First In Human Clinical Investigation of the FIRE1* System in Heart Failure Patients_ Pilot Study of the FIRE1TM System in Heart Failure Patients

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The objectives of this clinical investigation are:1. To demonstrate that the FIRE1* Sensor can be safely deployed into the inferior vena cava (IVC) 2. To demonstrate that the FIRE1* Sensor can provide a signal to the FIRE1* External System3. To…

Ethical review	Approved WMO
Status	Completed
Health condition type	Heart failures
Study type	Observational invasive

Summary

ID

NL-OMON53958

Source
ToetsingOnline

Brief title
Clinical Investigation of FIRE1 System in HF Patients -FUTURE HF

Condition

- Heart failures

Synonym
Heart Failure

Research involving
Human

Sponsors and support

Primary sponsor: FIRE1 (Foundry Innovation and Research 1 Ltd)

Source(s) of monetary or material Support: Industry sponsored by FIRE1

Intervention

Keyword: Cardiovascular disease, FIRE1, Heart Failure

Outcome measures

Primary outcome

Safety

The primary, composite endpoint is success of the FIRE1* Sensor at 3 months (12 weeks), including the following:

1. Procedural success defined as Sensor deployment at the intended site without acute device or procedural related complications and

2. Freedom from Sensor complications, including device migration, clinically significant fracture and/ or clinically significant perforation of the Inferior Vena Cava (IVC), or symptomatic caval thrombosis

Technical

Technical success defined as signal acquisition

1. Immediately post implantation and

2. At an attended clinic visit within the first 3 months (12 weeks) of Sensor implantation

Secondary outcome

Secondary outcomes

1. Freedom from symptomatic access site thrombosis confirmed by ultrasound (US)

2. Freedom from a significant haematoma (defined as requiring intervention, transfusion, or prolonging hospitalisation)

3. Frequency and severity of device and procedure-related adverse events (AEs)

4. Successful transmission of a FIRE1* Sensor reading from the patient*s home

to the FIRE1* Web App

Other Clinical Outcomes

1. Assessment of FIRE1* System Data, clinical parameters, and other metrics

including, but not limited to, activity monitoring, blood pressure (BP),

respiration, and weight

2. Quality of Life (QoL) assessment

3. Functional status assessment, as measured by New York Heart Association

(NYHA) functional classification and 6-Minute Walk Test (6MWT)

4. Accuracy of FIRE1* System Data

5. Response of the FIRE1* System Data to clinical perturbations

6. Rate of successful transmission of collected data to the FIRE1* Web App

7. Adherence to taking FIRE1* System readings in the home

8. Frequency of HF Hospitalisations (HFH)

9. Rates of HF mortality, cardiovascular mortality and all-cause mortality

10. Number and frequency of HF medication changes

11. Human factors evaluation of FIRE1* System

Study description

Background summary

3. CLINICAL INVESTIGATION BACKGROUND
Heart failure (HF) is a growing global healthcare issue with an estimated

worldwide prevalence of 26 million patients. Despite recent advances in cardiac intervention, device therapy and pharmacology the resultant economic burden remains significant. Indeed HF accounts for 1-3% of all hospital admissions with an average length of stay between 5-10 days and an estimated 1-2% of healthcare expenditure in the USA and Europe (Ambrosy et al., 2014). The majority (60%) of these costs are driven by hospitalisation for acute decompensation (Heidenreich et al., 2013). Additionally, readmission rates following an acute decompensation are high with 24% of patients readmitted within 30 days, and 46% readmitted within 60 days of discharge. With the majority (90%) of HF admissions occurring in those with known chronic heart failure (CHF), there remains an essential role for the development of novel therapies and interventions to detect prognostic physiological changes early in the course of decompensation to facilitate and optimize medical intervention in a bid to reduce HF associated hospitalisation, morbidity and mortality. (Ambrosy et al., 2014). With the ageing of the worldwide population, as well as increased survival from ischaemic heart disease, HF rates will continue to increase, along with the resultant global economic burden.

The majority of HF patients present with symptoms attributable to volume overload such as dyspnea (89%), rales (68%) and peripheral oedema (66%) (Koniari, Parissis, Paraskevaidis, and Anastasiou- Nana, 2012). Timely and accurate assessment and management of volume overload is therefore a critical component of HF management. Early detection of volume overload allows prompt intervention with pharmacological agents, aiming to restore euvolaemia with out-patient treatment, without progressing to hospital admission. Conversely, detection of volume depletion/dehydration is an important factor in preventing symptomatic hypotension and renal dysfunction due to over-diuresis. Traditionally, volume status is determined by clinical examination including: assessment of the height of the jugular venous pressure above the sternal angle, auscultation of the lung fields for signs of pulmonary oedema, assessment of peripheral oedema, and monitoring of patients* weight. Clinical measurement of volume status, however, can be difficult and has been shown to correlate poorly with clinical status. The absence of physical and radiological signs of congestion does not necessarily correlate with normal pulmonary capillary wedge pressure (Chakko, Woska, and Martinez, 1991) nor confidently exclude volume overload. It is well documented that volume/pressure changes precede development of clinical symptoms and therefore detection of these changes before symptoms arise provides a potential target for optimising the care of patients with HF.

Haemodynamic monitoring using an indwelling pulmonary artery pressure (PAP) monitor as an index of volume has been shown to significantly reduce hospitalisations in patients with NYHA III HF (Abraham et al., 2011). Evidence from the CHAMPION trial demonstrated that when using an implantable PAP monitoring system (CardioMEMS), lowering remotely monitored PAP would result in reduced HFH risk. CHAMPION clearly evidenced the benefit of accurate haemodynamic monitoring in HF patients, over and above clinical

assessment and standard of care HF management. A more recent trial was conducted to assess the utility of CardioMEMS in a broader HF population, the GUIDEHF trial. The GUIDE-HF trial enrolled 1000 HF patients with NYHA class II-IV to CardioMEMS-guided management vs standard of care (no CardioMEMS). Results show that there was no difference between cohorts in the primary endpoints of the study, which assessed cumulative HF events and mortality at 12 months. However, a pre-COVID analysis indicated the primary endpoint was significantly reduced in favour of CardioMEMS (Lindenfeld et al., 2021).

In many instances volume overload precedes pressure overload, with a relatively large change in volume resulting in little corresponding change in pressure, until a critical point is reached at which pressure increases (Moreno, Kotz, Gold, Reddy, and Tech, 1970). Recent work in HF patients has indicated that pressure based assessment of congestion in ambulatory HF patients does not accurately represent intravascular volume providing evidence of pressure-volume discordance (Yaranov et al., 2022). Therefore, detection of elevated PAP may signify impending decompensation later than increased volume. The inferior vena cava (IVC), continuously changes its diameter and collapsibility along the pressure-volume curve (Moreno et al., 1970). Proof of concept experiments in an animal model have shown that IVC changes were significantly more sensitive than cardiac filling pressures following manipulation of intravascular volume, vascular tone and cardiac dysfunction (Ivey et al., 2021). Changes in IVC diameter can therefore reflect changes in volume that occur prior to increasing pressure. We hypothesize monitoring the IVC diameter would allow earlier detection of congestion resulting in more rapid medical intervention to prevent an impending decompensation and subsequent hospitalisation.

Absolute IVC diameter and degree of collapsibility with inspiration (collapsibility index, CI) has been established as a sensitive and specific tool to estimate right arterial pressure (RAP) (Rudski et al., 2010). IVC dilation has been shown to be associated with an increased risk of early readmission and short-term mortality in patients hospitalized for acute decompensated HF (ADHF) (Jobs et al., 2017), while in patients with CHF, increasing IVC diameter has been demonstrated to correlate with adverse outcomes (Pellicori et al., 2013). It is therefore proposed that the use of an indwelling device which can monitor IVC geometry (size and collapsibility) may allow earlier detection of impending volume overload, allowing therapeutic interventions to take place more promptly thereby reducing HFH rates.

The FIRE1* System utilises a Sensor permanently implanted into the IVC that conforms to and changes with the geometry of the vessel. The Sensor does not contain a battery and is wirelessly energised by an external Belt and Hardware Unit. FIRE1* System Data are transmitted to the FIRE1* Web App for the primary purpose of displaying the data to the Investigator.

There are two generations of the FIRE1 System (Gen 1 and Gen 2), both of which are made up of the same type of components (i.e., the implantable FIRE1* Sensor

and Delivery System, the FIRE1* External System, and FIRE1* Web App) and with the same mode of operation. Learnings from the use of the first-generation System (*Gen 1*) with 4 patients have led to design enhancements to the implantable FIRE1* Sensor, the FIRE1* External System and the FIRE1* Web App, which are used to obtain data from the Sensor. No changes have been made to the delivery system used in the implantation procedure, or to the implantation procedure itself. Beyond the first 4 patients, additional patients will be enrolled and implanted with the FIRE1* Gen 2 Sensor. All enrolled patients will receive the FIRE1* Gen 2 External System. Differences in Sensor versions will be accounted for during data analysis, as data generated from Cohort A (i.e., 4 patients with the Gen 1 Sensor) will be analysed separately from data generated from Cohort B (i.e., patients with the Gen 2 Sensor).

This CIP provides information that is relevant to both the FIRE1* Gen 1 and Gen 2 Systems. Where information specifically relates to only Gen 1 or Gen 2 (System, Sensor, External System or Web App), the relevant generation will be specified.

Further information from the background literature review relating to the design of the

Study objective

The objectives of this clinical investigation are:
1. To demonstrate that the FIRE1* Sensor can be safely deployed into the inferior vena cava (IVC)
2. To demonstrate that the FIRE1* Sensor can provide a signal to the FIRE1* External System
3. To investigate the individual daily variability in FIRE1* System Data, including IVC area and IVC collapsibility, and their relationship to conventional clinical heart failure (HF) parameters
4. To investigate the changes in FIRE1* System Data that occur in the period before, during and after a HF decompensation

Study design

This is a prospective, single arm, multi-centre clinical investigation involving the implantation and monitoring of the FIRE1* System in approximately 50
HF patients recruited from up to 20 sites. HF patients at increased risk of HF events as evidenced by an acute HF admission/treatment in the prior 12 months or raised BNP or NT-proBNP levels, who provide informed consent, and successfully pass screening and baseline testing will be implanted with the novel FIRE1 Sensor.

The FIRE1* System utilises a Sensor permanently implanted into the IVC that

conforms to and continuously adapts to the vessel geometry.

When excited by an external radio frequency source, the FIRE1* Sensor is designed to track changes of the IVC geometry. In this investigation, device safety will be evaluated using radiological imaging modalities and physiological assessments detailed in the schedule of events. Daily data will be obtained from the patient using the FIRE1* System.

There are two generations of the FIRE1 System (Gen 1 and Gen 2), both of which are made up of the same type of components (i.e., the implantable FIRE1* Sensor and Delivery System, the FIRE1* External System, and FIRE1* Web App) and with the same mode of operation. Learnings from the use of the first-generation System (*Gen 1*) in 4 patients have led to design enhancements to the implantable FIRE1* Sensor, the FIRE1* External System and the FIRE1* Web App, which are used to obtain data from the Sensor. No changes have been made to the delivery system used during the implantation procedure, or to the implantation procedure itself.

Beyond the first 4 patients, additional patients will be enrolled and implanted with the FIRE1* Gen 2 Sensor. All enrolled patients will receive the FIRE1* Gen 2 External System. Differences in Sensor versions will be accounted for during data analysis, as data generated from Cohort A (i.e., 4 patients with the Gen 1 Sensor) will be analysed separately from data generated from Cohort B (i.e., patients with the Gen 2 Sensor). This Clinical Investigation Plan (CIP) provides information that is relevant to both the FIRE1* Gen 1 and Gen 2 Systems. Where information specifically relates to only Gen 1 or Gen 2 (System, Sensor, External System or Web App), the relevant generation will be specified.

The patient specific FIRE1* System Data could potentially be used as one input into the investigators clinical decision making for individual participants enrolled in the study. An illustrative treatment guidance, in line with current internationally accepted HF management guidelines, is provided and may be used, in conjunction with other available clinical data, by investigators following their analysis of the FIRE1* System Data.

The primary endpoints will be assessed at Month 3 and patients will continue to be followed with clinical visits until Month 24, followed by annual follow ups till month 60.

At a limited number of clinical investigation centres, additional data may be obtained from volume challenges (assessing the ability of the FIRE1* Sensor to detect changes in the IVC and provide a signal that reflects the acute volume change) and dedicated physiological data collection sessions (simultaneously record vital signs and FIRE1* System data while monitoring patient safety). These assessments will be performed after Month 3, and the data will be used to inform the feasibility of measuring respiration rate (RR) and heart rate (HR) using the FIRE1* Sensor.

The clinical investigation will be executed in 2 phases, i.e., phase 1 (n=14) and phase 2. Phase 1 is designed to assess the initial safety and technical feasibility of the FIRE1 system and the ability of the system to provide a signal. Phase 2 is an expansion of the clinical investigation to increase the number of subjects and thus increase the learnings associated with assessment of safety, technical feasibility, and data acquisition from the FIRE1 System. The Sponsor will obtain all necessary approvals prior to initiating this clinical investigation.

Intervention

NA

Study burden and risks

JUSTIFICATION OF CLINICAL INVESTIGATION DESIGN

Given the review of published literature referenced above, we propose that when used in the target HF population, the FIRE1* System should detect changes in volume status that precede clinical symptoms or deterioration allowing prompt intervention with medical therapy and a more rapid return to euvolaemia, thereby reducing the frequency of HFH.

The design of this clinical investigation is based on the evaluation of pre-clinical data and aligns with the results of the risk assessment relating to the FIRE1* System. The clinical evaluation process for the FIRE1* System incorporates both pre-clinical testing and risk assessment activities. An assessment of the current state-of-the-art in HF management and the expected clinical performance, effectiveness and safety of the FIRE1* System were completed. The clinical development stages starting with exploratory, pilot clinical investigations and moving to confirmatory pivotal clinical investigations for the FIRE1* System have been defined from this assessment and are outlined in FIRE1* System Clinical Evaluation Plan (CEP).

In line with the clinical development stages identified in the CEP, the intended purpose of this FIH clinical investigation is (1) to demonstrate that the FIRE1* Sensor can be safely deployed into the IVC, (2) to demonstrate that the FIRE1* Sensor can provide a signal to the FIRE1* External System, (3) to investigate the individual daily variability in FIRE1* System Data, including IVC area and IVC collapsibility, and their relationship to conventional clinical HF parameters, (4) to investigate the changes in FIRE1* System Data that occur in the period before, during and after a HF decompensation. As this is a proof-of-concept clinical investigation, in order to meet these outcomes, the device will be implanted in patients with a HF decompensation resulting in a HFH, HF treatment in a hospital day-care setting or urgent outpatient HF visit in the last 6 months and who meet all the

inclusion criteria and none of the exclusion criteria. The patients will be assessed over the period of 3 months for the primary endpoints. Assessment of the primary endpoints at 3 months was chosen as, based on pre-clinical data, it is believed that the Sensor will have become well endothelialized within the vessel, and as such, the safety of the implant can be adequately assessed.

A volume challenge of up to 500 ml of saline infusion (dependent on patient weight), may be performed after Month 3 in the initial phase of the clinical investigation to assess the ability of the FIRE1* Sensor to detect changes in volume and provide a signal that reflects this acute change. This volume challenge is limited to the patients enrolled in Phase 1 of the clinical investigation (n=14). The volume challenge will be coupled with invasive Right Heart Catheterization, (RHC) and non-invasive monitoring to provide haemodynamic assessment of the patients. This will ensure safety and provide comparative data for exploratory analyses of FIRE1* Sensor Data. Non-invasive monitoring may include, but is not limited to, electrocardiogram (ECG), blood pressure (BP), non-invasive oxygen saturation, noninvasive haemoglobin monitoring and respiration rate (RR). Intravascular ultrasound (IVUS) will also be used to record changes in internal vessel geometry during the challenge and compared to the FIRE1* Sensor signal. The volume challenge will only be performed if, in the opinion of the Investigator, the patient is stable and capable of tolerating the saline infusion without undue risk.

The data recorded by the FIRE1* System will be presented via the FIRE1* Web App which will allow investigators to explore FIRE1* System Data such as IVC area and CI measurements (Monitor Period). The Investigator will also be able to compare FIRE1* System Data with conventional clinical HF parameters recorded during the clinical investigation, particularly those recorded before, during and after a HF decompensation when treatment and/or hospitalisation have occurred.

The Investigator will be required to review the FIRE1* System Data on a regular basis. No clinical decisions or changes to patient care will be made based on this data alone. The information may prompt the Investigator to contact a patient to assess their HF status over the telephone or via an inclinic visit. The Investigator will be asked to document their decision-making process with respect to any additional assessments carried out and/or treatment changes made for these patients in accordance with institutional and standard guidelines for HF management. In line with current internationally accepted HF management guidelines (McDonagh et al., 2021; Maddox et al., 2021; Yancy et al., 2017), an illustrative treatment guidance is provided (see appendix 6), which may be used by investigators following their analysis of the FIRE1* System data and in conjunction with other available clinical data. If judged necessary by the clinical investigator, alterations in HF treatment may require an in-person clinic visit and will be recorded as an unscheduled visit. Relevant blood sampling, e.g., electrolytes and renal function, will be performed as deemed clinically indicated by the clinical

Investigator.

To maximise the observed variations in IVC area and fluid volume status during the clinical investigation with the minimum number of patients, standard clinical manoeuvres, such as standing from a seated position, may be performed during FIRE1* System recordings at clinical follow-up visits. The movements from these clinical perturbations will potentially trigger fluid shifts and allow changes in FIRE1* System Data to be explored. Patients will be asked to perform additional simple manoeuvres at home while obtaining FIRE1* readings (for example, a breath hold, sitting upright and moving to a standing position). The observed variations in FIRE1* System Data will be used to determine a patient*s individual normal IVC range, as measured by the FIRE1* Sensor. These insights will be valuable in learning more about how the information provided by the FIRE1* System may be operationalised to support the safe management of HF patients.

Dedicated physiological data collection sessions will be undertaken after 3 months to simultaneously record vital signs and FIRE1* System Data. Patient safety will be closely monitored throughout these data collection sessions. The data will be used to further inform the feasibility of using the FIRE1*System to measure additional signals such as RR and Heart Rate (HR) and to support algorithm development as part of ongoing system development.

As outlined in the CEP, confirming the preliminary safety of the FIRE1* System and successfully obtaining a signal from the Sensor in vivo are key objectives of this FIH clinical investigation. The exploratory assessments and learnings will be used as inputs into the further development of the FIRE1* System, including updated algorithms and refined treatment guidance to further aid management of HF patients in the future. This clinical investigation design ensures that the results generated from the investigation will be clinically relevant and scientifically valid, will adequately address the clinical objectives of the investigation and will further inform the benefit-risk analysis of the FIRE1* System.

This is an early-stage, exploratory pilot clinical investigation aimed at evaluating the limitations and potential benefits of the FIRE1* System. In accordance with ISO14155: 2020 Annex I, there is no mandatory pre-specification of a statistical hypothesis required for a pre-market exploratory clinical investigation. However, the information gained from this clinical investigation will be used to plan further steps of device development and crucial to this end is the attainment of sufficient HF ev

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. Adults aged 18 years or older with a diagnosis of HF for greater than 90 days, NYHA Class II or III HF and receiving treatment, in accordance with internationally recognized guidelines and institutional practices to include standard of care drug/device therapies as deemed appropriate.
2. a) Have experienced a HF decompensation in the past 12 months prior to consent, defined as either: Hospitalisation for HF, HF treatment in a hospital day-care setting or urgent outpatient HF visit for IV diuretics
OR
b) Elevated N-terminal-pro-brain natriuretic peptide (NT-proBNP) >= or brain natriuretic peptide (BNP) within 30 days prior to consent or at screening
- Subjects in sinus rhythm NT-proBNP >=800 pg/mL or BNP >=300 pg/mL
- Subjects with Atrial Fibrillation (AF) NT-proBNP >=1200 pg/m Lor BNP >=350 pg/mL.
For subjects treated with an angiotensin receptor neprilysin inhibitor (ARNI) only NT-proBNP values should be considered.

3. IVC diameter within the landing zone (between the hepatic and renal veins) of between 14 mm and 28 mm
4. Minimum landing zone length of 60 mm.
5. Provide informed consent for participation in the clinical investigation and be willing and able to comply with the required assessments, treatment instructions and follow-up visits.

Exclusion criteria

1. Significant comorbidity or FIRE1* System usability or compliance concern, that would interfere with the ability to safely complete or capably participate in the CIP.
2. Patients with an estimated Glomerular Filtration Rate < 30 ml/min at screening.
3. Patients that are pregnant or nursing or planning a pregnancy within 1 year of screening.
4. Expected lifespan from time of enrolment of < 1 year, as assessed by the Investigator.
5. Evidence of advanced, end-stage HF, with NYHA IV, and/or currently treated with intravenous inotropes and/or vasopressors.
6. Patients with abdominal circumference of greater than 128 cm at screening.
7. Patients who exceed angiographic table weight limit at screening.
8. Patients with IVC filter placement in situ, abnormal IVC or femoral venous anatomy, known congenital malformation, absence of IVC, or occlusive or free-floating thrombus in the IVC.
9. Patients who have an implantable ventricular assist device (Left Ventricular Assist Device (LVAD), Right Ventricular Assist Device (RVAD) or Biventricular Assist Device (BiVAD) in situ.
10. Patients with Cardiovascular Implantable Electronic Device (CIED) implanted <= 3 months prior to screening.
11. Patients who have received tissue/organ transplant or planned advanced therapies including a tissue/organ transplant or an implantation of a ventricular assist device within the next 180 days.
12. Patients who have planned procedures requiring a venous femoral access within 90 days of the FIRE1* Sensor implantation.
13. Patients with echocardiographic evidence of severe tricuspid stenosis or severe tricuspid regurgitation.
14. Patients with current echocardiographic evidence of severe aortic valve stenosis.
15. Patients with a known history of thrombophilia or other hypercoagulable state.
16. Patients with venous thrombosis or thromboembolism in the 6 months prior to screening.
17. Patients with conditions associated with occlusion of the IVC, iliac or common femoral veins (e.g., venous leg ulcers).

18. Patients with hypersensitivity or allergy to aspirin and/or antiplatelet agents used or FIRE1* Gen 2 Sensor components (Nitinol, Polyurethane (PU), Nylon, Polyethylene Terephthalate (PET) and Gold) or contrast media.
19. Patients with an active systemic infection at screening.
20. Participation in any other concurrent clinical investigation.

Study design

Design

Study type: Observational invasive

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Diagnostic

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	06-07-2023
Enrollment:	8
Type:	Actual

Medical products/devices used

Generic name:	FIRE1 System
Registration:	No

Ethics review

Approved WMO Date:	03-05-2023
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	22-12-2023
Application type:	Amendment

Review commission: METC Universitair Medisch Centrum Groningen (Groningen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
ClinicalTrials.gov	NCT04203576
CCMO	NL82305.000.22