Document Type:	Study Protocol
Official Title:	Real Life Multimarker Monitoring in Patients with Heart Failure
NCT Number:	NCT03507439
Document Date:	21-FEB-2020

Cover page of the integrated protocol

Real Life Multimarker Monitoring in Patients with Heart Failure

This protocol version is an integration of the following documents / sections:

Original protocol, Version 1.0, dated 06 Apr 2017

Amendment 1 (described in Section 15.1)
forming integrated protocol Version 2.0, dated 14 May 2018

Amendment 2 (described in Section 15.2)
forming integrated protocol Version 3.0, dated 06 Sep 2018

Amendment 3 (described in Section 15.3)
forming integrated protocol Version 4.0, dated 21 Feb 2020

Amendments not included in the consecutive numbering of amendments are local amendments not forming part of this integrated global protocol.

1. Title page - amended

Real Life Multimarker Monitoring in Patients with Heart Failure

REALIsM-HF pilot study

Test drug:	Not applicable		
Medical devices:	VitalPatch biosensor[1] (VitalConnect[1], USA) DynaPort Move Monitor (McRoberts, NL)		
Clinical study phase:	Not applicable	Date:	21 Feb 2020
Registration:	Not applicable	Version no.:	4.0
Sponsor's study no.:	19167		
Sponsor:	Bayer AG, D-51368 Leverkusen, Germany		
Sponsor's medical expert:	PPD Bayer AG Aprather Weg 18a 42113 Wuppertal, Germany Phone : PPD E-mail : PPD		

The study will be conducted in compliance with the protocol, ICH-GCP and any applicable regulatory requirements.

[1] Replacement of AVIVO MPM with VitalPatch Biosensor as per Amendment 2 (Section 15.2)

Signature of the sponsor's medically responsible person

The signatory agrees to the content of the final clinical study protocol as presented.

Name: PPD Role: PPD

Date: 24-Feb-2020 Signature: PPD

Signature of principal investigator

The signatory agrees to the content of the final clinical study protocol as presented.

Name: PPD

Affiliation: PPD

Date: 21-Feb-2020 Signature: PPD

Signed copies of this signature page are stored in the sponsor's study file and i PPD pective center's investigator site file.

In the protocol document, this page may remain unsigned.

2. Synopsis – amended

Title	Real Life Multimarker Monitoring in Patients with Heart Failure
Short title	REALIsM-HF pilot study
Clinical study phase	Exploratory study evaluating the clinical utility and feasibility of activity tracking in patients with HFrEF and HFpEF. All medicinal products are used in accordance with the terms of the marketing authorization. Additional diagnostic or monitoring procedures do not pose more than minimal additional risk or burden to the safety of the subjects compared to normal clinical practice.
Study objective(s)	The study aims to explore two marketed devices providing a multi-marker monitoring including physical activity under real-life conditions in patients with HFpEF and HFrEF. It aims to identify potential novel endpoints for future HFpEF trials by exploring clinically relevant changes over time and correlations/associations with conventional endpoints such as the six-minute-walking-distance (6MWD), biomarkers and clinical events. Furthermore, it aims to address the challenges and feasibility of implementing device-based measurements under real-life conditions. In addition, it is hypothesized that "subjective" items generated from patient experiences (PRO, QoL) in combination with an (objective) activity monitor would capture all relevant dimensions of exercise capacity in patients with HFpEF and HFrEF and thus can be used as patient centric approach in clinical studies. **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[2] 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, 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.[3]

[2] Replacement of AVIVO MPM with VitalPatch Biosensor as per Amendment 2 (Section 15.2)

[3] Tissue impedance deleted as per Amendment 3 (Section 15.3)

	• Assess the feasibility of activity tracking with two devices (VitalPatch biosensor[4] and DynaPort Move Monitor) in patients with heart failure • Correlation of activity data between VitalPatch biosensor[4] data on activity and DynaPort Move Monitor
	• Evaluate the relationship between physical activity levels, heart rate, 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)[5] • 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 [6,7] • Correlation between patch monitor collected data and patient clinical data from the start of the study (e.g. echocardiography, weight gain/loss, NYHA, heart rate) • Explore the relationship between physical activity (PA), 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[4]
Medical Devices **Device 1** **Device 2**	VitalPatch biosensor (VitalConnect, USA)[4] DynaPort Move Monitor (McRoberts, NL) The devices will be provided by BAYER to sites and used according to their approved labeling.
Background treatment	During the study duration changes in treatment for HF and comorbidities should be based on clinical need. There is no change of the therapy required according to the protocol.

[4] Replacement of AVIVO MPM with VitalPatch Biosensor as per Amendment 2 (Section 15.2)

[5] tissue impedance deleted as per Amendment 3 (Section 15.3)

[6] Transcutaneous thoracic impedance measurement and its correlation to biomarkers deleted as per Amendment 3 ((Section 15.3)

[7] Wording adapted as per Amendment 3 (Section 15.3)

Indication	Heart failure with preserved ejection fraction (HFpEF) and Heart failure with reduced ejection fraction (HFrEF)
Diagnosis and main criteria for inclusion /exclusion	Female and male subjects with a diagnosis of heart failure with preserved ejection fraction (HFpEF; EF ≥ 45%) or reduced ejection fraction (HFrEF; EF ≤ 35%) will be enrolled.[8]
Study design	Multi-center, non-blinded, non-randomized, observatory prospective patient study
Methodology[9]	This study will comprise a screening phase of up to 9 days including an optional hospitalization period, an outpatient phase of approximately 12 weeks and a follow up telephone call after 6 months Patients will be selected on the basis of their established diagnosis of HFrEF and HFpEF. The patients will have site visits at week 0 (screening visit and visit 1 within 9 days, during hospitalization phase or in ambulatory patients), week 1 after visit 1 / hospital discharge (visit 2; observational phase), week 11 post visit 1 / discharge (visit 3, observational phase) and week 12 post visit 1 / discharge (visit 4, observational phase). In addition, one follow up phone call at 6 month post discharge will be made to assess patient safety, well-being and clinical status. The VitalPatch[10] heart failure patch will be applied at visit 1 / hospital discharge (first VitalPatch biosensor patch)[10], at visit 2 (2nd patch, 3rd patch will be subsequently applied by the patient at home), and at visit 3 (4th patch, 5th patch will be subsequently applied by the patient at home). The Dynaport MoveMonitor belt will be applied at visit 2 and visit 3. The 6MWD test will be done at visit 1 / hospital discharge as well as visit 4 (12 weeks post visit 1 / discharge). Transthoracic echocardiography will be performed at visit 1 (within ± 72 hours). The KCCQ questionnaire will be performed at visit 1 / prior to discharge, at week 3 after visit 1 / discharge, and at visit 4. Daily and weekly PRO will be performed in parallel with the DynaPort MoveMonitor monitoring periods (visit 2, week 2-3) and visit 3 (week 11-12). Biomarkers reflecting cardiac structure and function will be examined as well as candidate biomarkers that may predict outcomes. Daily physical activity (duration and intensity) will be recorded during repeated respective 5-day (Vital Patch) and 7-day (DynaPort MoveMonitor) time periods until 3 months after visit 1 / discharge from hospital.

[8] Diagnosis extended as per Amendment 3 (Section 15.3)

[9] Methodology adapted to new conduct specifications as per Amendment 3 (Section 15.3)

Type of control	not applicable
Number of subjects	Due to the exploratory nature of this study, and to the multiplicity and the type of the observed parameters, the number of target subject was chosen to be comparable with other studies where a significant difference in PA was observed. The study will enroll enough subjects to have 80 subjects (HFpEF n=60, HFrEF n=20) who completed the main study, i.e. visit 4.
Primary variable(s)	Daily physical activity (amount, intensity, duration) obtained from the VitalPatch biosensor[11] / DynaPort Move Monitor device
Time point/frame of measurement for primary variable(s)	Baseline level and longitudinal changes over time of physical activity and the average of person-to-person physiological variability and the within-subject standard deviation between the baseline and 3-month post baseline measurements.[12]
Plan for statistical analysis	Statistical analyses will be of explorative and descriptive nature. The study is not aimed to confirm or reject pre-defined hypotheses. All variables will be analyzed descriptively with appropriate statistical methods: categorical variables by frequency tables (absolute and relative frequencies) and continuous variables by sample statistics (i.e. mean, standard deviation, minimum, median, quartiles and maximum). Continuous variables will be described by absolute value and as change from baseline per analysis time point, if applicable. The variability of biomarkers assumed to be normal distributed will be analyzed using a linear mixed effect model with subject as random factor, and time as fixed factor, possibly including additional covariates as may result from the assessment at baseline for subject stratification or as required for clinical interpretation. Based on this model, point estimates (LS-Means) and exploratory 90% confidence intervals will be calculated for comparing baseline and 3 months data. For biomarkers assumed to be log-normal distributed, the logarithms of the biomarker concentration will be analyzed, and results will be reported as ratio for comparing baseline and 3 months data. All analyses will be performed for the total study population (overall analysis). Subjects wearing at least once the VitalPatch biosensor[11] system and for which data was successfully collected over 5 days [13] will be included in the analysis. Sample size and disposition information by analysis time point will be displayed in a frequency table.

[10] Replacement of AVIVO MPM with VitalPatch Biosensor as per Amendment 2 (Section 15.2)

[11] Replacement of AVIVO MPM with VitalPatch Biosensor as per Amendment 2 (Section 15.2)

[12] Adapted to reflect the extension on non-hospitalized subjects as per Amendment 3 (Section 15.3)

[13] Adapted to reflect the limitations of the VitalPatch biosensor system as per Amendment 3 (Section 15.3)

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List of abbreviations

AE	adverse event
AF	atrial fibrillation
BNP	B-type natriuretic peptide
CABG	Coronary artery bypass graft
CRO	contract research organization
CRTD	Implantation of a cardiac resynchronization therapy device
DMP	data management plan
(e)CRF	(electronic) case report form
ECG	electrocardiogram
EDC	electronic data capture
EU	European Union
FPFV	first patient first visit
Gal 3	Galectin-3
GCP	good clinical practice
GDF 15	growth differentiation factor 15
GOLD	Global Initiative for Chronic Obstructive Lung Disease
HF	heart failure
HFmrEF	heart failure with mid-range ejection fraction
HFpEF	heart failure with preserved ejection fraction
HFrEF	heart failure and reduced ejection fraction
HRV	heart rate variability
hsTNT	high-sensitivity troponin T
ICH	International Conference of Harmonization
IEC	Independent ethics committee

IGFBP7	insulin-like growth factor binding protein 7
INN	international nonproprietary name
IRB	institutional review board
KCCQ	Kansas City Cardiomyopathy Questionnaire score
LPLV	last patient last visit
MedDRA	Medical Dictionary for Regulatory Activities
MPM	mobile patient monitoring
MRP	medical review plan
6MWD	six minute walking distance
NT-proBNP	N-terminal propeptide of BNP
NYHA	New York Heart Association
PA	physical activity
PCI	Percutaneous coronary intervention
PRO	patient reported outcome
QoL	quality of life
QRP	quality review plan
SAE	serious adverse event
SAP	statistical analysis plan
SOP	standard operating procedure
sST2	Soluble suppression of tumorigenicity 2

3. Introduction - amended

Rationale and Background

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 [1, 2].

Acute decompensated heart failure is constantly increasing in prevalence and is strongly associated with mortality and morbidity, including frequent hospitalizations [3, 4]. The high percentage (30 – 60%) of readmissions within 6 months is particularly noteworthy [5].

Heart failure with preserved ejection fraction (HFpEF) currently accounts for more than 50% of all HF cases and shows rising incidence [6], 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 CV 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.[7] Though intensively managed, these patients remain symptomatic and have substantially reduced functional capacity and quality of life (QoL).

Improvement in mortality remains the gold standard outcome for HF clinical trials, and indeed many therapies in patients with HFrEF were able to reduce the risk of death. However, in HFpEF patients, the competing risk for death by complex comorbidities is substantial among these patients. Effectively targeting mechanisms related to HFpEF may improve underlying pathophysiology and subsequently patient status; however, this may be insufficient to alter overall mortality among HFpEF patients. Thus, in an older HFpEF population due to the competing risk for death, it may be prohibitively difficult to improve mortality as a singular goal of therapy. Reducing the risk of hospitalizations is an important consideration as they are associated with poor outcomes, high costs and impaired QoL. However, one of the major issues is that it may reflect regional practices [8].

Thus, alternate patient centric outcomes reflecting “patient journey” should be pursued as reasonable basis for drug approval in HFpEF. 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.

The traditional approach for vital signs and biometrical data monitoring is based on in-hospital spot-check measurements, which do not effectively characterize human physiology in real life environment. Current trends in the assessment of physical activity focus on the measures of amount and frequency of activities using activity monitors in real life environment. Biometrical data monitored from arrival to the hospital, throughout the hospital stay, and continued at home, based on new device technology offers a unique opportunity to explore these new endpoints in HF patients. In patients with HFpEF, small changes in physical activity are likely to be important effects of interventions aimed at enhancing physical activity and improvement of QoL. Therefore, in order for investigators to interpret the effect of interventions on physical activity, activity monitors that have been properly validated in these patient groups are needed.

As these new digital technologies are technically validated but not yet fully clinically validated, it is not clear whether clinical studies should harness the power of mobile health data to improve therapeutic outcomes and trial efficiency. These analytic devices need to be further evaluated for their clinical feasibility and the ability to identify clinically relevant changes. Furthermore, it is unlikely that an activity monitor can fully capture patients' experience of physical activity. For example, in chronic obstructive pulmonary disease patients, qualitative research has shown that patients experience symptoms while being active, or have to adapt their lifestyle, features that will unlikely be captured using activity monitors alone. Such a patient-centered concept should therefore include a PRO questionnaire in addition to tracking of physical activity. Conversely, a PRO questionnaire alone will also not allow assessment of physical activity patterns or detection of small changes in physical activity on a day-to-day basis. Unfortunately, the currently available PROs that aim to measure physical activity in HFpEF patients do not follow best practice as set out in the guidelines published by the US Food and Drug Administration (FDA).[9] Thus, in addition to testing the feasibility of activity tracking with two different devices, the present study aims to identify a set of non-redundant items for a potential PRO questionnaire in HFpEF. The data in HFrEF will help generate hypotheses and aid in determining the feasibility of physical activity tracking with different devices in patients with HFrEF as well as HFpEF.

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.

It is hypothesized that “subjective” items generated from patient experiences (PRO) in combination with an (objective) activity monitor would capture all relevant dimensions of physical activity in patients with HFpEF.

The VitalPatch biosensor[14] is a wearable, wireless physiological monitoring and arrhythmia detection system that is used by patients to aid clinicians in the identification, diagnosis and management of various clinical conditions, events and/or trends. It consists primarily of the wearable sensor (monitoring device) and a portable secured data transmitter (mobile phone with bluetooth and wireless connection). VitalPatch is manufactured by VitalConnect (USA), and is fully approved by the USA FDA, CE marked in the European Union, CMDR registered and ISO 13485 certified.[14]

The VitalPatch biosensor[14] will be used to monitor patients’ cardiovascular status. The cardiac monitoring device will be worn as specified in Section 9.7.1.

The system is intended to continuously measure, record and store ECG data. The system can detect (but is not limited to) higher degree AV-blocks > I°, SVTs (e.g. atrial fibrillation [AF], atrial flutter, paroxysmal SVTs), ventricular ectopy, bradyarrhythmias, conduction disorders and heart rate variability. Apart from safety assessments, also the patient’s everyday physical activity (frequency, duration, intensity) will be tracked.

[14] Replacement of AVIVO MPM with VitalPatch Biosensor as per Amendment 2 (Section 15.2)

Details of the cardiac monitoring and the device to be worn by the patient will be outlined in a manual that will be provided to all participating centers.

The DynaPort Move Monitor – the second activity tracker used in the present study -is a wearable device worn in an elastic strap on the lower back for ambulatory monitoring of physical activity for up to 7 days. DynaPort Move Monitor is manufactured by McRoberts BV (Netherlands). This device is US FDA approved, CE marked in the European Union and ISO 13485 certified.[15] The DynaPort Move Monitor consists of three orthogonally mounted accelerometers, a tri-axial magnetometer, a temperature sensor and a barometer. Accelerometer data were collected at 100 Hz and stored on an internal flash memory drive. The DynaPort Move Monitor is attached centrally over the lower back with an elastic belt around the waist. The MoveMonitor distinguishes movement patterns (walking, shuffling, cycling, stair climbing) and body positions (standing, sitting, lying) during long-term measurements, and it measures the intensity (acceleration) at which movements such as walking are performed. The data collected will be uploaded to a secured cloud server, and the positions and accelerations of the 3 sensors will be analyzed with the MoveMonitor software. The software translates the recorded acceleration signals into basic activities (walking, shuffling, cycling, stair climbing) and postures (standing, sitting, lying) and quantifies the time spent in each of these activities or postures.

Benefit-risk assessment

The patients will not benefit from this study as they are treated according to standard of care and will receive no investigational drug. The devices, the questionnaires and the blood biomarkers will not have an influence on the treatment of the patients as these are only observational assessments which will have no effect on the well-being or disease progression of the patients.

Both devices have a CE mark and an FDA approval and are safe and well tolerated. All medicinal products are used in accordance with the terms of the marketing authorization.

The patients will have no direct individual therapeutic advantage from the participation in this clinical investigation, but their participation in the investigation is likely to contribute to benefits for specific patient groups.

All potential risks arising from the patients' participation in the clinical investigation have been carefully assessed and found acceptable; they are outweighed by the foreseeable benefits for specific patient groups, especially for the population included in this study – patients with HFpEF - in the development of an effective treatment for HFpEF.

Additional diagnostic or monitoring procedures do not pose more than minimal additional risk or burden to the safety of the subjects compared to normal clinical practice.

Therefore, the overall risk/benefit ratio is considered favorable for study participants.

Details of the cardiac monitoring and the devices to be worn by the patient will be outlined in a manual.

4. Study objectives - amended

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[15] 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, 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[16]
- Assess the feasibility of activity tracking with two devices (VitalPatch biosensor[15] and DynaPort Move Monitor) in patients with heart failure
- Correlation of activity data between VitalPatch biosensor[15] data on activity and DynaPort Move Monitor
- Evaluate the relationship between physical activity levels, heart rate, 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)[16]
- 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 [16]
- Correlation between patch monitor collected data and inpatient clinical data during hospital stay (e.g. echocardiography, weight gain/loss, NYHA, heart rate)
- Explore the relationship between PA, 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[17]

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[15] Replacement of AVIVO MPM with VitalPatch Biosensor as per Amendment 2 (Section 15.2)

[16] Tissue impedance deleted as per Amendment 3 (Section 15.3)

[17] Replacement of AVIVO MPM with VitalPatch Biosensor as per Amendment 2 (Section 15.2)

5. Study design - amended

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:

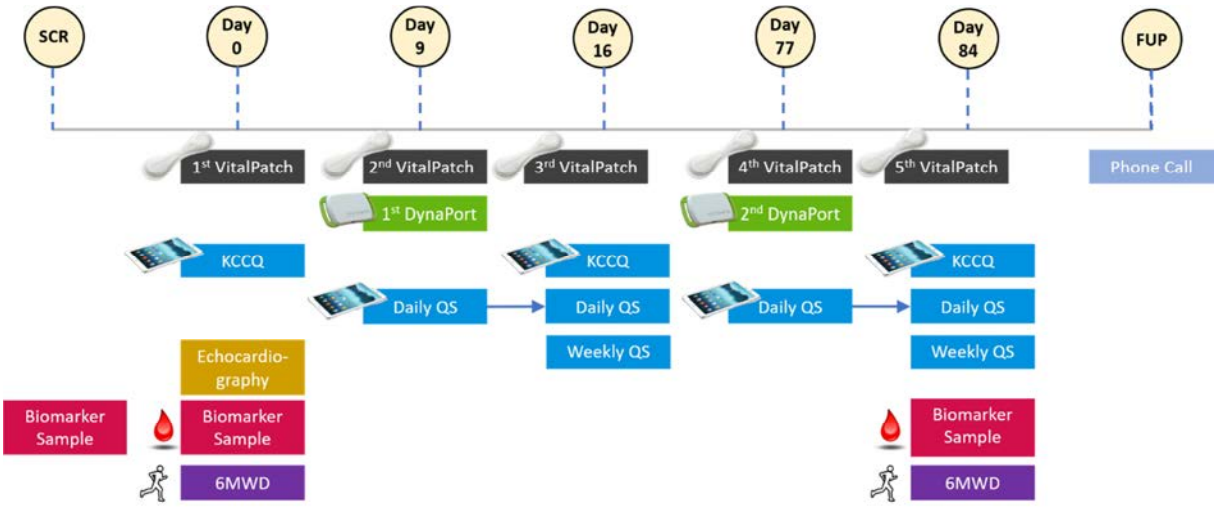
- Approx. 60 subjects with established diagnosis of heart failure with preserved ejection fraction (HFpEF; EF ≥ 45%) and
- Approx. 20 subjects with established diagnosis of heart failure with reduced ejection fraction (HFrEF; EF ≤ 35%).

All patients will receive the VitalPatch biosensor[17] at 5 monitoring periods (5 patches each subject in total, monitoring period 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 5-1: Study design - amended[18]



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

[18] Replacement of AVIVO MPM with VitalPatch Biosensor as per Amendment 2 (Section 15.2), simplification of number and timing of study-related procedures as per Amendment 3 (Section 15.3)

Primary variables

- Daily physical activity (amount, duration and intensity) obtained from the VitalPatch biosensor[18] /DynaPort Move Monitor device

Secondary variables

- 6MWD
- Other activity information obtained from the VitalPatch biosensor[18] /DynaPort Move Monitor device such as sleep movements and patterns, sit-to stand behavior (DynaPort)
- QoL as measured with the Kansas City Cardiomyopathy Questionnaire score (KCCQ)/PRO
- Plasma/serum biomarkers
- Blood pressure and heart rate, cardiac function parameters measured by echocardiography
- ECG derived readouts: heart rate variability (HRV)
- NYHA class

Results of the primary and secondary variables obtained at 3 months post-baseline (week 11-12) versus baseline (visit 1).

Justification of the design

The open study design is considered acceptable and justified, because the variables of the study are objectively measured results that are unlikely to be subject to investigator or study patient induced bias.

Male and female patients will be enrolled into this study. There are no reasons to date (i.e. safety reasons) to exclude women from these investigations.

The chosen study design is considered to be appropriate to establish a baseline for potential further objectives for the evaluation of efficacy of treatment responses in patients with heart failure, particularly HFpEF. The statistical analysis of this trial is performed in an exploratory manner.

This pilot study serves as a preparatory study designed to test the performance characteristics and capabilities of new measures, procedures, recruitment criteria, and operational strategies that are under consideration for use in a subsequent, larger, interventional study; cohort study is the appropriate study design for this pilot study. The aims and methods of this pilot study are aligned with the goals of potentially subsequent studies in BAYER's target indications. The study will contribute to the development and design of future studies by clarifying and sharpening the research hypotheses to be studied, assessing the clinical utility of emerging readouts, identifying relevant factors that could create barriers to subsequent study completion, evaluating the acceptability of methods and instruments to participants, measuring the time required for study participation, and providing concrete estimates of the expected rates of missing data and participant attrition.

In addition, the study aims to estimate baseline values and standard deviation of potential pharmacodynamic outcome measures related to the physical activity (e.g. movement intensity, daily steps) to give information for sample size calculations in subsequent trials. Furthermore, the study will improve the understanding of study questionnaires or data collection tools

However, results from these kinds of studies can be influenced by unpredictable confounding factors.

End of study

The end of the study as a whole will be reached as soon as the last visit of the last subject has been reached in all centers in all participating countries (EU and non-EU).

6. Study population

6.1 Inclusion criteria - amended

1. Written informed consent signed before any study-specific procedure
2. Men or women aged 45 years and older
3. Established diagnosis of chronic heart failure NYHA class II-IV
4. Worsening heart failure requiring hospitalization for the initiation of intensification of heart failure therapy with ***at least one*** of the following
    - BNP ≥ 100 pg/mL or NT-proBNP ≥ 400 pg/mL (sinus rhythm) or
      BNP ≥ 300 pg/mL or NT-proBNP ≥ 1200 pg/mL (atrial fibrillation)
    - Radiographic evidence of pulmonary congestion (interstitial edema, pulmonary venous hypertension, vascular congestion, pleural effusion)
    - Catheterization documented elevated filling pressures at rest (left ventricular end-diastolic pressure ≥15 mmHg or pulmonary capillary wedge pressure ≥20 mmHg) or with exercise (pulmonary capillary wedge pressure ≥25 mmHg)

   OR

   Ambulatory patients with a history of heart failure on individually optimized treatment with HF medications unless contraindicated or not tolerated[19], for at least 12 weeks and ***at least one*** of the following
    - Hospitalization for heart failure within the past 12 months or
    - BNP ≥ 100 pg/mL or NT-proBNP ≥ 400 pg/mL (sinus rhythm) or
      BNP ≥ 300 pg/mL or NT-proBNP ≥ 1200 pg/mL (atrial fibrillation)

[19] Inclusion criteria extended to ambulatory subjects with chronic heart failure as per Amendment 3 (Section 15.3)

5. For HFrEF only
    - EF ≤ 35% assessed by any imaging modality (e.g. echocardiography, cardiac magnetic resonance, cine levocardiography) within 12 months prior to study inclusion
6. For HFpEF only
    - EF ≥ 45% assessed by any imaging modality (e.g. echocardiography, cardiac magnetic resonance, cine levocardiography) within 12 months prior to study inclusion
7. Willingness to wear the DynaPort Move Monitor accelerometer belt and VitalPatch biosensor[20] during the trial
8. Body size allows wearing of the accelerometer belt as confirmed by ability to comfortably fasten the test belt provided for the screening process

6.2 Exclusion criteria - amended

1. Inability to comply with planned study procedures or to comply with study protocol requirements; this includes completing required data collection, and attending required follow up study visits
2. Hemoglobin <8.0 g/dl[21]
3. Acute coronary syndrome or percutaneous coronary intervention within 3 months prior to informed consent
4. Listing for heart transplantation and / or anticipated implantation of a ventricular assist device
5. Inability to exercise: wheelchair / scooter / walker dependent; dependent on supplemental oxygen
6. Known clinically significant persistent coronary ischemia (based on medical history, a preexisting or a recent clinical stress test)
7. HF is *not* the primary factor limiting activity within the last three months as indicated by the patient affirming #1, #2 or #3 of the following questionnaire:

   My ability to be active is *most* limited by:

   #1 - Joint, foot, leg, hip or back pain

   #2 - Unsteadiness or dizziness impairing daily mobility

   #3 - Lifestyle, weather, or I just don't like to be active
8. Occurrence of any of the following within 3 months prior to informed consent:
    - Myocardial infarction
    - Hospitalization for unstable angina

[20] Replacement of AVIVO MPM with VitalPatch Biosensor as per Amendment 2 (Section 15.2)

[21] Exclusion criterion modified to improve enrolment as per Amendment 3 (Section 15.3)

- Stroke or transient ischemic attack
- Coronary artery bypass graft (CABG)
- Percutaneous coronary intervention (PCI)
- Implantation of a cardiac resynchronization therapy device (CRTD)
- Major surgery (that could interfere with patients' ability to exercise)

9. PCI, CABG or implantation of a CRTD planned between randomization and Visit 4
10. Subject who cannot tolerate placement of external patch monitor on chest in the proposed location (ECG lead II orientation)
11. Subject with known allergies or hypersensitivities to adhesives or hydrogels
12. deleted[22]
13. Severe uncorrected valvular heart disease
14. Known clinically relevant ventricular arrhythmias (sustained ventricular tachycardia, ventricular flutter or fibrillation)
15. Severe pulmonary disease with any of the following:
    - Requirement of continuous (home) oxygen or
    - History of chronic obstructive pulmonary disease ≥ GOLD III
16. Previous (within 30 days or 5 half-lives of the investigational drug, whichever is longer) or concomitant participation in another clinical study with investigational medicinal product(s) or device(s)
17. Any condition or therapy, which would make the patient unsuitable for the study, or life expectancy less than 12 months (e.g. active malignancy)
18. Heavy alcohol consumption or the use of illicit drugs that, in the opinion of the investigator, may interfere with the patient's safety and / or compliance
19. Patients who regularly (> 1x per week) swim, do water aerobics or go to the sauna, unwilling to omit this activity while needing to wear the study specific medical devices[23]
20. Active myocarditis
21. Primary hypertrophic cardiomyopathy
22. Constrictive pericarditis or pericardial tamponade
23. Close affiliation with the investigational site; e.g. a close relative of the investigator, dependent person (e.g. employee or student of the investigational site)
24. Previous participate in the study

[22] exclusion criterion deleted (referred to restrictions of the AVIVO patch) as per Amendment 3 (Section 15.3)

[23] exclusion criterion specified as per Amendment 3 (Section 15.3)

6.3 Justification of selection criteria

Bayer develops several investigational medicinal products for the indication HFpEF for which until now no successful treatment is available. Until now all endpoints failed and were not predictive for the outcome of the patient's disease progression. Bayer intends to develop new endpoints and variables, which later might be useful to monitor pharmacodynamics effects and for the prediction of disease progression in interventional studies with new drugs.

Digital device-derived biomarkers are of high interest regarding the identification of new potential endpoints, especially for patient populations where no predictable biomarkers are available.

The new European guidelines (2016) for heart failure (HF) include the concept of HF with intermediate left ventricular ejection fraction (heart failure with mid-range ejection fraction, HFmrEF), i.e. an LVEF between 40 and 49%.[1] However, a substantial heterogeneity may exist within patients with HFmrEF. In particular, this group may include both patients with de novo HF and patients with HF with previously reduced LVEF who have recovered their systolic function. Furthermore, considering the technical variability of echocardiographic assessment of ejection fraction as well as the biological variability, patients within the mid-range ejection fraction may represent patients with HFpEF as well as HFrEF. For the purpose of this study, it is critical to study well defined patient groups with either HFpEF or HFrEF to avoid a relevant overlap between both groups. Therefore, the inclusion criteria with respect to ejection fraction differ from current guidelines slightly. However, cut-off values used in the present study have also been used in several previous studies in patients with heart failure.

This study serves as a pilot study to identify a baseline for several digital biomarkers in HFpEF patients. In parallel some HFrEF patients are included for which a baseline for some of the device readouts is already available derived from studies with implantable cardioverter-defibrillator and cardiac resynchronization therapy devices. They serve as internal plausibility control.

Therefore, it is essential to include HFpEF and HFrEF patients in this study.

6.4 Withdrawal of subjects from study

6.4.1 Withdrawal

Withdrawal criteria

An excessive rate of withdrawals (either patients discontinuing study medication or study withdrawal) can render the study non-interpretable. Therefore, un-necessary withdrawal of patients should be avoided, and all efforts should be taken to motivate patients to comply with all the study specific procedures and to be followed until the end of the trial to complete all study procedures and to detect the occurrence of cardiovascular events/assess the vital status. A patient has the right to withdraw from the study at any time and for any reason without prejudice to his or her future medical care by the physician or the institution. Patients who withdraw consent after enrolling will be evaluated to the time of withdrawal. If possible, the final assessment should be performed on all patients at the time of withdrawal. Patients should not be withdrawn from follow-up unless the patient explicitly withdraws consent to be contacted. All efforts should therefore be made to minimize the number of patients who withdraw such consent as, in general, no further information on cardiovascular events and survival status may be collected after that point.

Patient will be withdrawn from the study for the following reasons:

- At their own request or at the request of their legally acceptable representative. At any time during the study and without giving reasons, a subject may decline to participate further. The subject will not suffer any disadvantage as a result.
- If, in the investigator's opinion, continuation of the study would be harmful to the patient's well-being,
- At the specific request of the sponsor and in liaison with the investigator (e.g. obvious non-compliance, safety concerns).
- Occurrence of adverse events or intercurrent diseases which the investigator judges unacceptable for continuation of participation in the study, or have from the investigator’s point of view, a negative impact on the patient’s individual risk-benefit ratio. (Investigators are obliged to reassess the patient’s individual risk-benefit ratio on a continuous basis. Factors like anticipated treatment effect, progression of underlying disease, occurrence of side effects and alternative treatment options have to be considered).
- In case a patient is diagnosed while on study with any disease condition listed within the exclusion criteria,
- Pertinent non-compliance with the conditions for the trial or instructions by the investigator.
- Although not preferred, patient may interrupt their monitoring program of study due to reasonable circumstances/reasons at any time (e.g. hospitalization, safety reasons, and side effects). If an interruption lasts longer than 14 days in a row, it is at the discretion of the investigator to discontinue the study participation, and the Case Report Form (CRF) of the termination visit must be completed. In case program has to be interrupted for less than 14 days, activity monitoring has to be restarted.
- Inclusion and exclusion criteria are being violated.

The reason of discontinuation and the specific details must be recorded in the CRF. The investigator should determine one primary reason for discontinuation (only one choice is permitted).

All safety relevant data until removal will be collected and reported.

Any patient removed from the study due to an AE must be monitored until symptoms subside/stabilize or until there is a satisfactory explanation of the changes observed.

Data collected until the time a patient discontinues participation in the study will be handled in the same manner as data for patients completing the study.

Any decision for withdrawal of individual patients will be made after mutual agreement between the investigator and the sponsor.

Depending on the time point of withdrawal, a withdrawn subject is referred to as either "screening failure" or "dropout" as specified below:

Screening failure

A subject who, for any reason (e.g. failure to satisfy the selection criteria), terminates the study before the time point used for the definition of "dropout" (see below) is regarded a "screening failure".

The participation of an initial "screening failure" subject at a later time point is acceptable if he/she meets all selection criteria.

In any case, the investigator has to ensure that the repeated screening procedures do not expose the subject to an unjustifiable health risk. Also, for re-screening, the subject has to re-sign the informed consent form, even if it was not changed after the subject's previous screening.

Dropout

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.

General procedures

In all cases, the reason for withdrawal must be recorded in the CRF and in the subject's medical records.

The subject may object to the generation and processing of post-withdrawal data as specified in Section 13.4.

Any subject removed from the trial will remain under medical supervision until discharge or transfer is medically acceptable.

Details for the premature termination of the study as a whole (or components thereof) are provided in Section 12 (Premature termination of the study).

6.4.2 Replacement

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.

6.5 Subject identification

The patient number is a 9-digit number consisting of:

Digits 1 to 5 = Unique center number

Digits 6 to 9 = Current patient number within the center

7. Treatments

7.1 Treatments to be administered

Subjects will not be treated with an interventional drug.

7.2 Identity of study treatment

Not applicable.

7.3 Treatment assignment

Not applicable.

7.4 Dosage and administration

Not applicable.

7.5 Blinding

Not applicable.

7.6 Drug logistics and accountability

Not applicable.

7.7 Treatment compliance

Not applicable

8. Non-study therapy

8.1 Prior and concomitant therapy

In accordance with standard local or international heart failure guidelines, all patients should be on standard HF therapy (an angiotensin-converting-enzyme inhibitor or angiotensin II receptor blocker, beta-blockers, mineralocorticoid receptor antagonist, angiotensin receptor-neprilysin inhibitor, as applicable), unless contraindicated or (to the investigator's knowledge) not tolerated. Concomitant therapy of comorbidities is allowed. During the study duration change of the background medications for heart failure should be based on clinical need. There is no change of the therapy required according to the protocol. All concomitant medication will be documented in the eCRF.

All medication taken 30 days before study start (initiated and stopped before study start) is termed prior medication.

All medication taken after enrollment for any indication (either initiated before study start or during the study) is termed concomitant medication and has to be documented. Information to

be collected for medication includes: trade name or INN, start date, stop date/ongoing, dose, unit, frequency, application route and indication.

8.2 Post-study therapy

There is no defined post-study therapy. Patients will continue their usual medical treatments, unless otherwise decided by the attending physician.

9. Procedures and variables

9.1 Tabular schedule of evaluations - amended

The investigator documents an initial visit, follow-up visits and the end of observation/final visit for each patient in the electronic case report form (eCRF). The end of observation visit will be documented after 12 weeks; a final follow-up call will be performed 6 months after visit 1 / discharge from hospital.[24]

Activities to be performed are summarized in the study flow chart in Table 9–1.

[24] Adapted to reflect the option to include ambulatory patients as per Amendment 3 (Section 15.3)

Table 9–1: Tabulated overview on study procedures and variables collected during the study - amended[25]

Study period	Screening phase		Observational phase				Safety FU call
Visit number	**Scr[1]**	**1**	**2**		**3**	**4**	**5**
Visit type	**site**	**site**	**site**		**site**	**site**	**☎**
	Screen assess	**At discharge / ambulatory visit**					
Week after discharge / Visit 1			**2**	**3**	**11**	**12**	
Day and allowed deviations	**-9 → -1**	**0**	**9±2**	**16±2**	**77±2**	**84±2**	**6 months ±4 weeks**
Signed informed consent form	●						
Inclusion / exclusion criteria	●						
KCCQ		●		●		●	
Daily and weekly PRO*			→----1st----←		→----2nd----←		
Demographic data	●						
Medical and surgical history	●						
Height	●						
Weight	●	●	●			●	
12-lead ECG	●	●				●	
NYHA class	●	●	●			●	
Blood pressure and heart rate	●	●	●		●	●	
Adverse Events incl. healthcare resources	●	●	●		●	●	●
Concomitant medication	●	●	●		●	●	●
Echocardiography		●[5]					
Six-minute walking distance		●				●	
DynaPort (for 7 days)[2] →start ←end			→----1st----←		→----2nd----←		
VitalPatch[26] (for 5 days)[2] →start ←end		→--1st--←	→ 2nd and 3rd ←		→ 4th and 5th ←		
Blood sample for biomarkers[3]	●[4]	●				●	

[1] during hospitalization; alternatively, in ambulatory patients

[2] DynaPort monitoring periods: For one week, after Visit 2 (Days 9-16) and from Visit 3 to Visit 4 (Days 77-84)
VitalPatch monitoring periods: first 5 days after hospital discharge / Visit 1 (Day 0-5), one week after Visit 2 (Day 9-16) and from Visit 3 to Visit 4 (Days 77-84)

[3] central lab assessments: NTproBNP, hs-copeptin, hs-TNT, optionally: GDF15, IGFBP7, sST2, Gal3

* Concurrently evaluating PRO will be completed daily and weekly during DynaPort and VitalPatch parallel monitoring period

[4] only applicable to hospitalized patients

[5] within ± 72 h of Visit 1 / discharge day

[25] Adaption of timing and number of study related measurements to simplify procedures as per Amendment 3 (Section 15.3)

[26] Replacement of AVIVO MPM with VitalPatch Biosensor as per Amendment 2 (Section 15.2)

9.2 Visit description - amended

Enrollment / Screening Visit - amended

Patients hospitalized with worsening HF will be asked to participate in this study; alternatively, also ambulatory patients can be enrolled.[27] The investigator will inform the patient about the study. This will include discussing the consent form and asking the patient to read and – when agreeing to participate – sign the informed consent.

The following activities will be performed at the enrollment/screening visit after signing patient informed consent:

- Check for inclusion / exclusion criteria
- Recording of

  Demographic data (including weight and height)
  Medical and surgical history
  Concomitant medication
  Adverse events (AEs) including the use of healthcare resources (e.g. HF hospitalizations and urgent visits for HF)[28]
- Recording of a 12-lead ECG
- Measurement of blood pressure and heart rate
- NYHA classification
- Blood sampling for biomarkers only for hospitalized patients

Visit 1 (Day 0) - amended

This visit will take place up to 9 days after the screening visit, potentially at discharge from the hospital. The following activities will be performed:

- Recording of
  Weight
  Concomitant medication
  AEs including the use of healthcare resources[28]
- Recording of a 12-lead ECG
- Conduct of echocardiography within ± 72 h of discharge day
- NYHA classification
- Measurement of blood pressure and heart rate
- Determination of 6MWD[29]
- Completion of KCCQ

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[27] Adapted to reflect the option to include ambulatory patients as per Amendment 3 (Section 15.3)

[28] Physical examination deleted to simplify study procedures as per Amendment 3 (Section 15.3)

[29] 6MWD shifted from Visit 2 to Visit 1 as per Amendment 3 (Section 15.3)

- Blood sampling for biomarkers
- Patients will get a VitalPatch biosensor attached to their chest, which they will wear for up to 5 days after Visit 1 / discharge from hospital[27]
- Subjects will be informed how to wear and apply the VitalPatch biosensor [13]

Outpatient Phase

Visit 2 (Day 9 ± 2 days) - amended

Patients will return to the clinic 9 days (± 2 days) after Visit 1 / discharge[27]. The following activities will be performed:

- Recording of
  Weight
  Concomitant medication
  AEs including the use of healthcare resources
- NYHA classification[28, 29]
- Measurement of blood pressure and heart rate
- The VitalPatch biosensor[13] device attached at Visit 1 will be collected
- Subjects will receive another two VitalPatch biosensor patches which they will wear consecutively for up to 5 days each. One VitalPatch biosensor patch will be attached to the subject's chest at the site, the other one has to be attached by the patient after removal of the first one after 5 days. Subjects will be informed how to wear and apply the VitalPatch biosensor.[31]
- In addition, subjects will receive the DynaPort Move Monitor device which they will wear for 7 days. Subjects will be informed how to wear and apply the DynaPort MoveMonitor.
- Instruction to patient to complete KCCQ (Day 16 ± 2 days)
- Completion of PRO daily and weekly during DynaPort Move Monitor and VitalPatch[13] monitoring period.

Visit 3 (Day 77 ± 2 days) - amended

Patients will return to the clinic 77 days (± 2 days) after discharge. The following activities will be performed:

- Recording of
  Concomitant medication
  AEs including the use of healthcare resources[28]
- Measurement of blood pressure and heart rate
- Daily and weekly PRO during wearing of DynaPort Move Monitor and VitalPatch[30] devices

- The VitalPatch biosensor[30] patches and the DynaPort Move Monitor device will be collected will be collected
- Subjects will receive another two VitalPatch biosensor patches which they will wear consecutively for up to 5 days each. One VitalPatch biosensor patch will be attached to the subject's chest at the site, the other one has to be attached by the patient after removal of the first one after 5 days.[31]
- In addition, subjects will receive another DynaPort Move Monitor device which will be put on at the site and which will be worn for 7 days.[31]

Visit 4 (Day 84 ± 2 days) - amended

Patients will return to the clinic 84 days (± 2 days) after discharge. The following activities will be performed:

- Recording of
  Weight
  Concomitant medication
  AEs including the use of healthcare resources[28]
- Recording of a 12-lead ECG
- NYHA classification[32]
- Measurement of blood pressure and heart rate
- Determination of 6MWD
- Completion of KCCQ/PRO
- Blood sampling for biomarkers
- The VitalPatch biosensor[30] patches and the DynaPort Move Monitor device will be collected.

Follow-up visit (safety follow-up call)

Six months after discharge the investigator will phone the patient for a final safety follow-up. The following will be asked:

- Concomitant medication
- AEs including the use of healthcare resources

[30] Replacement of AVIVO MPM with VitalPatch Biosensor as per Amendment 2 (Section 15.2)

[31] Procedures for VitalPatch and DynaPort MoveMonitor simplified as per Amendment 3 (Section 15.3)

[32] Second echocardiography deleted to simplify procedures as per Amendment 3 (Section 15.3)

9.3 Population characteristics

9.3.1 Demographic

Male and female patients 45 years of age or older will be included into the study. Demographic characteristics (including sex, age in years, year of birth, height, weight, race/ethnicity) will be documented at Visit 1. The body mass index (BMI) will be calculated based on height and weight.

9.3.2 Medical history

Medical history findings (i.e. previous diagnoses, diseases or surgeries) meeting all criteria listed below will be collected as available to the investigator:

- Start before signing of the informed consent
- Considered relevant for the subject's study eligibility.

Detailed instructions on the differentiation between (i) medical history and (ii) adverse events can be found in Section 9.6.1.1.

9.4 Efficacy

Not applicable

9.5 Pharmacokinetics / pharmacodynamics

Not applicable

9.6 Safety

9.6.1 Adverse events

9.6.1.1 Definitions

Adverse Event (AE):

Any untoward medical occurrence (i.e. any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a patient or clinical investigation subject after providing written informed consent for participation in the study. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal product.

A surgical procedure that was planned prior to the start of the study by any physician treating the subject should not be recorded as an AE (however, the condition for which the surgery is required may be an AE).

In the following differentiation between medical history and AEs, the term "condition" may include abnormal e.g. physical examination findings, symptoms, diseases, laboratory, ECG.

- Conditions that started before signing of informed consent and for which no symptoms or treatment are present until signing of informed consent are recorded as medical history (e.g. seasonal allergy without acute complaints).

- Conditions that started before signing of informed consent and for which symptoms or treatment are present after signing of informed consent, at *unchanged intensity*, are recorded as medical history (e.g. allergic pollinosis).
- Conditions that started or deteriorated after signing of informed consent will be documented as adverse events. This includes intercurrent illnesses.

Definition of serious adverse event (SAE)

An SAE is classified as any untoward medical occurrence that, at any dose, meets any of the following criteria (a – f):

a. Results in death

b. Is life-threatening

The term 'life-threatening' in the definition refers to an event in which the subject was at risk of death at the time of the event, it does not refer to an event which hypothetically might have caused death if it were more severe.

c. Requires inpatient hospitalization or prolongation of existing hospitalization

A hospitalization or prolongation of hospitalization will not be regarded as an SAE if at least one of the following exceptions is met:

- The admission results in a hospital stay of less than 12 hours
- The admission is pre-planned
(e.g. elective or scheduled surgery arranged prior to the start of the study; admission is part of the study procedures as described in Section 9.2)
- The admission is not associated with an AE
(e.g. social hospitalization for purposes of respite care).

However, it should be noted that invasive treatment during any hospitalization may fulfill the criterion of 'medically important' and as such may be reportable as an SAE dependent on clinical judgment. In addition, where local regulatory authorities specifically require a more stringent definition, the local regulation takes precedence.

d. Results in persistent or significant disability / incapacity

Disability means a substantial disruption of a person's ability to conduct normal life's functions.

e. Is a congenital anomaly / birth defect

f. Is another serious or important medical event as judged by the investigator

9.6.1.2 Classifications for adverse event assessment

All AEs will be assessed and documented by the investigator according to the categories detailed below.

9.6.1.2.1 Seriousness

For each AE, the seriousness must be determined according to the criteria given in Section 9.6.1.1.

9.6.1.2.2 Intensity

The intensity of an AE is classified according to the following categories:

Mild: A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.

Moderate: A type of AE that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.

Severe: A type of AE that requires intensive therapeutic intervention. The event interrupts usual activities of daily living, or significantly affects clinical status. The event possesses a significant risk of harm to the research participant and hospitalization may be required.

9.6.1.2.3 Causal relationship

The relationship of an AE to the device must be assessed by the investigator based on all information available at the time of the completion of the CRF.

The assessment is based on the question whether there was a “reasonable causal relationship” to the device in question.

Possible answers are “yes” or “no”

An assessment of “no” would include:

1. The existence of a highly likely alternative explanation, e.g. mechanical bleeding at surgical site.

or

2. Non-plausibility, e.g. the subject is struck by an automobile when there is no indication that wearing the device caused disorientation that may have caused the event.

An assessment of “yes” indicates that that the AE is reasonably associated with the use of the device.

Important factors to be considered in assessing the relationship of the AE to the device include:

- The temporal sequence from wearing the device: The event should occur after the device is applied. The length of time from wearing the device to event should be evaluated in the clinical context of the event.
- Underlying, concomitant, intercurrent diseases:
  Each event should be evaluated in the context of the natural history and course of the disease being treated and any other disease the patient may have.
- Concomitant medication or treatment:
  The other drugs the patient is taking or the treatment the patient receives should be examined to determine whether any of them might have caused the event in question.

- Exposure to physical and / or mental stresses: The exposure to stress might induce adverse changes in the recipient and provide a logical and better explanation for the event.
- The assessment is not possible.

Causal relationship to protocol-required procedure(s)

The assessment of a possible causal relationship between the AE and protocol-required procedures is based on the question whether there was a "reasonable causal relationship" to protocol-required procedures.

Possible answers are "yes" or "no"

9.6.1.2.4 Action taken with study treatment

Not applicable.

9.6.1.2.5 Other specific treatment(s) of adverse events

- None
- Remedial drug therapy
- Other

9.6.1.2.6 Outcome

The outcome of the AE is to be documented as follows:

- Recovered/resolved
- Recovering/resolving
- Recovered/resolved with sequelae
- Not recovered/not resolved
- Fatal
- Unknown

9.6.1.3 Assessments and documentation of adverse events

The investigator has to record on the respective AE CRF page, all adverse events occurring in the period between the signing of the informed consent and the end of the follow-up phase; after the end of the follow-up phase there is no requirement to actively collect AEs including deaths. The type of information that should be assessed and recorded by the investigator for each AE is listed in Section 9.6.1.2.

"Death" should not be recorded as an AE on the AE page. Instead, "death" is the outcome of underlying AE(s).

For all serious adverse events (SAEs) Bayer has to carry out a separate assessment for expectedness, seriousness and causal relationship regarding study procedures and Bayer drugs/devices.

9.6.1.4 Reporting of serious adverse events - amended

The definition of serious adverse events (SAEs) is given in the Section 9.6.1.1. Each SAE must be followed up until resolution or stabilization by submission of updated reports to the designated recipient.

Any serious adverse events-will be reported by the investigator to Bayer. Bayer will process these cases according to Bayer standard procedures and report as described below. In addition, all adverse events related to the VitalPatch biosensor[33] or the DynaPort Move Monitor, which are both non-investigational devices in the Post-Marketing phase, will be reported by the investigator to the respective legal manufacturers, which would fulfill their reporting obligations to competent authorities and Notified bodies.

In addition, for any adverse events related to any non-Bayer drugs/devices, investigators are recommended to use the national applicable system for reporting of spontaneous AEs.

Investigator's notification of the sponsor

All investigators will be thoroughly instructed and trained on all relevant aspects of the investigator's reporting obligations for SAEs. This information, including all relevant contact details, is summarized in the investigator site file. This information will be updated as needed.

The investigator must report immediately (within 24 hours of the investigator's awareness) all SAEs occurring during the period defined in Section 9.6.1.3 to the recipient detailed in the instructions for SAE reporting included in the Investigator File. For this, an AE page and the complementary SAE pages in the CRF must be completed for each SAE.

SAEs occurring after the protocol-defined study period will be processed by the sponsor according to all applicable regulations.

Notification of the IECs / IRBs

Notification of the IECs/IRBs about suspected, unexpected, serious adverse reactions [SUSARs] is not applicable because there is no investigational product in this study. Notification of the IECs/IRBs about all SAEs related to study procedure will be performed by Bayer and/or by the investigator according to all applicable regulations.

Notification of the authorities

The processing and reporting of all relevant events (e.g. SAEs, SUSARs) to the authorities will be done by the sponsor according to all applicable regulations.

Reporting obligations for non-Bayer drugs/devices incl. VitalPatch biosensor[33] and the DynaPort Move Monitor will be fulfilled by the respective Marketing Authorization holders/Manufacturers based on the information provided by the investigator via spontaneous reporting.

[33] Replacement of AVIVO MPM with VitalPatch Biosensor as per Amendment 2 (Section 15.2)

Sponsor's notification of the investigational site

Notification of the investigational sites about suspected, unexpected, serious adverse reactions [SUSARs] is not applicable because there is no investigational product in this study. Notification of all investigational sites about all SAEs related to study procedure will be performed by Bayer according to all applicable regulations.

9.6.1.5 Expected adverse events

The expectedness of AEs for Bayer drugs/devices will be determined according to the applicable core company reference documents and according to all local regulations.

9.6.2 Pregnancies

The investigator must report to Bayer any pregnancy occurring in a female subject during her participation in this study. The outcome of the pregnancy should be followed up carefully, and any outcome of the mother and the child at delivery should be reported.

For a pregnancy in the partner of a male study subject, all efforts will be made to obtain similar information on course and outcome, subject to the partners consent.

For all reports, the forms provided are to be used. The investigator should submit them within the same timelines as an SAE.

9.6.3 Further safety – amended

- **Vital signs**

Blood pressure, heart rate and body weight will be measured at time points given in the study flow charts in Table 9–1 as standard at the investigational site.

- **Electrocardiogram/echocardiography**

The standard 12-lead ECG will be evaluated by the investigator and the following parameters will be recorded in the eCRF: HR, PR interval, QRSD interval, QT interval (uncorrected). QTcB (QT interval frequency-corrected according to Bazett's formula) will also be calculated but will not be valid for evaluation. The frequency-corrected QT interval will be calculated by data management according to the formulas of both Bazett and Fridericia.

All ECGs recorded during the study will be evaluated by a physician. He / she will document the diagnosis(es) including an overall assessment of the findings and their clinical relevance.

Any clinically relevant abnormality will be documented as an AE or SAE. Judgement normal/abnormal, including specification of abnormal findings

An echocardiography will be performed at Visit 1 / discharge from the hospital (within ± 72 hours).[27]

- **Physical examination** [28]

A general physical examination as routine at the center will not need to be performed, but a targeted exam might be triggered by symptoms. Abnormal physical examination findings are recorded either as medical history or as adverse events (see Section 9.6.1.1).

- **Laboratory evaluations**

In the event of implausible results, the laboratory may measure additional parameters to assess the quality of the sample (e.g. clotted or hemolyzed) and to verify the results. The results from such additional analyses may neither be included in the clinical database of this study nor evaluated further. If the results are relevant, the investigator will be informed to determine follow-up activities outside of this protocol.

- **Healthcare Resource Utilization** [34]

The use of Healthcare Resources in conjunction with AEs, in particular due to HF, needs to be documented, for example with regard to the time points or periods affected (e.g. hospitalizations for HF, urgent visits for HF to an emergency department or outpatient facility).

9.7 Other procedures and variables

9.7.1 VitalPatch biosensor[35]/DynaPort Move Monitor devices - amended

VitalPatch biosensor[35]

VitalPatch biosensor will be provided by Bayer to sites. Subjects will wear the VitalPatch biosensor for overall 5 periods of 5 days each (for details on time periods see Table 9–1).[35]

Parameters obtained from the VitalPatch biosensor[35] are:

- ECG and parameters derived from ECG, like e.g. heart rate, HRV, AF burden, arrhythmias etc.
- Respiratory rate[36]
- Skin temperature[35]
- Step count[35]
- Physical activity (duration and intensity)
- Posture

DynaPort Move Monitor

DynaPort Move Monitor will be provided by Bayer to sites. Subjects will wear the DynaPort Move Monitor device for 2 periods of 7 days each (for details on time periods see Table 9–1).

[34] Added as per Amendment 3 (Section 15.3)

[35] Replacement of AVIVO MPM with VitalPatch Biosensor as per Amendment 2 (Section 15.2)

[36] Thoracic impedance measurement is not supported by the VitalPatch device. Changed as per Amendment 3 (Section 15.3)

Parameters obtained from the DynaPort Move Monitor device are:

1. **Physical activity**
    - Type of activity
    - Transitions between type of activity
    - Steps
    - Movement duration
    - Movement frequency
    - Movement intensity
2. **Energy Expenditure**
    - Basal metabolic rate (BMR)
    - Diet Induced Thermo Genesis (DIT)
    - Activity-Related Energy Expenditure (AEE)
    - Total Energy Expenditure (TEE)
    - Physical Activity Ratio (PAR)
    - Physical Activity Level (PAL)
3. **Sleep Movements**
    - Going Out of Bed
    - Night's Rest Detection
    - Postures
    - Movement Time
    - Movement Intensity
    - Transitions

9.7.2 Quality of life assessment/PRO - amended

Quality of life will be assessed using the KCCQ [10]. The total score will be documented.

PRO will be completed daily and weekly during DynaPort Move Monitor and VitalPatch[37] monitoring.

[37] Replacement of AVIVO MPM with VitalPatch Biosensor as per Amendment 2 (Section 15.2)

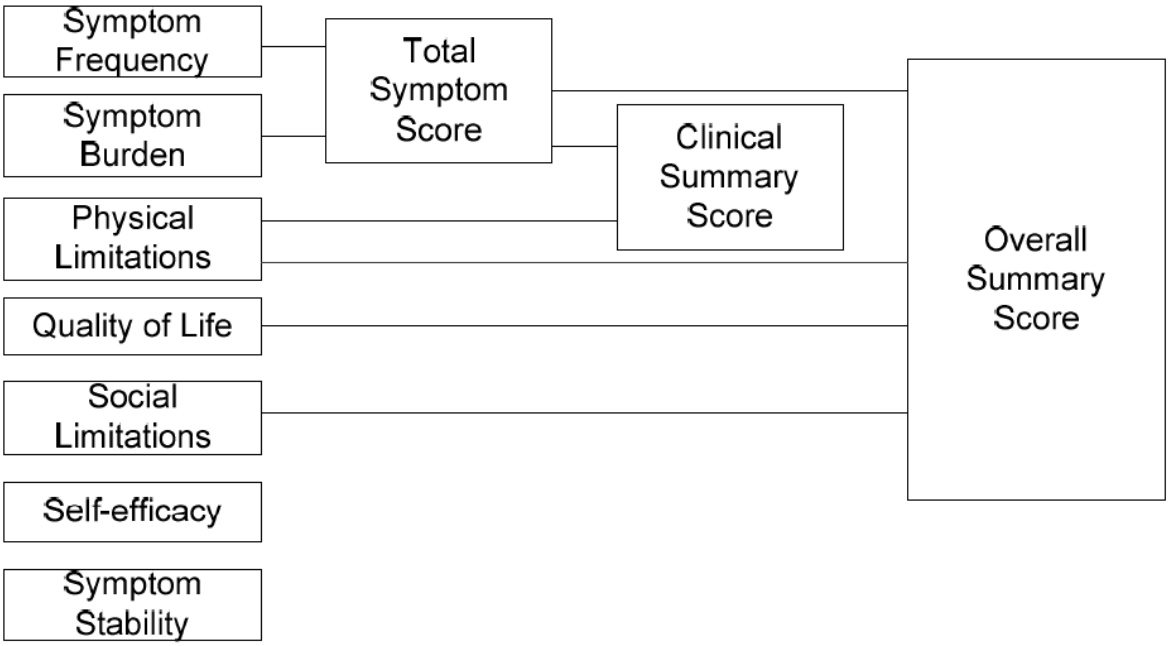
KCCQ

The KCCQ is the leading health-related quality-of-life measure for patients with HF. It was developed in the late 1990s to early 2000s by Dr. John Spertus at the Mid-America Heart Institute, Kansas City, MO, USA. It is a 23-item questionnaire that independently measures the impact of patients' HF, or its treatment, on 7 distinct domains:

1. Symptom Frequency – the KCCQ Symptom scale quantifies the frequency of clinical symptoms in HF, including fatigue, shortness of breath, paroxysmal nocturnal dyspnea, and edema / swelling.
2. Symptom Burden – the KCCQ Symptom burden scale quantifies the severity of clinical symptoms in HF, including fatigue, shortness of breath and edema / swelling.
3. Physical Limitation – the KCCQ Physical limitation scale measures the limitations patients experience, due to their HF, in performing routine activities.
4. Quality of Life – the KCCQ Quality of life scale is designed to reflect patients' assessment of their quality of life, given the current status of their HF.
5. Social Limitations – the KCCQ Social limitation scale quantifies the extent to which HF symptoms impair patients' abilities to interact in social roles.
6. Self-efficacy – numerous studies have underscored the importance of patients being engaged in the management of their disease. The KCCQ Self-efficacy scale quantifies patients' perception of how to prevent HF exacerbations and manage complications when they arise.
7. Symptoms Stability– unlike the other 5 domains that provide cross-sectional quantification of patients' current status, the KCCQ Symptom stability domain measures recent changes in patients' symptoms. As a measure of change, it is most interpretable as a baseline assessment of the stability of patients' symptoms at the start of the study and thereafter.

In addition, there are 3 summary scores, a Total Symptom Score that combines the Symptom Frequency and the Symptom Burden scores, a Clinical Summary Score that combines the Total Symptom and Physical Limitation scores to replicate the NYHA classification; and an Overall Summary Score that includes the Total Symptom, Physical Limitation, Social Limitations, and Quality of Life scores (Figure 9-1).

Figure 9-1 Kansas City Cardiomyopathy Questionnaire score



The exploratory daily QoL-Questionnaire is provided in Appendix 16.1.

KCCQ and PRO will be collected using electronic versions of the questionnaires on a tablet computer, which will be hand out to the patient for the duration of the study.

9.7.3 Six-minute walking distance

The walking distance after 6 minutes walking will be determined and documented.

The 6MWD test must be performed in accordance with the American Thoracic Society Guideline [11].

According to the guideline, the 6MWD test should be carried out indoors, along a long, flat, straight, enclosed corridor with hard surface that is seldom traveled. The walking course should be preferably 30 m in length, but not less than 25 m (longer walking courses should be shortened to 30 m). The length of the corridor and turnaround points should be marked. Patients will be instructed to walk alone, not run, from one end to the other end of the walking course, at their own pace, while attempting to cover as much ground as possible in 6 minutes. During the walk, patients are allowed to stop, lean against the wall and rest, but should resume walking as soon as they feel able to do so. The resting time will be included in the 6 minutes. A “warm-up” period before the test should not be performed. The patients should sit at rest in a chair, located near the starting position, for at least 10 minutes before the test starts. Investigators should not walk with the patients. Moreover, only standardized phrases for encouragement must be used during the test. To allow reproducibility, standardized phrases should be used every minute according to the following pattern: After the first minute, tell the patient the following (in even tones): “You are doing well. You have 5 minutes to go.” When the timer shows 4 minutes remaining, tell the patient the following: “Keep up the good work. You have 4 minutes to go.”

When the timer shows 3 minutes remaining, tell the patient the following: “You are doing well. You are halfway done.” When the timer shows 2 minutes remaining, tell the patient the following: “Keep up the good work. You have only 2 minutes left.”

When the timer shows only 1 minute remaining, tell the patient: “You are doing well. You have only 1 minute to go.” To reduce the variability of the 6MWD tests, it is of utmost importance that all 6MWD tests are performed under the same conditions, which must be the same as baseline conditions. Wheelchair or scooter dependent / supplemental oxygen patients or those on continuous oxygen for severe pulmonary disease are excluded from the study. The use of a cane is allowed in cane dependent patients, but then these patients need to use the same cane at every 6MWD test throughout the study. If a supplemental oxygen therapy should be implemented during the trial, if it is implemented already at baseline, the subsequent 6MWD test at Visit 4 / premature discontinuation visit has to be performed under the same “baseline” conditions (same flow of oxygen, same application route, and same way of carrying the oxygen bottle). The same applies if the need for walking aids should arise during the trial already at baseline. In that case the same walking aids should also be used at the Visit 4 / premature discontinuation test.

However, this should be avoided, and if not possible, at least the same conditions should be met in both 6MWD tests. For quality reasons, the inhalation of supplemental oxygen and the use of walking aids during the 6MWD tests must be documented in the eCRF.

9.7.4 Laboratory parameters

Blood samples will be collected as given in Table 9–1and the following biomarkers will be determined in plasma/serum by a central laboratory using validated assays platforms including appropriate quality controls:

- NTproBNP
- hs-Copeptin
- hs-TNT

Further biomarkers may be tested:

- GDF15
- IGFBP7
- sST2
- Gal3

Details on the collection, processing, storage and shipment of biomarker samples will be provided in separate documents (e.g. sample handling sheets or lab manual). In addition to the biomarkers listed above, other biomarkers deemed relevant to gain further knowledge about the pathomechanisms of the disease may be measured, based on newly emerging data from other ongoing studies and / or literature data.

9.8 Appropriateness of procedures / measurements

All laboratory and safety parameters as well as the methods to measure them, are standard variables/ methods in clinical studies and/ or clinical practice. They are widely used and generally recognized as reliable, accurate and relevant.

10. Statistical methods and determination of sample size

10.1 General considerations - amended

All statistical details including calculated variables and proposed format and content of tables will be detailed in the Statistical Analysis Plan (SAP). The SAP will be finalized before study database lock. Statistical analysis will be performed using SAS or R; the versions used for both types of software will be specified in the SAP.

Statistical analyses will be of explorative and descriptive nature. The study is not aimed to confirm or reject pre-defined hypotheses; however, particular attention will be given to the ejection fraction (preserved versus reduced) as stratification factor.

All variables will be summarized with appropriate statistical methods: categorical variables by frequency tables (absolute and relative frequencies) and continuous variables by sample statistics (i.e. mean, standard deviation, minimum, median, quartiles and maximum). Continuous variables will be described by absolute value and as change from baseline per analysis time point, as applicable.

Data from VitalPatch[38] and DynaPort devices is expected to include missing values, as result of compliance in wearing the device. The amount of missing data within a day cannot be predicted and will be an outcome of the study. Missing data within day will be assessed by vendors according their validated algorithms of data pre-processing and quality check. No imputation will be performed in case day monitoring did not pass quality checks. The amount of missing monitoring will be assessed prior each statistical analysis and in presence of outliers the exclusion of subjects' data may occur.

All analyses will be performed for the FAS population (overall analysis) and separately for each participating country if subject numbers are sufficient and if required for local reasons.

Sample size and disposition information by analysis time point will be displayed in a frequency table.

All therapies documented will be coded using the World Health Organization – Drug Dictionary. Medical history, any diseases and AEs will be coded using the latest Medical Dictionary for Regulatory Activities (MedDRA) version.

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.

10.2 Analysis sets - amended

In absence of intervention and randomization the statistical analysis sets are defined on the base of a successful monitoring under the VitalPatch biosensor[38] patch.

Full analysis set (FAS)

The FAS population consists of all subjects that are included into the study and that are wearing at least one VitalPatch biosensor[38] patch and for which data was successfully collected over the whole week. The FAS will be used to display baseline characteristics, assess parameter variability, correlative analyses.

[38] Replacement of AVIVO MPM with VitalPatch Biosensor as per Amendment 2 (Section 15.2)

Safety analysis set (SAF)

The SAF population consists of all patients with a planned study procedure after signing the informed consent that are wearing at least one VitalPatch biosensor[38] patch and for which data was successfully collected over the whole week will be included in the SAF. The SAF will be used to display safety analyses.

10.3 Variables and planned statistical analyses

Given the descriptive nature of the study and the multivariate nature of the statistical approach used, all of the variables mentioned in section 9 are suitable to be analyzed.

In addition, variables including patient heart failure information (preserved vs reduced ejection fraction) or other clinical endpoints (e.g. re-hospitalization for heart failure, cardiovascular death, emergency visits) will be considered as well in the statistical analysis, possibly in interaction with other relevant parameters.

10.3.1 Analysis of demography, disease details, prior and concomitant medication and other baseline data

Summary statistics (arithmetic mean, standard deviation, median, minimum and maximum for quantitative variables) will be presented for total and study part. Frequency tables for qualitative data will be provided.

Unsupervised patient stratification at baseline will be carried out by means of the following multivariate techniques which allow the simultaneous analysis of many variables such as from demographics, disease history (MedDRA terms), co-morbidities, prior and concomitant medication, AEs, NYHA classification, ECG judgement, vital signs, KCCQ/PRO scores, and biomarkers (laboratory data). Continuous variables will be arbitrary discretized in tertiles or quartiles according their density distribution or according existing clinical ranges of normality. Multiple correspondence analyses will be used, subjects will be displayed in bi-dimensional maps and the homogeneity of the population towards all the variables under assessment will be observed. If groups of subjects with specific co-occurrences for one or more parameters could be separated by the others in the bi-dimensional map (at 95% confidence ellipse) those will be flagged and eventually considered as separate population for the analysis. In the latter case, the parameter(s) responsible for the separation will be identified using the map of contribution of variable categories to the dimensions, and could be used as covariate in modeling. No additional investigations for comparative purposes will be performed.

10.3.2 Analysis of data within the hospitalization phase - amended

Data collected in the hospitalization phase for which records will be available until visit 1 (from hospitalization and at hospital discharge, respectively) will be analyzed by means of multivariate techniques in order to describe changes and quantify the variability of changes in this early phase, and eventually identify subjects with extreme behavior in one or more of the parameters under measurement. Changes in the parameters from 12-lead ECG, vital signs, KCCQ/PRO scores, and biomarkers will be described using multilevel Partial Least Square analysis. Such model allows conducting a paired analysis of subjects before and after hospitalization, hence to observe a potential effect of hospitalization on the observed parameters. If an effect will be observed, the parameters sensitive to hospitalization will be

assessed using linear mixed model as described in Section 10.3.3.1 but within the hospitalization time frame.

For VitalPatch[39] data collected in this frame only the day to day variability will be of interest.

10.3.3 Analysis of primary and secondary outcomes

10.3.3.1 Assessment of variability

The variability between subjects and within subjects across time for each of the parameters of interest will be described using a linear mixed model (LMM) with subject as random factor, and time as fixed factor, possibly including additional covariates as may result from the assessment at baseline for patient stratification or as required for clinical interpretation.

In addition to effects and interactions of fixed effects parameters LMMs will be used to estimate simultaneously parameters of the variance and covariance components of random effects due to subjects.

The LMM for the parameter of interest (Y) as selected among the molecular and digital biomarkers available (i.e. laboratory parameters and device generated digital data) will have the following base annotation:

$$Y_{st} = \beta_0 + \beta_1 \cdot TIME_t + S_{0s} + \varepsilon_{st}$$

Where S is subject (random) and TIME represents visit, with baseline as reference.

The HF type (preserved/reduced) will be included in the model (here denoted as C), as random factor, and the effect on intercept or slope will be assessed:

$$Y_{st} = \beta_0 + (\beta_1 + C_{1s}) \cdot TIME_t + S_{0s} + C_{0s} + \varepsilon_{st}$$

Where C_{1s} will be the effect of HF type on the slope (e.g., if changes in physical activity are different between the two sub-populations) and C_{0s} will be the effect on the intercept (e.g., if the two sub-populations have different baseline values).

Given the high number of parameters involved and the exploratory nature of the study, all of the possible models will not be addressed here, and the base model will be extended as appropriate depending on the specific question to address and the given subset of parameters involved.

Testing of random effects and visualization of residuals will be performed in order to highlight single subjects (or sub-group) showing outstanding or peculiar characteristics.

Estimates from the model will be used to quantify the ability of a parameter to measure clinically relevant changes over time. The intraclass correlation coefficient (ICC) will be used as key statistic when considering the relative proportion of within- and between-individual variation is the expected correlation among measurements from the same individual, it can indicate the degree of difference between individuals and will also be used as measure reliability (ability to reflect true between-individual differences). For any sample, the ICC will be calculated with estimates from LMMs of both between-individual variance and within-individual variance, according the following:

$$ICC = \tau^2 / (\tau^2+\sigma^2)$$

[39] Replacement of AVIVO MPM with VitalPatch Biosensor as per Amendment 2 (Section 15.2)

where τ^2 is a commonly used symbol for between-individual variance (variance of S_{0s} term in in the base model above) and σ^2 for within-individual variance (variance of ε_{st} in the base model). Then, ICC will be the proportion of total variance ($\tau^2+\sigma^2$) attributable to between-individual differences (τ^2).

In addition, point estimates (LS-Means) and exploratory 90% confidence intervals will be calculated for comparing baseline and 3 months data by HF type (preserved/reduced), and may include intermediate time points if available.

10.3.3.2 Analysis of correlations - amended

Given the high degree of collinearity expected within each set of data, multivariate approaches will be considered in order to take in account the covariance structure and properly assess simultaneously the correlation of variables within and between datasets consisting of multiple variables, such as digital or biomarker datasets.

The relationship between variables as obtained from a given source or technology will be assessed by means of Canonical Correlation. This analysis allows investigating the relationship between two multivariate sets of variables, such as the one obtained using the VitalPatch biosensor[40] or DynaPort Move Monitor device, and another one as obtained from other contexts, such as contexts defined by the following data sets: i) echocardiography parameters set, ii) 12-lead ECG parameters set, and iii) a composite set including biomarkers, 6MWD score, KCCQ total score, and vital signs (blood pressure, heart rate). Such model will possibly indicate which combination of the many parameters observed using the device will better reflect a clinical context as given by ECG, KCCQ, or other data.

The correlation of digital biomarkers and AEs or concomitant medication (CM) will be tested by means of partial least square analysis (PLS-DA). The Y-matrix to use for PLS-DA regression can be – depending on the resulting complexity – i) a joint matrix of AEs and CMs; ii) grouping variable identifying subjects with similar AE and CMs (the latter obtained by multiple correspondence analysis and kernel based clustering). Such model will possibly indicate which combination of the many parameters observed using the device will better reflect a clinical profile as obtained from observed frequencies in AEs and CMs.

10.3.4 Analysis of safety data

The SAF population will be used to display safety analyses.

Summary statistics (arithmetic mean, standard deviation, median, minimum and maximum for quantitative variables) or frequency tables will be provided as applicable.

10.4 Determination of sample size

Due to the exploratory nature of this study, the number and the diversity of parameters used to measure physical activity, or which could affect this outcome in “real-life” conditions, no modeling for power estimation was performed. The number of subjects was set to be comparable to other studies which involved the assessment of physical activity on daily life (activity monitoring) and where a significant difference in PA was observed (60 subject in

[40] Replacement of AVIVO MPM with VitalPatch Biosensor as per Amendment 2 (Section 15.2)

average). Also considering the expected variability due to measurement under unstandardized conditions [12] a number of 80 subjects (HFpEF n=60, HFrEF n=20) who completed the main study (i.e. visit 4) was defined as target.

11. Data handling and quality assurance

11.1 Data recording

The data collection tool for this study will be eCRF; a validated electronic data capture system called RAVE. Subject data necessary for analysis and reporting will be entered/transmitted into a validated database or data system (CIE/TOSCA; SAS).

Data required according to this protocol will be recorded by investigational site personnel via data entry into the internet based EDC software system RAVE, which Bayer has licensed from Medidata Solutions Worldwide. RAVE has been validated by Medidata Solutions Worldwide and Bayer for use in its clinical studies. RAVE allows for the application of software logic to set-up data entry screens and data checks to ensure the completeness and accuracy of the data entered by the site personnel. Bayer extensively applies the logic to ensure data are complete and reflect the clinical data requirements of the study. Data queries resulting from the application of the software logic are resolved by the site personnel. The data are stored at a secure host facility maintained by Medidata Solutions Worldwide and transferred on a periodic basis to Bayer's internal computer system via a secure Virtual Private Network.

All access to the RAVE system is through a password-protected security system that is part of the RAVE software. All internal Bayer and external investigator site personnel seeking access must go through a thorough RAVE training process before they are granted access to RAVE for use in Bayer's clinical studies. Training records are maintained.

All personnel with access to the RAVE system are supported by a Service Desk staffed with trained personnel to answer questions and ensure access is maintained such that data entry can proceed in a timely manner.

The RAVE System contains a system-generated audit trail that captures any changes made to a data field, including who made the change, why the change was made and the date and time it was made. This information is available both at the investigator’s site and at Bayer. Data entries made in the RAVE EDC screens are supported by source documents maintained for all subjects enrolled in this study.

Source documentation

The site must implement processes to ensure availability of all required source documentation. A source document checklist (not part of this protocol) will be used at the site to identify the source data for key data points collected and the monitor will work with the site to complete this.

It is the expectation of the sponsor that all data entered into the CRF has source documentation available at the site.

Data recorded from screening failures

At minimum, the following data should be recorded in the CRF:

- Demographic information (subject number; year of birth / age; sex; if applicable race / ethnicity)
- Date of informed consent
- Relevant inclusion/exclusion criteria
- Reason for premature discontinuation
- Date of last visit

These data will be transferred to the respective database.

For screening failures with an SAE, the following data should be collected in the CRF in addition to the data specified above:

- All information related to the SAE such as:
  - The SAE itself
  - Concomitant medication
  - Medical history
  - Other information needed for SAE complementary page

11.2 Monitoring

In accordance with applicable regulations, GCP, and sponsor's/CRO's procedures, monitors will contact the site prior to the start of the study to review with the site staff the protocol, study requirements, and their responsibilities to satisfy regulatory, ethical, and sponsor's requirements. When reviewing data collection procedures, the discussion will also include identification and documentation of source data items.

The sponsor/designee will monitor the site activity to verify that the:

- Data are authentic, accurate and complete.
  Supporting data may be requested (example: blood glucose readings to support a diagnosis of diabetes).
- Safety and rights of subjects are being protected
- Study is conducted in accordance with the currently approved protocol
- Any other study agreements, GCP, and all applicable regulatory requirements are met.

The investigator and the head of the medical institution (where applicable) agrees to allow the monitor direct access to all relevant documents.

11.3 Data processing

Data will be collected as described in Section 11.1. Clinical data management will be performed in accordance with applicable sponsor's standards and data cleaning procedures. This is applicable for data recorded on CRF as well as for data from other sources (e.g. IVRS, laboratory, ECG, PRO, adjudication committees).

For data coding (e.g. AEs, medication), internationally recognized and accepted dictionaries will be used.

11.4 Missing data

Missing data will not be replaced.

11.5 Audit and inspection

To ensure compliance with GCP and regulatory requirements, a member of the sponsor's (or a designated CRO's) quality assurance unit may arrange to conduct an audit to assess the performance of the study at the study site and of the study documents originating there. The investigator/institution will be informed of the audit outcome.

In addition, inspections by regulatory health authority representatives and IEC(s)/IRB(s) are possible. The investigator should notify the sponsor immediately of any such inspection.

The investigator/institution agrees to allow the auditor or inspector direct access to all relevant documents and allocate his/her time and the time of his/her staff to the auditor/inspector to discuss findings and any issues. Audits and inspections may occur at any time during or after completion of the study.

11.6 Archiving

Essential documents shall be archived safely and securely in such a way that ensures that they are readily available upon authorities' request.

Patient (hospital) files will be archived according to local regulations and in accordance with the maximum period of time permitted by the hospital, institution or private practice. Where the archiving procedures do not meet the minimum timelines required by the sponsor, alternative arrangements must be made to ensure the availability of the source documents for the required period.

The investigator/institution notifies the sponsor if the archival arrangements change (e.g. relocation or transfer of ownership).

The investigator site file is not to be destroyed without the sponsor's approval.

The contract with the investigator/institution will contain all regulations relevant for the study center.

12. Premature termination of the study

The sponsor has the right to close this study (or, if applicable, individual segments thereof [e.g. centers]) at any time, which may be due but not limited to the following reasons:

- If risk-benefit ratio becomes unacceptable owing to, for example,
  - Safety findings from this study (e.g. SAEs)
- If the study conduct (e.g. recruitment rate; drop-out rate; data quality; protocol compliance) does not suggest a proper completion of the trial within a reasonable time frame.

The investigator has the right to close his/her center at any time.

For any of the above closures, the following applies:

- Closures should occur only after consultation between involved parties. Final decision on the closure must be in writing.
- All affected institutions (e.g. IEC(s)/IRB(s); study center; head of study center) must be informed as applicable according to local law.
- All study materials (except documentation that has to remain stored at site) must be returned to the sponsor. The investigator will retain all other documents until notification is given by the sponsor for destruction.
- In the event of a partial study closure, ongoing subjects, including those in post study follow-up, must be taken care of in an ethical manner.

Details for individual subject's withdrawal can be found in Section 6.4.1.

13. Ethical and legal aspects

13.1 Investigator(s) and other study personnel

All other study personnel not included in this section are identified in a separate personnel list (not part of this clinical study protocol) as appropriate. This list will be updated as needed; an abbreviated version with personnel relevant for the centers will be available in each center's investigator site file.

Whenever the term 'investigator' is noted in the protocol text, it may refer to either the principal investigator at the site, or an appropriately qualified, trained and delegated individual of the investigational site.

The principal investigator of each center must sign the protocol signature page and must receive all required external approvals (e.g. ethics committee, sponsor) before subject recruitment may start at the respective center. Likewise, all amendments to the protocol must be signed by the principal investigator and must have received all required external approvals before coming into effect at the respective center.

A complete list of all participating centers and their investigators, as well as all required signature documents, will be maintained in the sponsor's study file.

The global sponsor of this study is identified on the title page of this protocol. If required by local law, local co-sponsors will be nominated; they will be identified on the respective country-specific signature pages.

13.2 Funding and financial disclosure - amended

Funding

This study will be funded by its sponsor.

Collaborator of this study is VitalConnect Inc., 224 Airport Parkway Suite 300, San Jose, California 95110, USA.[41]

[41] Replacement of AVIVO MPM with VitalPatch Biosensor as per Amendment 2 (Section 15.2)

Financial disclosure

Each investigator (including principal and/or any sub investigators) who is directly involved in the treatment or evaluation of research subjects has to provide a financial disclosure according to all applicable legal requirements. All relevant documentation will be filed in the trial master file.

13.3 Ethical and legal conduct of the study

The procedures set out in this protocol, pertaining to the conduct, evaluation, and documentation of this study, are designed to ensure that the sponsor and investigator abide by Good Clinical Practice (GCP) guidelines and the guiding principles detailed in the Declaration of Helsinki. The study will also be carried out in keeping with applicable local law(s) and regulation(s).

Documented approval from appropriate IEC(s)/IRBs will be obtained for all participating centers/countries before start of the study, according to GCP, local laws, regulations and organizations. When necessary, an extension, amendment or renewal of the IEC/IRB approval must be obtained and also forwarded to the sponsor. The responsible unit (e.g. IEC/IRB, head of the study center/medical institution) must supply to the sponsor, upon request, a list of the IEC/IRB members involved in the vote and a statement to confirm that the IEC/IRB is organized and operates according to GCP and applicable laws and regulations.

Strict adherence to all specifications laid down in this protocol is required for all aspects of study conduct; the investigator may not modify or alter the procedures described in this protocol.

Modifications to the study protocol will not be implemented by either the sponsor or the investigator without agreement by both parties. However, the investigator or the sponsor may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to the trial subjects without prior IEC/IRB/sponsor approval/favorable opinion. As soon as possible, the implemented deviation or change, the reasons for it and if appropriate the proposed protocol amendment should be submitted to the IEC/IRB/head of medical institution/sponsor. Any deviations from the protocol must be explained and documented by the investigator.

Details on discontinuation of the entire study or parts thereof can be found in Section 12.

13.4 Subject information and consent

All relevant information on the study will be summarized in an integrated subject information sheet and informed consent form provided by the sponsor or the study center. A sample subject information and informed consent form is provided as a document separate to this protocol.

Based on this subject information sheet, the investigator or designee will explain all relevant aspects of the study to each subject, prior to his/her entry into the study (i.e. before any examinations and procedures associated with the selection for the study are performed or any study-specific data is recorded on study-specific forms).

The investigator will also mention that written approval of the IRB/IEC has been obtained.

Each subject will be informed about the following aspects of premature withdrawal:

- Each subject has the right to withdraw from the study at any time without any disadvantage and without having to provide reasons for this decision.
- The subject's data that have been collected until the time of withdrawal will be retained and statistically analyzed in accordance with the statistical analysis plan.
- Subject-specific data on the basis of material obtained before withdrawal may be generated after withdrawal (e.g. image reading, analysis of biological specimen such as blood, urine or tissues); these data would also be retained and statistically analyzed in accordance with the statistical analysis plan. The subject has the right to object to the generation and processing of this post-withdrawal data. The subject's oral objection may be documented in the subject's source data.

Each subject will have ample time and opportunity to ask questions.

Only if the subject voluntarily agrees to sign the informed consent form and has done so, may he/she enter the study. Additionally, the investigator will personally sign and date the form. The subject will receive a copy of the signed and dated form.

The signed informed consent statement is to remain in the investigator site file or, if locally required, in the patient's note/file of the medical institution.

In the event that informed consent is obtained on the date that baseline study procedures are performed, the study record or subject´s clinical record must clearly show that informed consent was obtained prior to these procedures.

1. If the subject is not capable of providing a signature, a verbal statement of consent can also be given in the presence of an impartial witness (independent of the sponsor and the investigator). This is to be documented by a signature from the informing physician as well as by a signature from the witness.

The informed consent form and any other written information provided to subjects will be revised whenever important new information becomes available that may be relevant to the subject's consent, or there is an amendment to the protocol that necessitates a change to the content of the subject information and / or the written informed consent form. The investigator will inform the subject / legal representative or proxy consenter of changes in a timely manner and will ask the subject to confirm his/her participation in the study by signing the revised informed consent form. Any revised written informed consent form and written information must receive the IEC/IRB`s approval / favorable opinion in advance of use.

13.5 Publication policy and use of data

All data and results and all intellectual property rights in the data and results derived from the study will be the property of the sponsor who may utilize them in various ways, such as for submission to government regulatory authorities or disclosure to other investigators.

Regarding public disclosure of study results, the sponsor will fulfill its obligations according to all applicable laws and regulations. The sponsor is interested in the publication of the results of every study it performs.

The sponsor recognizes the right of the investigator to publish the results upon completion of the study. However, the investigator, whilst free to utilize study data derived from his/her center for scientific purposes, must obtain written consent of the sponsor on the intended

publication manuscript before its submission. To this end, the investigator must send a draft of the publication manuscript to the sponsor within a time period specified in the contract. The sponsor will review the manuscript promptly and will discuss its content with the investigator to reach a mutually agreeable final manuscript.

13.6 Compensation for health damage of subjects / insurance

The sponsor maintains clinical trial insurance coverage for this study in accordance with the laws and regulations of the country in which the study is performed.

13.7 Confidentiality

All records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available.

Subject names will not be supplied to the sponsor. Only the subject number will be recorded in the CRF, and if the subject name appears on any other document (e.g. pathologist report), it must be obliterated before a copy of the document is supplied to the sponsor. Study findings stored on a computer will be stored in accordance with local data protection laws. As part of the informed consent process, the subjects will be informed in writing that representatives of the sponsor, IEC/IRB, or regulatory authorities may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws.

If the results of the study are published, the subject's identity will remain confidential.

The investigator will maintain a list to enable subjects to be identified.

14. Reference list

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15. Protocol amendments

15.1 Amendment 1

Amendment 1 is dated 14 May 2018.

15.1.1 Overview of changes to the study protocol

This amendment was written to clarify issues with the sites and to improve the enrollment rate.

Modification 1: Time window added for conduct of echocardiography

Description of the modification of the study plan: A time window of 'within ± 72 of discharge day' was added for the conduct of the echocardiography in Visit 1.

Rationale for introducing the modification:

To clarify an issue with the sites

List of all CSP sections affected by this modification: Sections 9.1, 9.2, 9.6.3

Modification 2: Exclusion criterion for hemoglobin changed

Description of the modification of the study plan: The exclusion criterion for hemoglobin was changed from <11.0 g/dl to <10.0 g/dl.

Rationale for introducing the modification:

To reflect the 'real world' condition of HF patients as most patients' average hemoglobin is <10 g/dl, especially for acutely decompensated patients.

List of all CSP sections affected by this modification: Section 6.2

Modification 3: Addition of weekly PRO

Description of the modification of the study plan: In addition to daily PRO already planned in the protocol, weekly PRO was added to Visits 2 and 3.

Rationale for introducing the modification:

To clarify an issue with the sites

List of all CSP sections affected by this modification: Sections 2, 9.1, 9.2, 9.7.2

15.1.2 Changes to the protocol text

In this section on changes to the protocol text, all protocol sections affected by the respective amendment are detailed; the sequence of the sections follows the structure of the most recent previous protocol version.

As applicable, changes to the protocol text are highlighted as follows:

- **Editing of an existing portion** Comparative presentation of "old text" versus "new text", with "old text" referring to the most recent previous protocol version. Deletions are ~~crossed out~~ in the "old text". Additions are <u>underlined</u> in the "new text".
- **Tables / figures / sections** The term "amended" is added to the caption/heading.

Corrections of typos or omissions are not highlighted.

15.1.2.1 Section 9.1 Time window added for conduct of echocardiography

This section was changed as a result of Modification 1.

Old text

(…)

Table 1: Tabulated overview on study procedures and variables collected during the study

Study period	Hospitalization phase		Outpatient phase					Safety FU call
Visit number	Scr[1]	1	2			3	4	5
Visit type	site		site			site	site	☎
	Screen assess	At hospital discharge						
Week after discharge			1	2	3	11	12	
Day and allowed deviations		0	9±2	16±2	23±2	77±2	84±2	6 months ±4 weeks

(…)

Echocardiography		●					●	
Six-minute walking distance			●				●	
DynaPort (for 7 days)[2] start→ ←end			→----1st----←			→----2nd----←		
AVIVO (for 7 days)[2] →start ←end	→---1st---← →--2nd-←→--3rd-←→--4th--←					→----5th----←		
Blood sample for biomarkers[3]	●	●	●				●	

[1] within 72 hours after hospitalization

[2] DynaPort monitoring periods: Second week after hospital discharge (Days 7-14) and Week 11 to 12 (Days 77-84)

AVIVO monitoring periods: up to 7 days during the hospital stay, first week after hospital discharge (Day 0-7), during weeks 2 and 3 (Day 7-14, Day 17-23) and Week 11 to 12 (Days 77-84)

[3] central lab assessments: NTproBNP, hs-copeptin, hs-TNT, optionally: GDF15, IGFBP7, sST2, Gal3

* Concurrently evaluating PRO will be completed daily during DynaPort and AVIVO parallel monitoring period

New text

(…)

Table 1: Tabulated overview on study procedures and variables collected during the study

Study period	Hospitalization phase		Outpatient phase					Safety FU call
Visit number	**Scr[1]**	**1**	**2**			**3**	**4**	**5**
Visit type	**site**		**site**			**site**	**site**	☎
	Screen assess	**At hospital discharge**						
Week after discharge			**1**	**2**	**3**	**11**	**12**	
Day and allowed deviations		**0**	**9±2**	**16±2**	**23±2**	**77±2**	**84±2**	**6 months ±4 weeks**

(…)

Echocardiography		●[4]					●	
Six-minute walking distance			●				●	
DynaPort (for 7 days)[2] start→ ←end			→----1st----←			→----2nd----←		
AVIVO (for 7 days)[2] →start ←end	→---1st---← →--2nd-←→--3rd-←→--4th--←					→----5th----←		
Blood sample for biomarkers[3]	●	●	●				●	

[1] within 72 hours after hospitalization

[2] DynaPort monitoring periods: Second week after hospital discharge (Days 7-14) and Week 11 to 12 (Days 77-84)

AVIVO monitoring periods: up to 7 days during the hospital stay, first week after hospital discharge (Day 0-7), during weeks 2 and 3 (Day 7-14, Day 17-23) and Week 11 to 12 (Days 77-84)

[3] central lab assessments: NTproBNP, hs-copeptin, hs-TNT, optionally: GDF15, IGFBP7, sST2, Gal3

* Concurrently evaluating PRO will be completed daily during DynaPort and AVIVO parallel monitoring period

[4] within ± 72 of discharge day

15.1.2.2 Section 9.2 Time window added for conduct of echocardiography

This section was changed as a result of Modification 1.

Old text

(…)

Visit 1 (Day 0)

At discharge from the hospital the following activities will be performed:

- Recording of
  - Weight
  - Concomitant medication
  - AEs
- Physical examination
- Recording of a 12-lead ECG

- Conduct of echocardiography
- Measurement of blood pressure and heart rate

(…)

New text

(…)

Visit 1 (Day 0)

At discharge from the hospital the following activities will be performed:

- Recording of
  Weight
  Concomitant medication
  AEs
- Physical examination
- Recording of a 12-lead ECG
- Conduct of echocardiography within ± 72 of discharge day
- Measurement of blood pressure and heart rate

15.1.2.3 Section 9.6.3 Time window added for conduct of echocardiography

This section was changed as a result of Modification 1.

Old text

(…)

- **Electrocardiogram/echocardiography**

The standard 12-lead ECG will be evaluated by the investigator and the following parameters will be recorded in the eCRF: HR, PR interval, QRSD interval, QT interval (uncorrected). QTcB (QT interval frequency-corrected according to Bazett's formula) will also be calculated but will not be valid for evaluation. The frequency-corrected QT interval will be calculated by data management according to the formulas of both Bazett and Fridericia.

All ECGs recorded during the study will be evaluated by a physician. He / she will document the diagnosis(es) including an overall assessment of the findings and their clinical relevance.

Any clinically relevant abnormality will be documented as an AE or SAE. Judgement normal/abnormal, including specification of abnormal findings

An echocardiography will be performed at discharge from the hospital and on Day 84.

(…)

New text

(…)

- **Electrocardiogram/echocardiography**

The standard 12-lead ECG will be evaluated by the investigator and the following parameters will be recorded in the eCRF: HR, PR interval, QRSD interval, QT interval (uncorrected). QTcB (QT interval frequency-corrected according to Bazett's formula) will also be calculated but will not be valid for evaluation. The frequency-corrected QT interval will be calculated by data management according to the formulas of both Bazett and Fridericia.

All ECGs recorded during the study will be evaluated by a physician. He / she will document the diagnosis(es) including an overall assessment of the findings and their clinical relevance.

Any clinically relevant abnormality will be documented as an AE or SAE. Judgement normal/abnormal, including specification of abnormal findings

An echocardiography will be performed at discharge from the hospital (within ± 72 of discharge day) and on Day 84.

(…)

15.1.2.4 Section 6.2 Exclusion criterion for hemoglobin changed

This section was changed as a result of Modification 2.

Old text

1. Inability to comply with planned study procedures or to comply with study protocol requirements; this includes completing required data collection, and attending required follow up study visits
2. Hemoglobin <~~11~~.0 g/dl

(…)

New text

1. Inability to comply with planned study procedures or to comply with study protocol requirements; this includes completing required data collection, and attending required follow up study visits
2. Hemoglobin <10.0 g/dl

(…)

15.1.2.5 Section 2 Addition of weekly PRO

This section was changed as a result of Modification 3.

Old text

(…)

Methodology

(…)

Daily PRO will be performed ~~daily~~ in parallel with the DynaPort Move Monitor monitoring periods (visit 2, week 1-2) and visit 3 (week 11-12)

(…)

New text

(…)

Daily and weekly PRO will be performed in parallel with the DynaPort Move Monitor monitoring periods (visit 2, week 1-2) and visit 3 (week 11-12)

(…)

15.1.2.6 Section 9.1 Addition of weekly PRO

This section was changed as a result of Modification 3.

Old text

(…)

Table 1: Tabulated overview on study procedures and variables collected during the study

Study period	**Hospitalization phase**		**Outpatient phase**					**Safety FU call**
Visit number	**Scr[1]**	**1**	**2**			**3**	**4**	**5**
Visit type	**site**		**site**			**site**	**site**	**☎**
	Screen assess	**At hospital discharge**						
Week after discharge			**1**	**2**	**3**	**11**	**12**	
Day and allowed deviations		**0**	**9±2**	**16±2**	**23±2**	**77±2**	**84±2**	**6 months ±4 weeks**
Signed informed consent form	●							
Inclusion / exclusion criteria	●							
KCCQ		●		●			●	
Daily PRO*			→----1st----←			→----2nd----←		

(…)

* Concurrently evaluating PRO will be completed daily during DynaPort and AVIVO parallel monitoring period

New text

(…)

Table 1: Tabulated overview on study procedures and variables collected during the study

Study period	Hospitalization phase		Outpatient phase					Safety FU call
Visit number	**Scr[1]**	**1**	**2**			**3**	**4**	**5**
Visit type	**site**		**site**			**site**	**site**	☎
	Screen assess	**At hospital discharge**						
Week after discharge			**1**	**2**	**3**	**11**	**12**	
Day and allowed deviations		**0**	**9±2**	**16±2**	**23±2**	**77±2**	**84±2**	**6 months ±4 weeks**
Signed informed consent form	●							
Inclusion / exclusion criteria	●							
KCCQ		●		●			●	
Daily and weekly PRO*			→----1st----←			→----2nd----←		

(…)

* Concurrently evaluating PRO will be completed daily and weekly during DynaPort and AVIVO parallel monitoring period

15.1.2.7 Section 9.2 Addition of weekly PRO

This section was changed as a result of Modification 3.

Old text

(…)

Visit 2 (Day 9 ± 2 days)

(…)

- Instruction to patient to complete KCCQ (Day 16 ± 2 days)
- Completion of PRO daily during DynaPort Move Monitor and AVIVO parallel monitoring period.

(…)

Visit 3 (Day 77 ± 2 days)

(…)

- Measurement of blood pressure and heart rate
- daily PRO during wearing of DynaPort Move Monitor and AVIVO MPM devices

(…)

New text

(…)

Visit 2 (Day 9 ± 2 days)

(…)

- Instruction to patient to complete KCCQ (Day 16 ± 2 days)
- Completion of PRO daily and weekly during DynaPort Move Monitor and AVIVO parallel monitoring period.

(…)

Visit 3 (Day 77 ± 2 days)

(…)

- Measurement of blood pressure and heart rate
- Daily and weekly PRO during wearing of DynaPort Move Monitor and AVIVO MPM devices

(…)

15.1.2.8 Section 9.7.2 Addition of weekly PRO

This section was changed as a result of Modification 3.

Old text

Quality of life will be assessed using the KCCQ [10]. The total score will be documented.

PRO will be completed daily during DynaPort Move Monitor and AVIVO MPM parallel monitoring.

(…)

New text

Quality of life will be assessed using the KCCQ [10]. The total score will be documented.

PRO will be completed daily and weekly during DynaPort Move Monitor and AVIVO MPM parallel monitoring.

(…)

15.2 Amendment 2

Amendment 2 is dated 06 Sep 2018.

15.2.1 Overview of changes to the study protocol

This amendment was issued to address the discontinuation of AVIVO Mobile Patient Monitoring (MPM) devices by Medtronic Inc. for commercial and clinical trial use effective September 20, 2018. These devices will be replaced by VitalConnect VitalPatch biosensors for use in this study.

Modification 1: Replacement of AVIVO MPM with VitalPatch Biosensor

Description of modification to the study plan:

Medtronic AVIVO Mobile Patient Monitoring systems will be replaced by VitalConnect VitalPatch biosensors for use in this study.

Rationale for introducing the modification:

Effective on 20-Sep-2018, AVIVO MPM devices utilized in the study will be discontinued by the manufacturer Medtronic. The VitalPatch biosensor manufactured by VitalConnect will serve as a replacement monitoring device. As a result of this change, the monitoring period for each device will decrease from 7 to 5 days. Step count and skin temperature are the only additional parameters that will be collected with the VitalPatch biosensor as this data was not available with the AVIVO MPM patches. With the exception of these two additional parameters, all data collected, analyzed and reported in the context of this study will remain unaffected by this change. The VitalPatch biosensor is USA FDA approved, CE Marked in EU, ISO 13485 certified and Canada CMDR registered.

List of all CSP sections affected by this modification: Sections 1, 2, 3, 4, 5, 6.1, 9.1, 9.2, 9.6.1.4, 9.7.1, 9.7.2, 10.1, 10.2, 10.3.2, 10.3.3.2, 13.2, and 16.1

15.2.2 Changes to the protocol text

In this section on changes to the protocol text, all protocol sections affected by the respective amendment are detailed; the sequence of the sections follows the structure of the most recent previous protocol version.

As applicable, changes to the protocol text are highlighted as follows:

- **Editing of an existing portion** — Comparative presentation of "old text" versus "new text", with "old text" referring to the most recent previous protocol version. Deletions are ~~crossed out~~ in the "old text". Additions are <u>underlined</u> in the "new text".
- **Tables / figures / sections** — The term "amended" is added to the caption/heading.

Corrections of typos or omissions are not highlighted.

15.2.2.1 Section 1 Replacement of AVIVO MPM with VitalPatch Biosensor

This section was changed as a result of Modification 1.

Old text

(…)

Medical devices:	~~AVIVO Mobile Patient Monitoring System (MPM)~~ (~~Medtronic~~, USA)
	DynaPort Move Monitor (McRoberts, NL)

(…)

New text

(…)

Medical devices: VitalPatch biosensor
(VitalConnect, USA)
DynaPort Move Monitor (McRoberts, NL)

(…)

15.2.2.2 Section 2 Replacement of AVIVO MPM with VitalPatch Biosensor

This section was changed as a result of Modification 1.

Old text

(…)

Secondary objectives:

- Association between ~~AVIVO MPM~~ 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 tissue impedance, heart rate, 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 (~~AVIVO MPM system~~ and DynaPort Move Monitor) in patients with heart failure

Correlation of activity data between ~~AVIVO MPM~~ data on activity and DynaPort Move Monitor

(…)

- Explore longitudinal changes in transcutaneous thoracic impedance measurement (~~AVIVO MPM~~) and thus as a surrogate of fluid status in patients with acute HF and after stabilization

(…)

- 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 ~~AVIVO MPM~~

(…)

Medical Devices	
Device 1	~~AVIVO MPM system~~ (~~Medtronic~~, USA)
Device 2	DynaPort Move Monitor (McRoberts, NL) The devices will be provided by BAYER to sites and used according to their approved labeling.

(…)

The ~~AVIVO~~ heart failure patch will be applied after successful screening (first ~~AVIVO~~ patch), after discharge (2nd Patch), at visit 2 (3rd patch), at week 2 after discharge (patch 4) and visit 3. The Dynport MoveMonitor belt will be applied at visit 2 and visit 3. The 6MWD test will be done at visit 2 (first week after discharge) as well as week 12 post discharge (visit 4).

(…)

Primary variable(s)	Daily physical activity (amount, intensity, duration) obtained from the ~~AVIVO MPM~~/DynaPort Move Monitor device

(…)

All analyses will be performed for the total study population (overall analysis). Subjects wearing at least once the ~~AVIVO MPM~~ system and for which data was successfully collected over a whole week will be included in the analysis.

(…)

New text

(…)

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 tissue impedance, heart rate, 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

(…)

- Explore longitudinal changes in transcutaneous thoracic impedance measurement (VitalPatch biosensor) and thus as a surrogate of fluid status in patients with acute HF and after stabilization

(…)

- 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

(…)

Medical Devices	

Device 1	VitalPatch biosensor (VitalConnect, USA)
Device 2	DynaPort Move Monitor (McRoberts, NL)
	The devices will be provided by BAYER to sites and used according to their approved labeling.

(…)

The VitalPatch heart failure patch will be applied after successful screening (first VitalPatch biosensor patch), after discharge (2nd Patch), at visit 2 (3rd patch), at week 2 after discharge (patch 4) and visit 3. The Dynport Move Monitor belt will be applied at visit 2 and visit 3. The 6MWD test will be done at visit 2 (first week after discharge) as well as week 12 post discharge (visit 4).

(…)

Primary variable(s)	Daily physical activity (amount, intensity, duration) obtained from the VitalPatch biosensor/DynaPort Move Monitor device

(…)

All analyses will be performed for the total study population (overall analysis). Subjects wearing at least once the VitalPatch biosensor system and for which data was successfully collected over a whole week will be included in the analysis.

(…)

15.2.2.3 Section 3 Replacement of AVIVO MPM with VitalPatch Biosensor

This section was changed as a result of Modification 1.

Old text

(…)

The ~~AVIVO Mobile Patient Management (MPM) System~~ is a wearable, wireless physiological monitoring and arrhythmia detection system that is used by patients to aid clinicians in the identification, diagnosis and management of various clinical conditions, events and/or trends. It consists primarily of the wearable sensor (monitoring device) and ~~the transmitter (portable data transmission device).~~

The ~~AVIVO MPM~~ will be used to monitor patients' cardiovascular status. The cardiac monitoring device will be worn as specified in Section 9.7.1.

(…)

~~The system is CE marked and US FDA cleared. Apart from safety assessments, also the patient's everyday physical activity (frequency, duration, intensity) will be tracked.~~

Details of the cardiac monitoring and the device to be worn by the patient will be outlined in a manual that will be provided to all participating centers.

The DynaPort Move Monitor – the second activity tracker used in the present study -is a wearable device worn in an elastic strap on the lower back for ambulatory monitoring of

physical activity for up to 7 days. The DynaPort Move Monitor consists of three orthogonally mounted accelerometers, a tri-axial magnetometer, a temperature sensor and a barometer.

(…)

New text

(…)

The VitalPatch biosensor is a wearable, wireless physiological monitoring and arrhythmia detection system that is used by patients to aid clinicians in the identification, diagnosis and management of various clinical conditions, events and/or trends. It consists primarily of the wearable sensor (monitoring device) and a portable secured data transmitter (mobile phone with bluetooth and wireless connection). VitalPatch is manufactured by VitalConnect (USA), and is fully approved by the USA FDA, CE marked in the European Union, CMDR registered and ISO 13485 certified.

The VitalPatch biosensor will be used to monitor patients' cardiovascular status. The cardiac monitoring device will be worn as specified in Section 9.7.1.

(…)

Details of the cardiac monitoring and the device to be worn by the patient will be outlined in a manual that will be provided to all participating centers.

The DynaPort Move Monitor – the second activity tracker used in the present study -is a wearable device worn in an elastic strap on the lower back for ambulatory monitoring of physical activity for up to 7 days. DynaPort Move Monitor is manufactured by McRoberts BV (Netherlands). This device is US FDA approved, CE marked in the European Union and ISO 13485 certified. The DynaPort Move Monitor consists of three orthogonally mounted accelerometers, a tri-axial magnetometer, a temperature sensor and a barometer.

(…)

15.2.2.4 Section 4 Replacement of AVIVO MPM with VitalPatch Biosensor

This section was changed as a result of Modification 1.

Old text

(…)

Secondary objectives:

- Association between ~~AVIVO MPM~~ 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 tissue impedance, heart rate, 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 (~~AVIVO MPM system~~ and DynaPort Move Monitor) in patients with heart failure
- Correlation of activity data between ~~AVIVO MPM~~ data on activity and DynaPort Move Monitor

(…)

- Explore longitudinal changes in transcutaneous thoracic impedance measurement (~~AVIVO MPM~~) and thus as a surrogate of fluid status in patients with acute HF and after stabilization

(…)

- 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 ~~AVIVO MPM~~

(…)

New text

(…)

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 tissue impedance, heart rate, 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

(…)

- Explore longitudinal changes in transcutaneous thoracic impedance measurement (VitalPatch biosensor) and thus as a surrogate of fluid status in patients with acute HF and after stabilization

(…)

- 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

(…)

15.2.2.5 Section 5 Replacement of AVIVO MPM with VitalPatch Biosensor

This section was changed as a result of Modification 1.

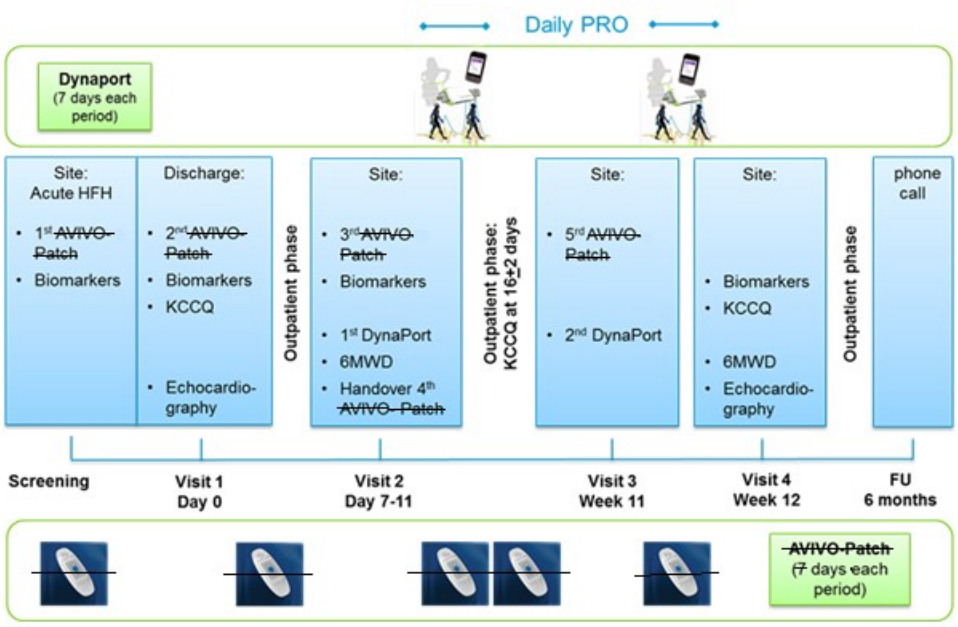
Old text

(…)

All patients will receive ~~AVIVO MPM system~~ at 5 monitoring periods (5 patches each subject in total, monitoring period ~~7~~ 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.

(…)

Figure 5-1: Study design



(…)

Primary variables

- Daily physical activity (amount, duration and intensity) obtained from the ~~AVIVO MPM~~ /DynaPort Move Monitor device

Secondary variables

- 6MWD
- Other activity information obtained from the ~~AVIVO MPM~~ /DynaPort Move Monitor device such as sleep movements and patterns, sit-to stand behavior (DynaPort)

(…)

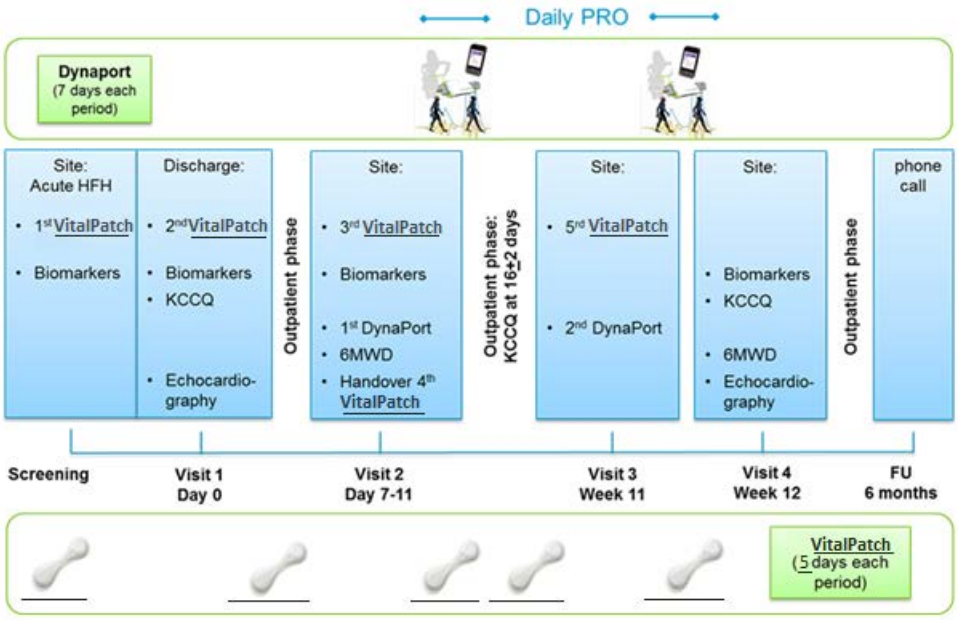
New text

(…)

All patients will receive VitalPatch biosensor at 5 monitoring periods (5 patches each subject in total, monitoring period 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.

(…)

Figure 5-1: Study design - amended



(…)

Primary variables

- Daily physical activity (amount, duration and intensity) obtained from the VitalPatch biosensor /DynaPort Move Monitor device

Secondary variables

- 6MWD
- Other activity information obtained from the VitalPatch biosensor /DynaPort Move Monitor device such as sleep movements and patterns, sit-to stand behavior (DynaPort)

(…)

15.2.2.6 Section 6.1 Replacement of AVIVO MPM with VitalPatch Biosensor

This section was changed as a result of Modification 1.

Old text

(…)

7. Willingness to wear the DynaPort Move Monitor accelerometer belt and ~~AVIVO MPM~~ during the trial

(…)

New text

(…)

7. Willingness to wear the DynaPort Move Monitor accelerometer belt and VitalPatch biosensor during the trial

(…)

15.2.2.7 Section 9.1 Replacement of AVIVO MPM with VitalPatch Biosensor

This section was changed as a result of Modification 1.

Old text

(…)

Table 1: Tabulated overview on study procedures and variables collected during the study – amended

Study period	**Hospitalization phase**		**Outpatient phase**					**Safety FU call**
Visit number	**Scr[1]**	**1**	**2**			**3**	**4**	**5**
Visit type	**site**		**site**			**site**	**site**	**☎**
	Screen assess	**At hospital discharge**						
Week after discharge			**1**	**2**	**3**	**11**	**12**	
Day and allowed deviations		**0**	**9±2**	**16±2**	**23±2**	**77±2**	**84±2**	**6 months ±4 weeks**

(…)

~~AVIVO~~ (for ~~7~~ days)[2] →start ←end	→---1st---← →--2nd-←→--3rd-←→--4th--← →----5th----←	

(…)

[1] within 72 hours after hospitalization
[2] DynaPort monitoring periods: Second week after hospital discharge (Days 7-14) and Week 11 to 12 (Days 77-84)
~~AVIVO~~ monitoring periods: up to ~~7~~ days during the hospital stay, first ~~week~~ after hospital discharge (Day 0-~~7~~), during weeks 2 and 3 (Day 7-~~14~~, Day 1~~7~~-~~24~~) and Week 11 to 12 (Days 77-~~84~~)
[3] central lab assessments: NTproBNP, hs-copeptin, hs-TNT, optionally: GDF15, IGFBP7, sST2, Gal3
* Concurrently evaluating PRO will be completed daily and weekly during DynaPort and ~~AVIVO~~ parallel monitoring period
[4] within ± 72 of discharge day

(…)

New text

(…)

Table 1: Tabulated overview on study procedures and variables collected during the study – amended

Study period	**Hospitalization phase**		**Outpatient phase**					**Safety FU call**
Visit number	**Scr[1]**	**1**	**2**			**3**	**4**	**5**
Visit type	**site**		**site**			**site**	**site**	☎
	Screen assess	**At hospital discharge**						
Week after discharge			**1**	**2**	**3**	**11**	**12**	
Day and allowed deviations		**0**	**9±2**	**16±2**	**23±2**	**77±2**	**84±2**	**6 months ±4 weeks**

(…)

VitalPatch (for 5 days)[2] →start ←end	→---1st---← →--2nd-←→--3rd-←→--4th--← →----5th----←	

(…)

[1] within 72 hours after hospitalization
[2] DynaPort monitoring periods: Second week after hospital discharge (Days 7-14) and Week 11 to 12 (Days 77-84)
VitalPatch monitoring periods: up to 5 days during the hospital stay, first 5 days after hospital discharge (Day 0-5), during weeks 2 and 3 (Day 7-12, Day 12-17) and Week 11 to 12 (Days 77-82)
[3] central lab assessments: NTproBNP, hs-copeptin, hs-TNT, optionally: GDF15, IGFBP7, sST2, Gal3
* Concurrently evaluating PRO will be completed daily and weekly during DynaPort and VitalPatch parallel monitoring period
[4] within ± 72 of discharge day

(…)

15.2.2.8 Section 9.2 Replacement of AVIVO MPM with VitalPatch Biosensor

This section was changed as a result of Modification 1.

Old text

(…)

Enrollment / Screening Visit

(…)

- Eligible patients will be included in the study and will wear the ~~AVIVO MPM patch~~ for up to ~~7~~ days during the hospital stay

(…)

Visit 1 (Day 0) - amended

(…)

- A new ~~AVIVO MPM patch~~ will be attached to subject`s chest, which they will wear for ~~7~~ days after discharge from hospital ~~(may be expanded until Days 9±2).~~
- Subjects will be informed how to wear and apply the ~~AVIVO MPM~~.

(…)

Visit 2 (Day 9 ± 2 days) - amended

(…)

- The ~~AVIVO MPM patch~~ device will be collected
- In addition subjects will receive the DynaPort Move Monitor device which they will also wear for 7 days. Subjects will be informed how to wear and apply the DynaPort Move Monitor.
- Subjects will receive another 2 ~~AVIVO MPM~~ patches which they will wear consecutively for ~~7~~ days each. One ~~AVIVO MPM~~ patch will be attached to the subject`s chest at the site, the other one has to be attached by the patient after removal of the first one after ~~7~~ days.
- Instruction to patient to complete KCCQ (Day 16 ± 2 days)
- Completion of PRO daily and weekly during DynaPort Move Monitor and ~~AVIVO parallel~~ monitoring period.

(…)

Visit 3 (Day 77 ± 2 days) - amended

(…)

- daily and weekly PRO during wearing of DynaPort Move Monitor and ~~AVIVO MPM~~ devices
- The ~~AVIVO~~ patches will be collected
- Subjects will receive another ~~AVIVO MPM~~ patch and the DynaPort Move Monitor device which they will wear for 7 days. The ~~AVIVO MPM patch~~ will be placed on subject`s chest and DynaPort Move Monitor belt will be put on at the site.

(…)

Visit 4 (Day 84 ± 2 days)

(…)

The ~~AVIVO MPM~~ patch and the DynaPort Move Monitor device will be collected.

(…)

New text

(…)

Enrollment / Screening Visit – amended

(…)

- Eligible patients will be included in the study and will wear the VitalPatch biosensor for up to 5 days during the hospital stay

(…)

Visit 1 (Day 0) - amended

(…)

- A new VitalPatch biosensor will be attached to subject`s chest, which they will wear for 5 days after discharge from hospital
- Subjects will be informed how to wear and apply the VitalPatch biosensor.

(…)

Visit 2 (Day 9 ± 2 days) - amended

(…)

- The VitalPatch biosensor device will be collected
- In addition subjects will receive the DynaPort Move Monitor device which they will wear for 7 days. Subjects will be informed how to wear and apply the DynaPort Move Monitor.
- Subjects will receive another 2 VitalPatch biosensor patches which they will wear consecutively for 5 days each. One VitalPatch biosensor patch will be attached to the subject`s chest at the site, the other one has to be attached by the patient after removal of the first one after 5 days.
- Instruction to patient to complete KCCQ (Day 16 ± 2 days)
- Completion of PRO daily and weekly during DynaPort Move Monitor and VitalPatch monitoring period.

(…)

Visit 3 (Day 77 ± 2 days) - amended

(…)

- daily and weekly PRO during wearing of DynaPort Move Monitor and VitalPatch devices

- The VitalPatch biosensor patches will be collected
- Subjects will receive another VitalPatch biosensor patch and the DynaPort Move Monitor device which they will wear for 5 and 7 days, respectively. The VitalPatch biosensor will be placed on subject`s chest and DynaPort Move Monitor belt will be put on at the site.

(…)

Visit 4 (Day 84 ± 2 days) - amended

(…)

The VitalPatch biosensor patch and the DynaPort Move Monitor device will be collected.

(…)

15.2.2.9 Section 9.6.1.4 Replacement of AVIVO MPM with VitalPatch Biosensor

This section was changed as a result of Modification 1.

Old text

(…)

Any serious adverse events-will be reported by the investigator to Bayer. Bayer will process these cases according to Bayer standard procedures and report as described below. In addition, all adverse events related to the ~~AVIVO Mobile Patient Management (MPM) System~~ or the DynaPort Move Monitor, which are both non-investigational devices in the Post-Marketing phase, will be reported by the investigator to the respective legal manufacturers, which would fulfill their reporting obligations to competent authorities and Notified bodies.

(…)

Reporting obligations for non-Bayer drugs/devices incl. ~~AVIVO Mobile Patient Management (MPM) System~~ and the DynaPort Move Monitor will be fulfilled by the respective Marketing Authorization holders/Manufacturers based on the information provided by the investigator via spontaneous reporting.

(…)

New text

(…)

Any serious adverse events-will be reported by the investigator to Bayer. Bayer will process these cases according to Bayer standard procedures and report as described below. In addition, all adverse events related to the VitalPatch biosensor or the DynaPort Move Monitor, which are both non-investigational devices in the Post-Marketing phase, will be reported by the investigator to the respective legal manufacturers, which would fulfill their reporting obligations to competent authorities and Notified bodies.

(…)

Reporting obligations for non-Bayer drugs/devices incl. VitalPatch biosensor and the DynaPort Move Monitor will be fulfilled by the respective Marketing Authorization holders/Manufacturers based on the information provided by the investigator via spontaneous reporting.

(…)

15.2.2.10 Section 9.7.1 Replacement of AVIVO MPM with VitalPatch Biosensor

This section was changed as a result of Modification 1.

Old text

(…)

9.7.1 ~~AVIVO MPM~~/DynaPort Move Monitor devices

~~AVIVO MPM system~~

~~AVIVO MPM system~~ will be provided by Bayer to sites. Subjects will wear the ~~AVIVO MPM patch~~ for overall 5 periods of ~~7~~ days each (for details on time periods see Table 1).

Parameters obtained from the ~~AVIVO MPM patch~~ are:

- ECG and parameters derived from ECG, like e.g. heart rate, HRV, AF burden, arrhythmias etc.
- Respiratory rate
- Transcutaneous thoracic impedance = fluid status
- Physical activity (duration and intensity)
- Posture

(…)

New text

(…)

9.7.1 VitalPatch biosensor/DynaPort Move Monitor devices - amended

VitalPatch biosensor

VitalPatch biosensor will be provided by Bayer to sites. Subjects will wear the VitalPatch biosensor for overall 5 periods of 5 days each (for details on time periods see Table 1).

Parameters obtained from the VitalPatch biosensor are:

- ECG and parameters derived from ECG, like e.g. heart rate, HRV, AF burden, arrhythmias etc.
- Respiratory rate
- Transcutaneous thoracic impedance = fluid status

- Skin temperature
- Step count
- Physical activity (duration and intensity)
- Posture

(…)

15.2.2.11 Section 9.7.2 Replacement of AVIVO MPM with VitalPatch Biosensor

This section was changed as a result of Modification 1.

Old text

(…)

Quality of life will be assessed using the KCCQ [10]. The total score will be documented.

PRO will be completed daily and weekly during DynaPort Move Monitor and ~~AVIVO MPM parallel~~ monitoring.

(…)

New text

(…)

Quality of life will be assessed using the KCCQ [10]. The total score will be documented.

PRO will be completed daily and weekly during DynaPort Move Monitor and VitalPatch monitoring.

(…)

15.2.2.12 Section 10.1 Replacement of AVIVO MPM with VitalPatch Biosensor

This section was changed as a result of Modification 1.

Old text

(…)

Data from ~~AVIVO~~ and DynaPort devices is expected to include missing values, as result of compliance in wearing the device.

(…)

New text

(…)

Data from VitalPatch and DynaPort devices is expected to include missing values, as result of compliance in wearing the device.

(…)

15.2.2.13 Section 10.2 Replacement of AVIVO MPM with VitalPatch Biosensor

This section was changed as a result of Modification 1.

Old text

(…)

10.2 Analysis sets

In absence of intervention and randomization the statistical analysis sets are defined on the base of a successful monitoring under the ~~AVIVO MPM~~ patch.

Full analysis set (FAS)

The FAS population consists of all subjects that are included into the study and that are wearing at least one ~~AVIVO MPM~~ patch and for which data was successfully collected over the whole week. The FAS will be used to display baseline characteristics, assess parameter variability, correlative analyses.

Safety analysis set (SAF)

The SAF population consists of all patients with a planned study procedure after signing the informed consent that are wearing at least one ~~AVIVO MPM~~ patch and for which data was successfully collected over the whole week will be included in the SAF. The SAF will be used to display safety analyses.

(…)

New text

(…)

10.2 Analysis sets - amended

In absence of intervention and randomization the statistical analysis sets are defined on the base of a successful monitoring under the VitalPatch biosensor patch.

Full analysis set (FAS)

The FAS population consists of all subjects that are included into the study and that are wearing at least one VitalPatch biosensor patch and for which data was successfully collected over the whole week. The FAS will be used to display baseline characteristics, assess parameter variability, correlative analyses.

Safety analysis set (SAF)

The SAF population consists of all patients with a planned study procedure after signing the informed consent that are wearing at least one VitalPatch biosensor patch and for which data was successfully collected over the whole week will be included in the SAF. The SAF will be used to display safety analyses.

(…)

15.2.2.14 Section 10.3.2 Replacement of AVIVO MPM with VitalPatch Biosensor

This section was changed as a result of Modification 1.

Old text

(…)

For ~~AVIVO~~ data collected in this frame only the day to day variability will be of interest.

(…)

New text

(…)

For VitalPatch data collected in this frame only the day to day variability will be of interest.

(…)

15.2.2.15 Section 10.3.3.2 Replacement of AVIVO MPM with VitalPatch Biosensor

This section was changed as a result of Modification 1.

Old text

(…)

This analysis allows investigating the relationship between two multivariate sets of variables, such as the one obtained using the ~~AVIVO MPM~~ or DynaPort Move Monitor device, and another one as obtained from other contexts, such as contexts defined by the following data sets: i) echocardiography parameters set, ii) 12-lead ECG parameters set, and iii) a composite set including biomarkers, 6MWD score, KCCQ total score, and vital signs (blood pressure, heart rate).

(…)

New text

(…)

This analysis allows investigating the relationship between two multivariate sets of variables, such as the one obtained using the VitalPatch biosensor or DynaPort Move Monitor device, and another one as obtained from other contexts, such as contexts defined by the following data sets: i) echocardiography parameters set, ii) 12-lead ECG parameters set, and iii) a composite set including biomarkers, 6MWD score, KCCQ total score, and vital signs (blood pressure, heart rate).

(…)

15.2.2.16 Section 13.2 Replacement of AVIVO MPM with VitalPatch Biosensor

This section was changed as a result of Modification 1.

Old text

(…)

Funding

This study will be funded by its sponsor.

Collaborator of this study is ~~Medtronic Inc., Patient Monitoring & Diagnostics, 8200 Coral Sea Street, NE Mounds View, Minnesota 55112~~, USA.

(…)

New text

(…)

Funding

This study will be funded by its sponsor.

Collaborator of this study is VitalConnect Inc., 224 Airport Parkway Suite 300, San Jose, California 95110, USA.

(…)

Section 16.1 Replacement of AVIVO MPM with VitalPatch Biosensor

Old text

(…)

- Provide a brief high-level outline of how the PRO items can be used to:
    - Validate activity monitoring data from wearable devices (~~AVIVO patch~~ and DynaPort Move Monitor)

(…)

New text

(…)

- Provide a brief high-level outline of how the PRO items can be used to:
    - Validate activity monitoring data from wearable devices (VitalPatch biosensor and DynaPort Move Monitor)

(…)

15.2.2.17 Section 16.1 Replacement of AVIVO MPM with VitalPatch Biosensor

This section was changed as a result of Modification 1.

Old text

(…)

- Provide a brief high-level outline of how the PRO items can be used to:

- Validate activity monitoring data from wearable devices (~~AVIVO patch~~ and DynaPort Move Monitor)

(…)

New text

(…)

- Provide a brief high-level outline of how the PRO items can be used to:
  - Validate activity monitoring data from wearable devices (VitalPatch biosensor and DynaPort Move Monitor)

(…)

15.3 Amendment 3

Amendment 3 is dated 21 Feb 2020.

15.3.1 Overview of changes to the study protocol

This amendment was issued to open the recruitment of the study to additional patients, especially patients with chronic heart failure (CHF) who show up in an unplanned outpatient visit but need no hospitalization, and to generally facilitate the conduct of the study at the sites.

Modification 1: Extension of the study population

Description of modification to the study plan:

In- and exclusion criteria were modified to allow participation of a wider range of patients with heart failure.

Rationale for introducing the modification:

Ambulatory, stable patients were added to the study population to also gain further insights into this group, in comparison to the hospitalized patients with worsening heart failure. The data generated is meant to be used as reference for future clinical development projects across various different heart failure subpopulations, to cover the complete clinical spectrum and various characteristics of the patient journey.

In addition, entry criteria were adjusted to match the situation of the subjects in scope. Specifically, the exclusion criterion for hemoglobin was changed from <10.0 g/dL to <8.0 g/dL . Low hemoglobin values are commonly observed due to dilution of the blood from excess fluid. Through application of standard diuretic therapy, it is expected that hemoglobin levels will quickly recover, and hemoglobin will not have an impact on exercise capacity.

List of all CSP sections affected by this modification: Sections 2, 5, 6.1, 6.2.

Modification 2: Simplification of number and timing of study-related procedures

Description of modification to the study plan:

The number of timing of the following measurements was aligned and - in some cases - reduced: physical exam, echocardiography, blood samples for biomarkers, vital patch application.

Rationale for introducing the modification:

Following the exchange of the AVIVO patch versus the VitalPatch in amendment 2 and limitations provided by the new device, adaptions of the timing of the planned measurements became necessary to facilitate the conduct of the study. In addition, the study team revisited procedures with limited value for the envisaged study objectives and optimized workflows for enhanced feasibility.

List of all CSP sections affected by this modification: Sections 2, 4, 5, 9.1, 9.2, 9.6.3, 9.7.1.

15.3.2 Changes to the protocol text

In this section on changes to the protocol text, all protocol sections affected by the respective amendment are detailed; the sequence of the sections follows the structure of the most recent previous protocol version.

As applicable, changes to the protocol text are highlighted as follows:

- **Editing of an existing portion** Comparative presentation of "old text" versus "new text", with "old text" referring to the most recent previous protocol version. Deletions are ~~crossed out~~ in the "old text". Additions are <u>underlined</u> in the "new text".
- **Tables / figures / sections** The term "amended" is added to the caption/heading.

Corrections of typos or omissions are not highlighted.

15.3.2.1 Section 2 Extension of study population and simplification of study procedures

This section was changed as a result of Modification 1 and 2 (tissue impedance was provided by the AVIVO patch but is not measured by the VitalPatch anymore).

Old text

Study objective(s)	The study aims to explore two marketed devices providing a multi-marker monitoring including physical 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 such as the six minute walking distance (6MWD), biomarkers and clinical events. […] **Secondary objectives:** […] • Assess the baseline level and longitudinal changes over time of ~~tissue impedance~~, heart rate, 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.

	[…] • Evaluate the relationship between physical activity levels, ~~tissue impedance~~, heart rate, 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) […] • Evaluate hs-copeptin as potential biomarker • ~~Explore longitudinal changes in transcutaneous thoracic impedance measurement (VitalPatch biosensor) and thus as a surrogate of fluid status in patients with acute HF and after stabilization~~ • ~~Correlate blood based biomarkers of congestion (e.g. NTproBNP/hs-copeptin) with functional marker (impedance)~~

New text

Study objective(s)	The study aims to explore two marketed devices providing a multi-marker monitoring including physical activity under real-life conditions in patients with HFpEF and HFrEF. It aims to identify potential <u>novel</u> endpoints for future HFpEF trials by exploring clinically relevant changes over time and correlations/associations with conventional endpoints such as the six-minute-walking-distance (6MWD), biomarkers and clinical events. […] **Secondary objectives:** […] • Assess the baseline level and longitudinal changes over time of heart rate, 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. […] • Evaluate the relationship between physical activity levels, heart rate, 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) […] • Evaluate hs-copeptin as potential biomarker

Further changes were introduced as a result of Modification 1 (extension of study population).

Old text

Diagnosis and main criteria for inclusion /exclusion	Female and male subjects with a diagnosis of ~~acute decompensated~~ heart failure with preserved ejection fraction (HFpEF; EF ≥ 45%) or ~~acute decompensated heart failure with~~ reduced ejection fraction (HFrEF; EF ≤ 35%) will be enrolled.

New text

Diagnosis and main criteria for inclusion /exclusion	Female and male subjects with a diagnosis of heart failure with preserved ejection fraction (HFpEF; EF ≥ 45%) or reduced ejection fraction (HFrEF; EF ≤ 35%) will be enrolled.

Further changes were introduced as a result of Modification 2 (simplification of study related procedures).

Old text:

Methodology	This study will ~~compromise~~ a hospital phase of ~~approximately 5.5~~ days including ~~the screening period~~, an outpatient phase of approximately ~~11~~ week ~~(depending on duration of hospital phase)~~ and a follow up telephone call after 6 months Patients will be selected on the basis of their established diagnosis of HFrEF and HFpEF. The patients will have site visits at weeks 0 (screening visit and ~~baseline~~ visit 1 during in hospitalization phase), week 1 after hospital discharge (visit 2; ~~outpatient~~ phase), week 11 post discharge (visit 3, ~~outpatient~~ phase) and week 12 post discharge (visit 4, ~~outpatient~~ phase). In addition, one follow up phone call at 6 month post discharge will be made to assess patient safety, well-being and clinical status. The VitalPatch heart failure patch will be applied after successful screening (first VitalPatch biosensor patch), ~~after discharge (2nd Patch)~~, at visit 2 (3rd patch), at ~~week 2 after discharge (patch 4) and~~ visit 3. The ~~Dynport~~ MoveMonitor belt will be applied at visit 2 and visit 3. The 6MWD test will be done at visit ~~2 (first week after~~ discharge) as well as ~~week 12 post discharge (visit 4)~~. Transthoracic echocardiography will be performed ~~prior to hospital discharge~~ at visit 1 ~~and visit 4~~. The KCCQ questionnaire will be performed at visit 1 prior to discharge, week 2 after discharge and at visit 4. Daily and weekly PRO will be performed in parallel with the DynaPort Move Monitor monitoring periods (visit 2, week 1-2) and visit 3 (week 11-12). Biomarkers reflecting cardiac structure and function will be examined as well as candidate biomarkers that may predict outcomes. Daily physical activity (duration and intensity) will be recorded during repeated 7-day time periods until 3 months after discharge from hospital.

New text

Methodology	This study will comprise a screening phase of up to 9 days including an optional hospitalization period or, alternatively starting after an unscheduled outpatient visit; an outpatient phase of approximately 12 weeks and a follow up telephone call after 6 months Patients will be selected on the basis of their established diagnosis of HFrEF and HFpEF. The patients will have site visits at week 0 (screening visit and visit 1 within 9 days, during hospitalization phase or in ambulatory patients), week 1 after visit 1 / hospital discharge (visit 2; observational phase), week 11 post visit 1 / discharge (visit 3, observational phase) and week 12 post visit 1 / discharge (visit 4, observational phase). In addition, one follow up phone call at 6 months post discharge will be made to assess patient safety, well-being and clinical status. The VitalPatch heart failure patch will be applied after successful screening (first VitalPatch biosensor patch), at visit 2 (2nd patch, 3rd patch will be subsequently applied by the patient at home), and at visit 3 (4th patch, 5th patch will be subsequently applied by the patient at home). The DynaPort MoveMonitor belt will be applied at visit 2 and visit 3. The 6MWD test will be done at visit 1 / hospital discharge) as well as visit 4 (12 weeks post visit 1 / discharge). Transthoracic echocardiography will be performed at visit 1 (within ± 72 hours). The KCCQ questionnaire will be performed at visit 1 / prior to discharge, week 3 after visit 1 / discharge and at visit 4. Daily and weekly PRO will be performed in parallel with the DynaPort MoveMonitor monitoring periods (visit 2, week 1-2) and visit 3 (week 11-12). Biomarkers reflecting cardiac structure and function will be examined as well as candidate biomarkers that may predict outcomes. Daily physical activity (duration and intensity) will be recorded during repeated respective 5-day (VitalPatch) and 7-day (DynaPort MoveMonitor) time periods until 3 months after visit 1 / discharge from hospital.

Old text

Time point/frame of measurement for primary variable(s)	Baseline level and longitudinal changes over time of physical activity and the average of person-to-person physiological variability and the within-subject standard deviation between the baseline and 3-month post ~~discharge~~ measurements.

New text

Time point/frame of measurement for primary variable(s)	Baseline level and longitudinal changes over time of physical activity and the average of person-to-person physiological variability and the within-subject standard deviation between the baseline and 3-month post baseline measurements.

Old text

Plan for statistical analysis	[…] All analyses will be performed for the total study population (overall analysis). Subjects wearing at least once the VitalPatch biosensor[11] system and for which data was successfully collected over ~~a whole week~~ will be included in the analysis.

New text

Plan for statistical analysis	[…] All analyses will be performed for the total study population (overall analysis). Subjects wearing at least once the VitalPatch biosensor[11] system and for which data was successfully collected over 5 days will be included in the analysis.

15.3.2.2 Section 4 Deletion of tissue impedance related objectives

This section was changed as a result of Modification 2 (tissue impedance was provided by the AVIVO patch, but is not measured by the VitalPatch anymore).

Old text

Secondary objectives:

[…]

- Assess the baseline level and longitudinal changes over time of ~~tissue impedance~~, heart rate, 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

[...]

- Evaluate the relationship between physical activity levels, ~~tissue impedance~~, heart rate, 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)

[…]

- Evaluate hs-copeptin as potential biomarker
- ~~Explore longitudinal changes in transcutaneous thoracic impedance measurement (VitalPatch biosensor) and thus as a surrogate of fluid status in patients with acute HF and after stabilization~~
- ~~Correlate blood based biomarkers of congestion (e.g. NTproBNP/hs-copeptin) with functional marker (impedance)~~
- Correlation between patch monitor collected data and inpatient clinical data during hospital stay (e.g. echocardiography, weight gain/loss, NYHA, heart rate)
- Explore the relationship between PA, 6MWD, PRO, biomarkers, adverse events/clinical outcomes

New text

Secondary objectives:

[…]

- Assess the baseline level and longitudinal changes over time of heart rate, 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

[...]

- Evaluate the relationship between physical activity levels, heart rate, 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)

[...]

- 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, heart rate)
- Explore the relationship between PA, 6MWD, PRO, biomarkers, adverse events/clinical outcomes

15.3.2.3 Section 5 Extension of study population and simplification of procedures

This section was changed as a result of Modification 1 and Modification 2.

Old text

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 ~~acute~~ heart failure will be included in this study. Overall 80 subjects have to complete at least all device monitoring periods:

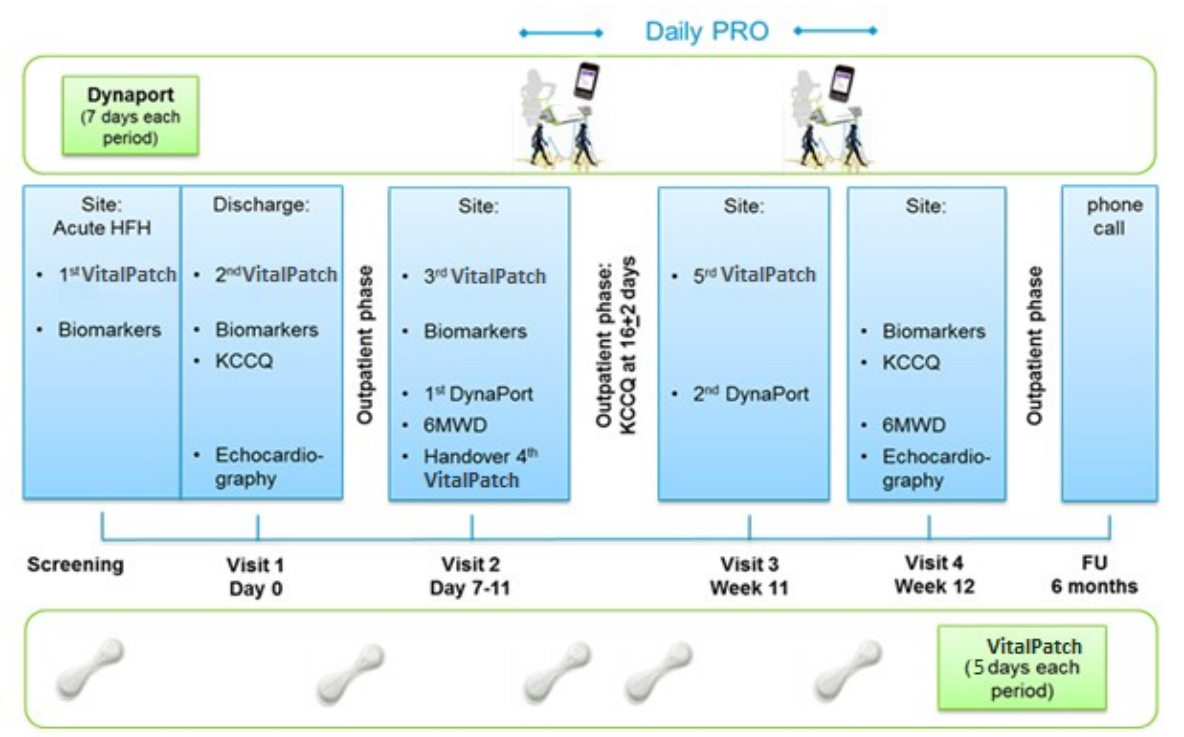
- 60 subjects with ~~acute decompensated~~ heart failure with preserved ejection fraction (HFpEF; EF ≥ 45%) and
- 20 subjects with ~~acute decompensated~~ heart failure with reduced ejection fraction (HFrEF; EF ≤ 35%).

[…]

Biomarkers will be investigated during the hospital stay and at the visit~~s 2 and~~ 4. A 6-minute walking test will be performed at ~~baseline (first week after~~ discharge) and after 11-12 weeks.

Design overview

Figure 5-1: Study design



Abbreviations: ~~HHF = heart failure hospitalization; 6MWD = 6-minute walking distance test, PRO = patient reported outcome; FU = follow up visit~~

New text

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:

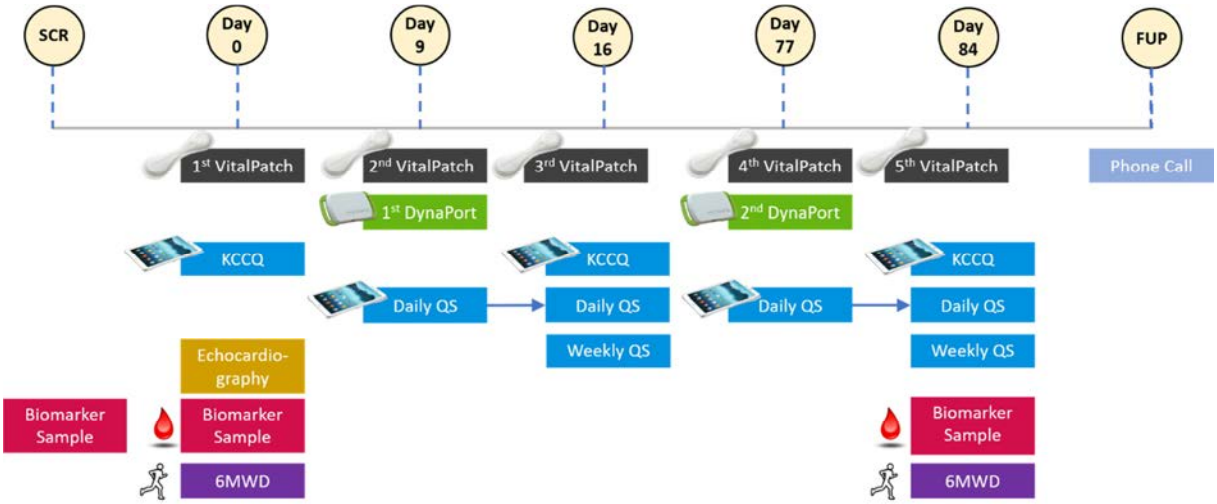
- Approx. 60 subjects with established diagnosis of heart failure with preserved ejection fraction (HFpEF; EF ≥ 45%) and
- Approx. 20 subjects with established diagnosis of heart failure with reduced ejection fraction (HFrEF; EF ≤ 35%).

[…]

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 5-1: 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

Old text

Secondary variables

- […]
- Plasma/serum biomarkers
- Blood pressure and heart rate, cardiac function parameters measured by echocardiography

- ~~Tissue impedance~~
- ECG derived readouts: heart rate variability (HRV)
- NYHA class

Results of the primary and secondary variables obtained at 3 months post-~~discharge~~ (week 11-12) versus baseline ~~(first week after discharge)~~.

New text

Secondary variables

- […]
- Plasma/serum biomarkers
- Blood pressure and heart rate, cardiac function parameters measured by echocardiography
- ECG derived readouts: heart rate variability (HRV)
- NYHA class

Results of the primary and secondary variables obtained at 3 months post-baseline (week 11-12) versus baseline (visit 1).

15.3.2.4 Section 6.1 Extension of study population

This section was changed as a result of Modification 1.

Old text

4. Worsening heart failure requiring hospitalization ~~within the last 72 hours~~ for the initiation of intensification of heart failure therapy with ***at least one*** of the following
    - BNP ≥ 100 pg/mL or NT-proBNP ≥ 400 pg/mL (sinus rhythm) or
    - BNP ≥ 300 pg/mL or NT-proBNP ≥ 1200 pg/mL (atrial fibrillation)
    - Radiographic evidence of pulmonary congestion (interstitial edema, pulmonary venous hypertension, vascular congestion, pleural effusion)
    - Catheterization documented elevated filling pressures at rest (left ventricular end-diastolic pressure ≥15 mmHg or pulmonary capillary wedge pressure ≥20 mmHg) or with exercise (pulmonary capillary wedge pressure ≥25 mmHg)
5. For HFrEF only
    - EF ≤ 35% assessed by any imaging modality (e.g. echocardiography, cardiac magnetic resonance, cine levocardiography) within ~~3~~ months prior to study inclusion

6. For HFpEF only
    - EF ≥ 45% assessed by any imaging modality (e.g. echocardiography, cardiac magnetic resonance, cine levocardiography) within ~~3~~ months prior to study inclusion

New text

4. Worsening heart failure requiring hospitalization for the initiation of intensification of heart failure therapy with ***at least one*** of the following
    - BNP ≥ 100 pg/mL or NT-proBNP ≥ 400 pg/mL (sinus rhythm) or
    - BNP ≥ 300 pg/mL or NT-proBNP ≥ 1200 pg/mL (atrial fibrillation)
    - Radiographic evidence of pulmonary congestion (interstitial edema, pulmonary venous hypertension, vascular congestion, pleural effusion)
    - Catheterization documented elevated filling pressures at rest (left ventricular end-diastolic pressure ≥15 mmHg or pulmonary capillary wedge pressure ≥20 mmHg) or with exercise (pulmonary capillary wedge pressure ≥25 mmHg)

    OR

    Ambulatory patients with a history of heart failure on individually optimized treatment with HF medications unless contraindicated or not tolerated, for at least 12 weeks and ***at least one*** one of the following
    - Hospitalization for heart failure within the past 12 months or
    - BNP ≥ 100 pg/mL or NT-proBNP ≥ 400 pg/mL (sinus rhythm) or
    - BNP ≥ 300 pg/mL or NT-proBNP ≥ 1200 pg/mL (atrial fibrillation)
5. For HFrEF only
    - EF ≤ 35% assessed by any imaging modality (e.g. echocardiography, cardiac magnetic resonance, cine levocardiography) within 12 months prior to study inclusion
6. For HFpEF only
    - EF ≥ 45% assessed by any imaging modality (e.g. echocardiography, cardiac magnetic resonance, cine levocardiography) within 12 months prior to study inclusion

15.3.2.5 Section 6.2 Extension of study population

This section was changed as a result of Modification 1.

Old text

2. Hemoglobin <~~10.0~~ g/dl

[…]

11. Subject with known allergies or hypersensitivities to adhesives or hydrogels
12. ~~Subject with implantable devices with active minute ventilation sensors~~
13. Severe uncorrected valvular heart disease

[…]

19. Patients who regularly (> 1x per week) swim ~~or~~ do water aerobics

New text

2. Hemoglobin <8.0 g/dl

[…]

11. Subject with known allergies or hypersensitivities to adhesives or hydrogels
12. deleted
13. Severe uncorrected valvular heart disease

[…]

19. Patients who regularly (> 1x per week) swim, do water aerobics, or go to the sauna, unwilling to omit this activity while needing to wear the study specific medical devices

15.3.2.6 Section 9.1 Simplification of study procedures

This section was changed as a result of Modification 2.

Old text

The investigator documents an initial visit, follow-up visits and the end of observation/final visit for each patient in the electronic case report form (eCRF). The end of observation visit will be documented after 12 weeks; a final follow-up call will be performed 6 months after discharge from hospital.

Activities to be performed are summarized in the study flow chart in ~~Table 1~~.

~~Table 1~~: Tabulated overview on study procedures and variables collected during the study - amended

Study period	~~Hospitalization~~ phase		~~Outpatient~~ phase					Safety FU call
Visit number	Scr[1]	1	2			3	4	5
Visit type	site		site			site	site	☎
	Screen assess	At ~~hospital~~ discharge						
Week after discharge			1	2	~~3~~	11	12	
Day and allowed deviations		0	9±2	16±2	~~23±2~~	77±2	84±2	6 months ±4 weeks
Signed informed consent form	●							
Inclusion / exclusion criteria	●							
KCCQ		●		●			●	
Daily and weekly PRO*			→----1st----←			→----2nd----←		
Demographic data	●							
Medical and surgical history	●							
~~Physical exam~~	~~●~~	~~●~~	~~●~~			~~●~~	~~●~~	
Height	●							
Weight	●	●	●				●	
12-lead ECG	●	●					●	
NYHA class	●	●	●				●	
Blood pressure and heart rate	●	●	●			●	●	
Adverse events	●	●	●			●	●	●
Concomitant medication	●	●	●			●	●	●
Echocardiography		●[4]					~~●~~	
Six-minute walking distance			~~●~~				●	
DynaPort (for 7 days)[2] →start ←end			→----1st----←			→----2nd----←		
VitalPatch (for 5 days)[2] →start ←end	~~→--1st--←-→--2nd-←-→--3rd-←-→--4th--←~~					~~→---5th---←~~		
Blood sample for biomarkers[3]	●	●	~~●~~				●	

[1] ~~within 72 hours~~ after hospitalization

[2] DynaPort monitoring periods: ~~Second week after hospital discharge (Days 7-14) and Week 11 to 12 (Days 77-84)~~

VitalPatch monitoring periods: ~~up to 5 days during the hospital stay, first 5 days after hospital discharge (Day 0-5), during weeks 2 and 3 (Day 7-12, Day 12-17) and Week 11 to 12 (Days 77-82)~~

[3] central lab assessments: NTproBNP, hs-copeptin, hs-TNT, optionally: GDF15, IGFBP7, sST2, Gal3

* Concurrently evaluating PRO will be completed daily and weekly during DynaPort and VitalPatch parallel monitoring period

[4] within ± 72 h of discharge day

New text

The investigator documents an initial visit, follow-up visits and the end of observation/final visit for each patient in the electronic case report form (eCRF). The end of observation visit will be documented after 12 weeks; a final follow-up call will be performed 6 months after visit 1 / discharge from hospital.

Activities to be performed are summarized in the study flow chart in Table 9-1.

Table 9–1: Tabulated overview on study procedures and variables collected during the study - amended

Study period	**Screening phase**		**Observational phase**				**Safety FU call**
Visit number	**Scr[1]**	**1**	**2**		**3**	**4**	**5**
Visit type	**site**	**site**	**site**		**site**	**site**	**☎**
	Screen assess	**At discharge / ambulatory visit**					
Week after discharge / Visit 1			**2**	**3**	**11**	**12**	
Day and allowed deviations	**-9 → -1**	**0**	**9±2**	**16±2**	**77±2**	**84±2**	**6 months ±4 weeks**
Signed informed consent form	●						
Inclusion / exclusion criteria	●						
KCCQ		●		●		●	
Daily and weekly PRO*			→----1st----←		→----2nd----←		
Demographic data	●						
Medical and surgical history	●						
●Height	●						
Weight	●	●	●			●	
12-lead ECG	●	●				●	
NYHA class	●	●	●			●	
Blood pressure and heart rate	●	●	●		●	●	
Adverse Events incl. healthcare resources	●	●	●		●	●	●
Concomitant medication	●	●	●		●	●	●
Echocardiography		●[5]					
Six-minute walking distance		●				●	
DynaPort (for 7 days)[2] →start ←end			→----1st----←		→----2nd----←		
VitalPatch (for 5 days)[2] →start ←end		→---1st---←	→ 2nd and 3rd ←		→ 4th and 5th ←		
Blood sample for biomarkers[3]	●[4]	●				●	

[1] within 4 days after hospitalization; alternatively, in ambulatory patients

[2] DynaPort monitoring periods: For one week, after Visit 2 (Days 9-16) and from Visit 3 to Visit 4 (Days 77-84)
VitalPatch monitoring periods: first 5 days after hospital discharge / Visit 1 (Day 0-5), one week after Visit 2 (Day 9-16) and from Visit 3 to Visit 4 (Days 77-84)

[3] central lab assessments: NTproBNP, hs-copeptin, hs-TNT, optionally: GDF15, IGFBP7, sST2, Gal3

* Concurrently evaluating PRO will be completed daily and weekly during DynaPort and VitalPatch parallel monitoring period

[4] only applicable to hospitalized patients

[5] within ± 72 h of Visit 1 / discharge day

15.3.2.7 Section 9.2 Simplification of study procedures

This section was changed as a result of Modification 2.

Old text

Enrollment / Screening Visit - amended

~~Within 72 hours after hospitalization patients with acute~~ HF will be asked to participate in this study. The investigator will inform the patient about the study. This will include discussing the consent form and asking the patient to read and – when agreeing to participate – sign the informed consent.

The following activities will be performed at the enrollment/screening visit after signing patient informed consent:

- Check for inclusion / exclusion criteria
- Recording of
  Demographic data (including weight and height)
  Medical and surgical history
  Concomitant medication
  Adverse events (AEs)
- ~~Physical examination~~
- Recording of a 12-lead ECG
- Measurement of blood pressure and heart rate
- NYHA classification
- Blood sampling for biomarkers
- ~~Eligible patients will be included in the study and will wear the VitalPatch biosensor for up to 5 days during the hospital stay~~

Visit 1 (Day 0)

~~At~~ discharge from the hospital the following activities will be performed:

- Recording of
  Weight
  Concomitant medication
  AEs
- ~~Physical examination~~
- Recording of a 12-lead ECG
- Conduct of echocardiography within ± 72 h of discharge day
- NYHA classification
- Measurement of blood pressure and heart rate
- Completion of KCCQ

- Blood sampling for biomarkers
- ~~A new~~ VitalPatch biosensor ~~will be~~ attached to ~~subject`s~~ chest, which they will wear for 5 days after discharge from hospital
- Subjects will be informed how to wear and apply the VitalPatch biosensor

Outpatient visits

Visit 2 (Day 9 ± 2 days)

Patients will return to the clinic 9 days (± 2 days) after discharge. The following activities will be performed:

- Recording of
  Weight
  Concomitant medication
  AEs
- ~~Physical examination~~
- NYHA classification
- Measurement of blood pressure and heart rate
- ~~Determination of 6MWD~~
- Blood sampling for biomarkers
- The VitalPatch biosensor device will be collected
- Subjects will receive another two VitalPatch biosensor patches which they will wear consecutively for 5 days each. One VitalPatch biosensor patch will be attached to the subject`s chest at the site, the other one has to be attached by the patient after removal of the first one after 5 days.
- In addition subjects will receive the DynaPort Move Monitor device which they will wear for 7 days. Subjects will be informed how to wear and apply the DynaPort MoveMonitor.
- Instruction to patient to complete KCCQ (Day 16 ± 2 days)
- Completion of PRO daily and weekly during DynaPort Move Monitor and VitalPatch monitoring period.

Visit 3 (Day 77 ± 2 days)

Patients will return to the clinic 77 days (± 2 days) after discharge. The following activities will be performed:

- Recording of
  Concomitant medication
  AEs
- ~~Physical examination~~
- Measurement of blood pressure and heart rate

- daily and weekly PRO during wearing of DynaPort Move Monitor and VitalPatch devices
- The VitalPatch biosensor patches will be collected
- Subjects will receive another VitalPatch biosensor ~~patch and the DynaPort Move Monitor device which they will wear for 5 and 7 days, respectively. The VitalPatch biosensor will be placed on subject`s chest and DynaPort Move Monitor belt will be put on at the site.~~

Visit 4 (Day 84 ± 2 days) - amended

Patients will return to the clinic 84 days (± 2 days) after discharge. The following activities will be performed:

- Recording of
  Weight
  Concomitant medication
  AEs
- ~~Physical examination~~
- Recording of a 12-lead ECG
- NYHA classification
- ~~Conduct of echocardiography~~
- Measurement of blood pressure and heart rate
- Determination of 6MWD
- Completion of KCCQ/PRO
- Blood sampling for biomarkers
- The VitalPatch biosensor ~~patch~~ and the DynaPort Move Monitor device will be collected.

Follow-up visit (safety follow-up call)

Six months after discharge the investigator will phone the patient for a final safety follow-up. The following will be asked:

- Concomitant medication
- AEs

New text

Enrollment / Screening Visit - amended

Patients hospitalized with worsening HF will be asked to participate in this study; alternatively, also ambulatory patients can be enrolled. The investigator will inform the patient about the study. This will include discussing the consent form and asking the patient to read and – when agreeing to participate – sign the informed consent.

The following activities will be performed at the enrollment/screening visit after signing patient informed consent:

- Check for inclusion / exclusion criteria
- Recording of

  Demographic data (including weight and height)
  Medical and surgical history
  Concomitant medication
  Adverse events (AEs) including the use of healthcare resources (e.g. HF hospitalizations and urgent visits for HF

- ~~Physical examination~~
- Recording of a 12-lead ECG
- Measurement of blood pressure and heart rate
- NYHA classification
- Blood sampling for biomarkers only for hospitalized patients

Visit 1 (Day 0)

This visit will take place up to 9 days after the screening visit, potentially at discharge from the hospital. The following activities will be performed:

- Recording of
  Weight
  Concomitant medication
  AEs including the use of healthcare resources
- Recording of a 12-lead ECG
- Conduct of echocardiography within ± 72 h of discharge day
- NYHA classification
- Measurement of blood pressure and heart rate

- Determination of 6MWD
- Completion of KCCQ
- Blood sampling for biomarkers
- Patients will get a VitalPatch biosensor attached to their chest, which they will wear for up to 5 days after Visit 1 / discharge from hospital
- Subjects will be informed how to wear and apply the VitalPatch biosensor

Outpatient visits

Visit 2 (Day 9 ± 2 days) - amended

Patients will return to the clinic 9 days (± 2 days) after Visit 1 / discharge. The following activities will be performed:

- Recording of
  Weight
  Concomitant medication
  AEs including the use of healthcare resources
- NYHA classification
- Measurement of blood pressure and heart rate
- Blood sampling for biomarkers
- The VitalPatch biosensor device attached at Visit 1 will be collected
- Subjects will receive another two VitalPatch biosensor patches which they will wear consecutively for up to 5 days each. One VitalPatch biosensor patch will be attached to the subject`s chest at the site, the other one has to be attached by the patient after removal of the first one after 5 days. Subjects will be informed how to wear and apply the VitalPatch biosensor.
- In addition subjects will receive the DynaPort Move Monitor device which they will wear for 7 days. Subjects will be informed how to wear and apply the DynaPort MoveMonitor.
- Instruction to patient to complete KCCQ (Day 16 ± 2 days)
- Completion of PRO daily and weekly during DynaPort Move Monitor and VitalPatch monitoring period.

Visit 3 (Day 77 ± 2 days)

Patients will return to the clinic 77 days (± 2 days) after discharge. The following activities will be performed:

- Recording of
  Concomitant medication
  AEs including the use of healthcare resources
- Measurement of blood pressure and heart rate
- Daily and weekly PRO during wearing of DynaPort Move Monitor and VitalPatch30 devices

- The VitalPatch biosensor patches will be collected
- Subjects will receive another two VitalPatch biosensor patches which they will wear consecutively for up to 5 days each. One VitalPatch biosensor patch will be attached to the subject's chest at the site, the other one has to be attached by the patient after removal of the first one after 5 days.
- In addition, subjects will receive another DynaPort Move Monitor device which will be put on at the site and which will be worn for 7 days.

Visit 4 (Day 84 ± 2 days)

Patients will return to the clinic 84 days (± 2 days) after discharge. The following activities will be performed:

- Recording of
  Weight
  Concomitant medication
  AEs including the use of healthcare resources
- Recording of a 12-lead ECG
- NYHA classification
- Measurement of blood pressure and heart rate
- Determination of 6MWD
- Completion of KCCQ/PRO
- Blood sampling for biomarkers
- The VitalPatch biosensor patches and the DynaPort Move Monitor device will be collected.

Follow-up visit (safety follow-up call)

Six months after discharge the investigator will phone the patient for a final safety follow-up. The following will be asked:

- Concomitant medication
- AEs including the use of healthcare resources

15.3.2.8 Section 9.6.3 Simplification of study procedures

This section was changed as a result of Modification 2.

Old text

- **Electrocardiogram/echocardiography**

[…]

An echocardiography will be performed at discharge from the hospital (within ± 72 ~~of discharge day~~) ~~and on Day 84~~.

- **Physical examination**

A general physical examination as routine at the center will ~~be performed at time points given in Table 1.~~ Abnormal physical examination findings are recorded either as medical history or as adverse events (see Section 9.6.1.1).

In the event of implausible results, the laboratory may measure additional parameters to assess the quality of the sample (e.g. clotted or hemolyzed) and to verify the results. The results from such additional analyses may neither be included in the clinical database of this study nor evaluated further. If the results are relevant, the investigator will be informed to determine follow-up activities outside of this protocol.

New text

[…]

An echocardiography will be performed at Visit 1 / discharge from the hospital (within ± 72 hours).

- **Physical examination**

A general physical examination as routine at the center will not need to be performed, but a targeted exam might be triggered by symptoms. Abnormal physical examination findings are recorded either as medical history or as adverse events (see Section 9.6.1.1).

- **Laboratory evaluations**

In the event of implausible results, the laboratory may measure additional parameters to assess the quality of the sample (e.g. clotted or hemolyzed) and to verify the results. The results from such additional analyses may neither be included in the clinical database of this study nor evaluated further. If the results are relevant, the investigator will be informed to determine follow-up activities outside of this protocol.

- **Healthcare Resource Utilization**

The use of Healthcare Resources in conjunction with AEs, in particular due to HF, needs to be documented, for example with regard to the time points or periods affected (e.g. hospitalizations for HF, urgent visits for HF to an emergency department or outpatient facility).

15.3.2.9 Section 9.7.1 Removal of thoracic impedance measurement

This section was changed as a result of Modification 2.

Old text

VitalPatch biosensor

VitalPatch biosensor will be provided by Bayer to sites. Subjects will wear the VitalPatch biosensor for overall 5 periods of 5 days each (for details on time periods see Table 1).

Parameters obtained from the VitalPatch biosensor are:

- ECG and parameters derived from ECG, like e.g. heart rate, HRV, AF burden, arrhythmias etc.
- Respiratory rate
- ~~Transcutaneous thoracic impedance = fluid status~~
- Skin temperature
- Step count
- Physical activity (duration and intensity)
- Posture

New text

VitalPatch biosensor

VitalPatch biosensor will be provided by Bayer to sites. Subjects will wear the VitalPatch biosensor for overall 5 periods of 5 days each (for details on time periods see Table 9-1).

Parameters obtained from the VitalPatch biosensor are:

- ECG and parameters derived from ECG, like e.g. heart rate, HRV, AF burden, arrhythmias etc.
- Respiratory rate
- Skin temperature
- Step count
- Physical activity (duration and intensity)
- Posture

16. Appendices

16.1 REALIsM-HF exploratory daily questionnaire to measure physical activity in heart failure - amended

Daily Patient-Reported Outcome Diary Items for REALIsM-HF Study

Objectives

- Develop patient-reported outcome (PRO) items that can be administered as a daily diary in the REALIsM-HF pilot study
- Provide a brief high-level outline of how the PRO items can be used to:

- Validate activity monitoring data from wearable devices (VitalPatch biosensor[42] and DynaPort Move Monitor)
- Measure symptom severity
- Facilitate the calculation of responder definitions/MIDs for activity and symptom data

- We hypothesized that "subjective" items generated from patient experiences (PRO, QoL) in combination with an (objective) activity monitor would capture all relevant dimensions of exercise capacity in patients with HFpEF and HFrEF and thus can be used as patient centric approach in clinical studies.

INSTRUCTIONS: We would like to know about your physical activities and heart failure symptoms in the past 24 hours. Physical activities are all activities that require "movement of your body," such as walking, housework, and lifting objects. Please complete this questionnaire in the evening before going to bed. Please select the response that best applies to your physical activities and symptoms in the past 24 hours.

- 24 hour interval captures nighttime symptoms, such as orthopnea and PND
- Shorter instructions are ideal for daily assessment
- Need to develop a training module for use in hospital

[42] Replacement of AVIVO MPM with VitalPatch Biosensor as per Amendment 2 (Section 15.2)

ITEM	RESPONSE SCALE
How much time did you spend carrying or lifting objects in the past 24 hours?	Did not carry or lift objects 1-10 minutes 11-30 minutes 31-60 minutes Greater than 60 minutes
How much time did you spend walking outside of the house in the past 24 hours?	Did not walk outside of the house 1-10 minutes 11-30 minutes 31-60 minutes Greater than 60 minutes
How much time did you spend walking in general (in any location) in the past 24 hours?	Did not walk outside of the house 1-10 minutes 11-30 minutes 31-60 minutes Greater than 60 minutes
How much time did you spend doing housework or chores in the past 24 hours?	Did not do housework or chores 1-10 minutes 11-30 minutes 31-60 minutes Greater than 60 minutes
How many flights of stairs did you climb in the past 24 hours?	Did not climb stairs 1 flight of stairs 2 flights of stairs 3 flights of stairs 4 flights of stairs 5 flights of stairs 6 flights of stairs 7 flights of stairs 8 flights of stairs 9 flights of stairs 10 or more flights of stairs
How much time did you spend exercising in the past 24 hours?	Did not exercise 1-10 minutes 11-30 minutes 31-60 minutes Greater than 60 minutes
In general, how physically active were you in the past 24 hours?	Not active at all A little active Somewhat active Very active Extremely active

ITEM	RESPONSE SCALE
Please rate your worst tiredness at rest (when NOT doing physical activities) in the past 24 hours	Not Tired At All 0 1 2 3 4 5 6 7 8 9 10 Extremely Tired
Please rate your worst tiredness during physical activities in the past 24 hours	Not Tired At All 0 1 2 3 4 5 6 7 8 9 10 Extremely Tired
Please rate your worst shortness of breath at rest (when NOT doing physical activities) in the past 24 hours	No Shortness of Breath 0 1 2 3 4 5 6 7 8 9 10 Extreme Shortness of Breath
Please rate your worst shortness of breath during physical activities in the past 24 hours	No Shortness of Breath 0 1 2 3 4 5 6 7 8 9 10 Extreme Shortness of Breath
Please rate the worst swelling in your legs, ankles, or feet in the past 24 hours	No Swelling 0 1 2 3 4 5 6 7 8 9 10 Extreme Swelling
In general, how bad were your heart failure symptoms in the past 24 hours?	No Symptoms 0 1 2 3 4 5 6 7 8 9 10 Extreme Symptoms
INSTRUCTIONS	Now we would like for you to think about how your physical activities and symptoms have changed since you were discharged from the hospital.
How have your physical activities changed since you were discharged from the hospital?	Very much more physically active Much more physically active A little more physically active No change in physical activities A little less physically active Much less physically active Very much less physically active
How has your feeling of tiredness changed since you were discharged from the hospital?	Very much improved Much improved Minimally improved No change Worse Much Worse Very much worse
How has your shortness of breath changed since you were discharged from the hospital?	Very much improved Much improved Minimally improved No change Worse Much Worse

ITEM	RESPONSE SCALE
	Very much worse
How has your swelling in your legs, ankles, or feet changed since you were discharged from the hospital?	Very much improved Much improved Minimally improved No change Worse Much Worse Very much worse

USE OF DIARY ITEMS TO VALIDATE ACTIVITY MONITOR

- Compare 1 week of activity monitor data with physical activity items from 1 week of diary monitoring
- Average diary data over 7 day period (must have ≥ 4 days to calculate a value)
- Physical Activity Diary Scores
    - Overall activity including carrying/lifting, walking outside, walking general, climbing stairs, housework, and exercise (average across items)
    - Individual item scores including general physical activity item
- Examine correlations between the activity monitor movement data and the physical activity diary scores

USE OF DIARY ITEMS TO CALCULATE RESPONDER DEFINITIONS

- Calculate average activity/symptom scores associated with change on anchor measures
- Anchor measures
    - General physical activity item (1 unit change on weekly average score)
    - 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)
- Address using data from each weekly interval