who show increased levels (≥ 10% increase) by treatment group. FAS population *Descriptive statistics and statistical analysis by treatment group*
Table 14.2-18	Mean daily light and moderate-to-vigorous non-sedentary daytime physical activity: absolute and change by week and treatment group. FAS population

Descriptive statistics and statistical analysis by treatment group

Table 14.2-19 Total weekly time spent in non-sedentary daytime physical activity: absolute and change by week and treatment group.

FAS population

Descriptive statistics and statistical analysis by treatment group

Table 14.2-20 Total weekly time spent in light non-sedentary daytime physical activity: absolute and change by week and treatment group.

FAS population

Descriptive statistics and statistical analysis by treatment group

Table 14.2-21 Total weekly time spent in moderate-to-vigorous non-sedentary daytime physical activity: absolute and change by week and treatment group.

FAS population

Descriptive statistics and statistical analysis by treatment group

Table 14.2-22 M6min: absolute and change between baseline at week 4, week 8 and week 12 by treatment group.

FAS population

Descriptive statistics and statistical analysis by treatment group

Table 14.2-23 Increase in M6min: proportion of patients at week 4, week 8 and week 12 by treatment group.

FAS population

Descriptive statistics and statistical analysis by treatment group

[redacted]

Table 14.2-27 Interdaily Stability (IS): absolute and change between baseline at two-week intervals by treatment group.

FAS population

Descriptive statistics

Table 14.2-28 Intradaily Variability (IV): absolute and change between baseline at two-week intervals by treatment group.

FAS population

Descriptive statistics

Table 14.2-29 L5 average: absolute and change between baseline at two-week intervals by treatment group.

FAS population

Descriptive statistics

Table 14.2-30 M10 average: absolute and change between baseline at two-week intervals by treatment group.

FAS population

Descriptive statistics

Table 14.2-31 Relative amplitude: absolute and change between baseline at two-week intervals by treatment group.

FAS population

Descriptive statistics

[redacted]

Table 14.2-33 Mean daily sedentary daytime physical activity: Parameters (Δ, c, k, t0) and standard error from non-linear least square regression by treatment group. Logistic function

FAS population

Descriptive statistics and statistical analysis (Δ)

Table 14.2-34 Mean daily light and moderate-to-vigorous non-sedentary daytime physical activity: Parameters (Δ, c, k, t0) and standard error from non-linear least square regression by treatment group. Logistic function

FAS population

Descriptive statistics and statistical analysis (Δ)

Table 14.2-35 M6min: Parameters (Δ, c, k, t0) and standard error from non-linear least square regression by treatment group. Logistic function

FAS population

Descriptive statistics and statistical analysis (Δ)

14.3 SAFETY DATA

Adverse events

Table 14.3.1-1 Summary of patients with TEAEs by treatment group

SAF population

Table 14.3.1-2 Number of TEAEs by SOC and PT by treatment group

SAF population

Table 14.3.1-3 Number of TEAEs by SOC, PT and maximum severity by treatment group

SAF population

Table 14.3.1-4 Number of suspected drug-related TEAEs by SOC and PT by treatment

	group
	SAF population
Table 14.3.1-5	Number of serious TEAEs by SOC and PT by treatment group
	SAF population
Table 14.3.1-6	Number of TEAEs leading to treatment discontinuation by SOC and PT by treatment group
	SAF population

Listings of Deaths, Other Serious and Significant Adverse Events

Table 14.3.2-1	List of Deaths
	SAF population
Table 14.3.2-2	List of patients with at least one serious adverse event
	SAF population
Table 14.3.2-3	List of patients with a fatal adverse event
	SAF population
Table 14.3.2-4	List of subjects with an adverse event leading to treatment discontinuation
	SAF population

Liver and Renal Events

Table 14.3.2-1	Liver Events
	SAF population
Table 14.3.2-2	Renal Events
	SAF population

Laboratory data

Table 14.3-4.1	Laboratory data: absolute values and changes from baseline by visit and treatment group
	SAF population
Table 14.3-4.2	Hemoglobin: notable values at any time post-baseline by treatment group
	SAF population
Table 14.3-4.3	ALT: notable values at any time post-baseline by treatment group
	SAF population
Table 14.3-4.4	AST: notable values at any time post-baseline by treatment group
	SAF population
Table 14.3-4.5	Creatinine: notable values at any time post-baseline by treatment group
	SAF population
Table 14.3-4.6	Potassium: notable values at any time post-baseline by treatment group
	SAF population
Table 14.3-4.7	Potassium Clearance: notable values at any time post-baseline by treatment group
	SAF population
Table 14.3-4.8	Laboratory data: Shift from baseline by treatment group
	SAF population

Vital signs

Table 14.3-6.1	Blood pressure: absolute values and changes from baseline by visit and treatment group
	SAF population
Table 14.3-6.2	Pulse rate: absolute values and changes from baseline by visit and treatment group
	SAF population

Treatment exposure

Table 14.3-7.1	Treatment exposure SAF population
Table 14.3-7.2	Treatment compliance SAF population

NYHA class

Table 14.3-8.1	NYHA class by visit and treatment group SAF population

Concomitant therapy

Table 14.3-11.1	Concomitant medication SAF population

8.2 Graphs (Section 14.2-14.3 in ICH E3)

Figure 14.2-1	6-minute walking test at baseline, week 4, week 8 and week 12 by treatment group. FAS population/PP population/FAS population subset patients without AE/SAE
Figure 14.2-2	Mean daily non-sedentary daytime activity in weekly intervals by treatment group. FAS population
Figure 14.2-3	Mean daily non-sedentary daytime activity in two-weekly intervals by treatment group. FAS population
Figure 14.2-4	PGA score at baseline, week 4, week 8 and week 12 by treatment group. FAS population
Figure 14.2-5	Total weekly time spent in non-sedentary daytime physical activity in weekly intervals by treatment group. FAS population
Figure 14.2-6	Total weekly time spent in light non-sedentary daytime physical activity in weekly intervals by treatment group. FAS population
Figure 14.2-7	Total weekly time spent in moderate-to-vigorous non-sedentary daytime physical activity in weekly intervals by treatment group.

FAS population

Figure 14.2-8 M6min at baseline, week 4, week 8 and week 12 by treatment group.

FAS population

8.3 Listings of Individual Subject Data and other Information to be Produced for the Clinical Study Report (Sections 16.1 and 16.2 according to ICH E3)

(Listing numbers refer to Appendix number in ICH E3. CRF check questions/reminders will not be listed.)

Listing 16.2.1-1.1 Discontinued Subjects, Reason for Discontinuation

Listing 16.2.1-1.2 Visit Dates

Listing 16.2.1-1.3 Study Termination

Listing 16.2.1-1.4 Screening failure subjects, Reason for SF

Listing 16.2.2-1.1 Protocol deviations

Listing 16.2.3-1.1 Patients excluded from the efficacy analysis

Listing 16.2.4-1.1 Demographic data

Listing 16.2.4-1.2 Medical History

Listing 16.2.4-1.3 Physical Examination at visit 1

Listing 16.2.4-1.4 Inclusion Criteria Not Met and Exclusion Criteria Met

Listing 16.2-5-1.1 Compliance and/or Drug Concentration Data

Listing 16.2.6-1.1 Variables from Actigraphy

Listing 16.2.6-1.2 NYHA class

Listing 16.2.6-1.3 PGA

Listing 16.2.6-1.4 6 minute walking test

[redacted]

Listing 16.2.7-1.1 Adverse events

Listing 16.2.7-1.2 Liver events

Listing 16.2.7-1.3 Renal events

Listing 16.2.8-1.1 Listing of Individual Laboratory Measurements by Subject (according to layout in section 12.4.1 in ICH E3, abnormal values should be flagged)

Listing 16.2.8-1.2 Vital signs

Listing 16.2.8-1.3 ECG

Listing 16.2.11-1.1 Concomitant medications

8.4 US Archival Listings (Appendix 16.4 according to ICH E3)

Not applicable

8.5 Multiple Imputation: To select the most appropriate MI method

Missing Data Pattern	Imputed Variable Type	Method	PROC MI Statement
Monotone	Continous	Linear regression	MONOTONE REG
		Predictive mean matching	MONOTONE REGPMM
		Propensity score	MONOTONE PROPENSITY
	Binary/ordinal	Logistic regression	MONOTONE LOGISTIC
	Nominal	Discriminant function	MONOTONE DISCRIM
Arbitrary	Continuous	With continuous covariates:	
		MCMC monotone method	MCMC monotone method
		MCMC full-data imputation	MCMC full-data imputation
		With mixed covariates:	
		FCS regression	FCS REG
		FCS predictive mean matching	FCS REGPMM
	Binary/ordinal	FCS logistic regression	FCS LOGISTIC
	Nominal	FCS discriminant function	FCS DISCRIM

Notes:
MCMC: Markov chain Monte Carlo method.
FCS : Fully conditional specification
Table extracted from the SAS/STAT PROC MI documentation