Document Type:	Statistical Analysis Plan
Official Title:	Real Life Multimarker Monitoring in Patients with Heart Failure
NCT Number:	NCT03507439
Document Date:	14-APR-2021

Title page

Real Life Multimarker Monitoring in Patients with Heart Failure

REALIsM-HF pilot study

Bayer study drug (BAY 1067197)

Clinical study phase:	Not applicable	**Date:**	14 APR 2021
Study No.:	19167	**Version:**	1.0
Author:	PPD		

Confidential

The information provided in this document is strictly confidential and is intended solely for the guidance of the clinical investigation. Reproduction or disclosure of this document, whether in part or in full, to parties not associated with the clinical investigation or its use for any other purpose without the prior written consent of the sponsor is not permitted.

Throughout this document, symbols indicating proprietary names (®, TM) are not displayed. Hence, the appearance of product names without these symbols does not imply that these names are not protected.

This Statistical Analysis Plan is produced on a word-processing system and bears no signatures.

The approval of the Statistical Analysis Plan is documented in a separate Signature Document.

Table of Contents

Table of Figures

Abbreviations

6MWD	6 minute walking distance
AE	adverse event
CLIPS	clinical pharmacology standard
CSP	clinical study protocol
CSR	clinical study report
DES1 / DES2	device set 1 / 2
e.g.	exempli gratia (for example)
EU	European Union
FAS	full analysis set
HF	heart failure
HFpEF	heart failure with preserved ejection fraction
HFrEF	heart failure with reserved ejection fraction
HR	heart rate
i.e.	id est (that is)
KCCQ	Kansas City Cardiomyopathy Questionnaire score
MedDRA	Medical Dictionary for Regulatory Activities
NYHA	New York Heart Association
PA	physical activity
PAL	physical activity level
PRO	patient reported outcome
QoL	quality of life
QS	questionnaire for patient reported outcomes (daily and weekly)
SAP	statistical analysis plan
SD	Standard deviation
TEAE	treatment-emergent adverse event
TEE	total energy expenditure
WHO-DD	World Health Organization – drug dictionary

1. Introduction

Heart failure (HF) is known to be a major public health problem and a major cause of mortality and morbidity. It has a prevalence of up to 22% in elderly, and aging of population worldwide will result in a further rise in the HF prevalence by 50% over the next 10-15 years.

Heart failure with preserved ejection fraction (HFpEF) currently accounts for more than 50% of all HF cases and shows rising incidence, and outcomes among these patients are as poor as those with HF and reduced ejection fraction (HFrEF). Previous HF trials have focused primarily on reduction of cardiovascular mortality and/or readmission risk, whereas studies among hospitalized patients have largely focused on acute symptoms. Given the fact that patients with HFpEF are much older and have significant comorbidity burden compared to their peers with HFrEF, it is difficult to conceive that one drug or device can reduce mortality or hospitalization risk in these patients. Though intensively managed, these patients remain symptomatic and have substantially reduced functional capacity and quality of life (QoL).

QoL/patient reported outcome (PRO) and exercise capacity is an increasingly recognized patient and caregiver concern and may present more pragmatic outcomes, but are currently not typically considered as primary endpoints for clinical trials in HF patients.

This study aims to explore two devices providing a multi-marker biometrical monitoring including daily activity under real-life conditions in patients with HFpEF and HFrEF. It aims to identify potential new endpoints for future HFpEF trials by exploring clinically relevant changes over time and correlations/associations with conventional endpoints and biomarkers.

Furthermore, it aims to define the challenges and test the feasibility of this approach under real-life conditions.

This Statistical Analysis Plan (SAP) is based on the Clincial Study Protocol (CSP) No. BAY 1067197 / 19167, Version 4.0, dated 21 FEB 2020 [1].

2. Study Objectives

Primary objective:

- Measurement and quantification of daily physical activity (PA) in patients with HFpEF and HFrEF under real life conditions by activity tracker/belt and patch

Secondary objectives:

- Association between VitalPatch biosensor and DynaPort Move Monitor data (e.g. different levels of activity) to adverse events/clinical outcome data occurring during the study period
- Assess the baseline level and longitudinal changes over time of heart rate (HR), respiratory rate and ECG-derived parameters and the average of person-to-person physiological variability and the within-patient standard deviation between the baseline and 3-month measurements
- Assess the feasibility of activity tracking with two devices (VitalPatch biosensor and DynaPort Move Monitor) in patients with heart failure
- Correlation of activity data between VitalPatch biosensor data on activity and DynaPort Move Monitor[1]
- Evaluate the relationship between physical activity levels, HR, respiratory rate and ECG-derived parameters and important measures in HFpEF; such as quality of life (QoL), patient reported outcome (PRO), biomarkers, outcomes (e.g. clinical endpoints such as hospitalization for heart failure, cardiovascular death, emergency visits)
- Support the development of HFpEF specific questions (PRO) for testing/validating cross-sectional and longitudinally
- Determine the variability of device derived biomarkers between subjects and within subjects over time in order to validate such biomarkers for clinical use in the context of heart failure
- Evaluate hs-copeptin as potential biomarker
- Correlation between patch monitor collected data and inpatient clinical data during hospital stay (e.g. echocardiography, weight gain/loss, NYHA, HR)[2]
- Explore the relationship between PA, 6-minute walking distance (6MWD), PRO, biomarkers, adverse events/clinical outcomes
- Investigate the accuracy of patients' self-reports (PRO, e.g. KCCQ) of time spent on PA in real life vs. objective assessment by the DynaPort Move Monitor and VitalPatch biosensor[3]

[1] Will not be adressed due to change from AVIVO to VitalPatch (ECG data only)

[2] Will not be adressed due to change in procedure schedule

[3] Meaningful assessment not possible given the provided variables.

Given the data situation (not all parameters provided by the vendor) and the low number of subjects (recruiting stopped early due to recruiting issues), not all the original objectives mentioned above will be addressed.

3. Study Design

This is a non-randomized, multi-center, observatory prospective patient study. The study will be conducted in several centers in EU and non-EU.

Patients hospitalized due to heart failure as well as ambulatory patients with heart failure will be included in this study. Overall approx. 80 subjects have to complete at least all device monitoring periods:

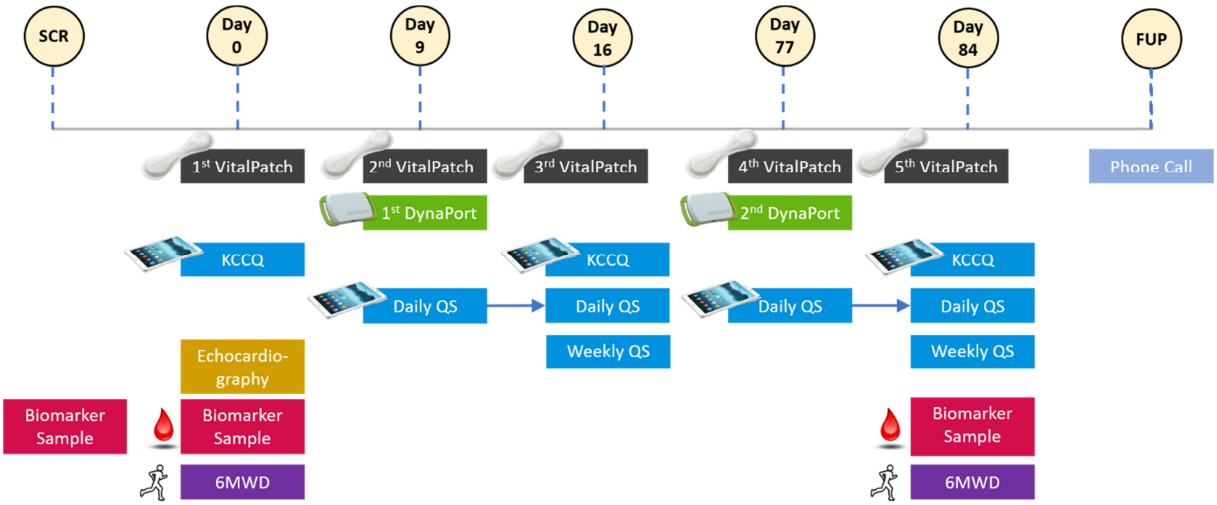
- Approx. 60 subjects with established diagnosis of heart failure with preserved ejection fraction (HFpEF; EF ≥ 45%) (Cohort 1) and
- Approx. 20 subjects with established diagnosis of heart failure with reduced ejection fraction (HFrEF; EF ≤ 35%) (Cohort 2).

All patients will receive the AVIVO / VitalPatch biosensor at 5 monitoring periods (5 patches each subject in total, monitoring period 7 / 5 days each period) and the DynaPort Move Monitor (belt) at 2 monitoring periods (7 day monitoring each period). Results from both devices are not visible to investigator and subjects to avoid bias on treatment decisions.

Biomarkers will be investigated during the hospital stay (only in case patient is hospitalized), at visit 1, and at visit 4. A 6-minute walking test will be performed at visit 1 / discharge and after 11-12 weeks.

Design overview

Figure 3–1: Study design



Abbreviations: KCCQ = Kansas City Cardiomyopathy Questionnaire score; QS = Questionnaire for patient reported outcomes (daily and weekly); 6MWD = 6 minute walking distance; FUP = follow up visit

4. General Statistical Considerations

4.1 General Principles

The statistical evaluation will be performed by using the software package SAS release 9.4 or higher (SAS Institute Inc., Cary, NC, USA).

All variables will be analyzed by descriptive statistical methods. The number of data available, mean, standard deviation, minimum, median, and maximum will be calculated for metric data. Frequency tables will be generated for categorical data.

The analysis will be based on the Clinical Pharmacology Standard (CLIPS), version 3.0 [2].

Tables and listings describing the impact of COVID-19 on the study will be created as appropriate. If needed, the onset of the COVID-19 pandemic will be considered as 11 MAR 2020 (date when the WHO declared the COVID-19 pandemic).

VitalPatch and AVIVO data will not be transferred to the clinical database and will be considered in the scope of the biomarker analyses.

All planned statistical analyses will be explorative. A confirmatory statistical analysis is not intended. Thus, no adjustment for the type I error level will be done.

4.2 Handling of Dropouts

A subject who discontinues study participation prematurely for any reason is defined as a "dropout" if the subject has already been started one device monitoring period.

As far as possible patients who are considered as dropouts will be replaced until a number of at least 60 evaluable datasets for HFpEF patients and 20 for HFrEF patients has been reached.

4.3 Handling of Missing Data

Missing data will not be replaced. Analyses will be performed considering all data observed for the respective analysis sets.

All missing or partial data will be presented in the subject data listing as they are recorded on the Case Report Form.

4.4 Interim Analyses and Data Monitoring

No interim analyses are planned. The final analysis will be performed after end of the study which is the date the analytical dataset is completely available.

4.5 Data Rules

4.5.1 Baseline

Baseline is defined as the first visit after the screening visit.

4.5.2 Repeated Measurements

If control measurements for the screening visit are available, the last value will be used for the calculation of descriptive statistics. If control measurements for a planned time point except screening are available, the first value (i.e. of the planned measurement) will be used for the calculation of descriptive statistics.

4.6 Blind Review

The results of the final data assessment will be documented in the final list of important deviations, validity findings and assignment to analysis sets. Any changes to the statistical analysis prompted by the results of the review of study data will be documented in an amendment and, if applicable, in the clinical study report (CSR).

5. Analysis Sets

5.1 Assignment of analysis sets

In absence of intervention and randomization the statistical analysis sets are defined as follows:

Full analysis set (FAS) [= Safety analysis set (SAF)]

All subjects that were enrolled into the study and that wore at least one device will be included in the FAS.

Device Set (DES)

All subjects with DynaPort parameters for least one wearing period will be included in the DES.

6. Statistical Methodology

6.1 Population characteristics

If not stated otherwise, analyses will be performed on the FAS population.

6.1.1 Subjects validity, disposition

Study sample size will be summarized by cohort and total, subject validity with reason for exclusion from analysis sets, subject disposition, and important deviations / validity findings will be summarized by total using frequency tables.

6.1.2 Demographics

Summary statistics (arithmetic mean, standard deviation, median, minimum, and maximum for quantitative variables) will be presented by cohort and total. Frequency tables for qualitative data will be provided. If the DES differs from the FAS, summary statistics and frequency tables for DES will be provided as well.

6.1.3 Medical and surgical history

The number of subjects with medical history findings will be summarized by classified data using frequency tables. The classification will be done according to the Medical Dictionary for Regulatory Activities (MedDRA) coding system using system organ class, high level terms and preferred terms. The most recent MedDRA version will be used.

6.1.4 Concomitant medication

The number of subjects that used concomitant medication will be analyzed using frequency tables based on classified data. The classification will be done according to the WHO-DD.

6.1.5 NYHA-classification

A frequency table will be created for the NYHA-classification by visit.

6.2 Efficacy

Not applicable.

6.3 Pharmacokinetics/pharmacodynamics

Not applicable.

6.4 Safety

If not stated otherwise, analyses will be performed on the FAS population.

6.4.1 Adverse Events (AEs)

Individual listings of AEs will be provided.

The incidence of AEs will be summarized by cohort using MedDRA terms.

Healthcare resources

Information regarding healthcare resources will be listed.

Serious adverse events and deaths

For serious AE outcomes, AEs leading to discontinuation and deaths, listings of subjects will be provided by cohort, subject and/or AE.

6.4.2 Vital Signs

Vital signs parameter will be summarized by cohort/total and visit using descriptive statistics including arithmetic mean, standard deviation (SD), median, minimum and maximum. Statistics will be presented for the original data and difference to baseline.

Graphical displays of individual data as well as mean values with standard deviations will be created for each parameter by cohort using planned sampling times.

6.4.3 ECG

All quantitative ECG parameters will be summarized by visit and cohort/total using descriptive statistics including arithmetic mean, SD, median, minimum, and maximum.

Graphical displays of individual data as well as mean values with standard deviations will be created for each parameter by cohort using planned sampling times.

Qualitative ECG parameters will be summarized by parameter, cohort and visit using frequency tables.

The number of subjects with QT, QTcB, and QTcF values ≤450 msec, >450-480 msec, >480-500 msec and >500 msec will be summarized by cohort.

6.4.4 Echocardiography

All quantitative echocardiography parameters will be summarized by visit and cohort/total using descriptive statistics including arithmetic mean, SD, median, minimum, and maximum.

Graphical displays of individual data as well as mean values with standard deviations will be created for each parameter by cohort using planned sampling times.

Qualitative echocardiography parameters will be summarized by parameter, cohort and visit using frequency tables.

6.5 Other evaluations

If not stated otherwise, analyses will be performed on the FAS population.

For each parameter (6-minute walking distance, KCCQ, PRO), subjects will be split into classes representing clinically relevant worsening versus no relevant change or improvement. The exact definition will be given in the respective subsection.

6.5.1 6-minute walking distance

The 6MWD will be summarized by visit and cohort/total using descriptive statistics including arithmetic mean, SD, median, minimum, and maximum.

A frequency table will be created for the comparison of the subjects with and without observed worsening according to the following definitions:

- Worsening: decrease in 6MWD by at least 30 meters
- No worsening: decrease in 6MWD by up to 30 meters, no change or increased 6MWD

6.5.2 Quality of life / PRO

6.5.2.1 KCCQ

The summary scores “Total Symptom Score”, “Clinical Summary Score”, and “Overall Summary Score” as well as the “Physical Limitation Scores” will be summarized using frequency counts by cohort and total.

A frequency table will be created for the comparison of the subjects with and without observed worsening according to the following definitions:

- Worsening: decrease in KCCQ score by at least 5 points
- No worsening: decrease in KCCQ score by up to 5 points, no change or increased KCCQ score

6.5.2.2 PRO

The “Overall Activity Score” will be calculated as the sum of the following mean items:

walking general, housework, and exercise.

The parameters

- Overall Activity Score
  - o General physical activity item (1 unit change on weekly average score)
  - o Physical activity impression of change item (2 unit change)
  - o Fatigue impression of change item (2 unit change)
  - o Shortness of breath impression of change item (2 unit change)
  - o Swelling impression of change item (2 unit change)

will be summarized using frequency count.

In addition, response with respect to the anchor measures derived from thee following individual items

- General physical activity item (1 unit change)

- Physical activity impression of change item (2 unit change)
- Fatigue impression of change item (2 unit change)
- Shortness of breath impression of change item (2 unit change)
- Swelling impression of change item (2 unit change)

will be tabulated using frequency tables.

A frequency table will be created for the comparison of the subjects with and without observed worsening according to the following definitions:

- Worsening: decrease in "Overall Activity Score" by at least 2 units
- No worsening: decrease in "Overall Activity Score" by up to 2 points, no change or increased "Overall Activity Score"

The univariate linear mixed model (LMM) for the repeated values of the "Overall Activity Score" is

$$Y_{ij} = \mu + S_i + \nu_j + \beta base_i + E_{ij}$$

where μ is a constant common to all observations, S_i is the normally distributed random variable with mean zero and variance σ_d^2 corresponding to subject i, ν_j is the fixed effect corresponding to visit j, and E_{ij} is a normally distributed random variable with mean zero and variance σ_ε^2, independent of S_i. The variable "base" is the baseline measurement included as covariate and β is the corresponding regression parameter.

Based on the described LMM, point estimates and 90% confidence intervals for the "Overall Activity Score" will be calculated.

6.5.3 Biomarker laboratory

Biomarker parameter will be summarized by cohort/total and visit using descriptive statistics including arithmetic mean, SD, median, minimum and maximum. Statistics will be presented for the original data and difference to baseline.

Graphical displays of individual data as well as mean values with standard deviations will be created for each parameter by cohort using planned sampling times.

6.5.4 Wearable data

6.5.4.1 DynaPort

The analysis of the DynaPort data will be performed on on the DES population.

Summary statistics for the wearing time of DynaPort data will be presented by cohort and wearing period.

The following parameters (mean, minimum and maximum over wearing period) will be analyzed:

- Steps
- Physical Activity Level (PAL)
- Total Energy Expenditure (TEE)

- Active time (Sum of standing, shuffling, walking, stair walking and cycling time)
- Time spent in different activity states (sedentary / light / moderate / vigorous)

The DynaPort parameters mentioned above will be summarized by cohort/total and visit using descriptive statistics including arithmetic mean, SD, median, minimum and maximum. Statistics will be presented for the original data and difference to baseline.

Graphical displays of individual data as well as mean values with standard deviations will be created for each parameter by cohort using planned sampling times.

The univariate LMM for the repeated values of the DynaPort parameters is

$$Y_{ij} = \mu + S_i + \nu_j + \beta base_i + E_{ij}$$

where μ is a constant common to all observations, S_i is the normally distributed random variable with mean zero and variance σ_d^2 corresponding to subject i, ν_j is the fixed effect corresponding to visit j, and E_{ij} is a normally distributed random variable with mean zero and variance σ_ε^2, independent of S_i. The variable "base" is the baseline measurement included as covariate and β is the corresponding regression parameter.

Based on the described LMM, point estimates and 90% confidence intervals for the DynaPort parameters will be calculated.

Subgroup analyses will be performed for the defined categories (worsening / no worsening) of 6MWD, KCCQ and PRO.

7. Document history and changes in the planned statistical analysis

7.1 Document history

- SAP Version 1.0, 14 APR 2021

7.2 Changes in the planned statistical analysis

The planned analysis described in the CSP were revised comprehensively for the following reasons:

- Lower number of subjects included
- Changes in procedure schedule
- Changes of device
- Changes of parameters provided by the vendor

8. References

[1] Integrated Clinical Study Protocol No. BAY 1067197 / 19167, version 4.0, dated 21 FEB 2020

[2] Clinical Pharmacology Standards (CLIPS), version 3.0, dated 05 AUG 2020