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Study Protocol

Design and rationale of MYOFLAME-19 randomised controlled trial: MYOcardial protection to reduce post-COVID inFLAMmatory heart disease using cardiovascular magnetic resonance Endpoints

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Abbreviations: AT, anaerobic threshold; ACS, acute coronary syndrome; BASG, Bundesamt für Sicherheit im Gesundheitswesen (Austrian Competent Authority); BfARm, Bundesinstitut für Arzneimittel und Medizinprodukte (German Competent Authority); ECG, electrocardiogram; CMR, cardiovascular magnetic resonance; COVID-19, coronavirus disease 2019; CPET, cardiopulmonary exercise testing; CRO, contract research organization; CVD, cardiovascular disease; CVS, cardiovascular syndrome; CSF, chronic fatigue syndrome; DSMC, Data Safety and Monitoring Committee; HF, heart failure; IIR, investigator-initiated research; IMP, investigational medicinal product; ITT, intention to treat; PP, per protocol; PASC, postacute sequelae of COVID disease; PWV, pulse wave velocity; RCT, randomized clinical trial; LVEF, left ventricular ejection fraction; LGE, late gadolinium enhancement; VO_2 max, the maximum rate of oxygen consumption attainable during physical exertion; W2, W6, W16, week 2, 6, 16; WOCBP, women of childbearing potential; MRC, Medical Research Council; EDV, end-diastolic volume; ESV, end-systolic volume; SAX, short axis; PEM, post exercise malaise; MACE, major adverse cardiovascular events; BNP, brain natriuretic peptide

#Myoflame-19 is a clinical trial of myocardial protection therapy in post-COVID inflammatory cardiac involvement.

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ABSTRACT

Background: Cardiac symptoms due to postacute inflammatory cardiac involvement affect a broad segment of previously well people with only mild acute coronavirus disease 2019 (COVID-19) illness and without overt structural heart disease. Cardiovascular magnetic resonance (CMR) imaging can identify the underlying subclinical disease process, which is associated with chronic cardiac symptoms. Specific therapy directed at reducing postacute cardiac inflammatory involvement before development of myocardial injury and impairment is missing.

Methods: Prospective multicenter randomized placebo-controlled study of myocardial protection therapy (combined immunosuppressive/antiremodeling) of low-dose prednisolone and losartan. Consecutive symptomatic individuals with a prior COVID-19 infection, no pre-existing significant comorbidities or structural heart disease, undergo standardized assessments with questionnaires, CMR imaging, and cardiopulmonary exercise testing (CPET). Eligible participants fulfilling the criteria of subclinical post-COVID inflammatory heart involvement on baseline CMR examination are randomized to treatment with either verum or placebo for a total of 16 weeks (W16). Participants and investigators remain blinded to the group allocation throughout the study duration. The primary efficacy endpoint is the absolute change of left ventricular ejection fraction to baseline at W16, measured by CMR, between the verum treatment and placebo group by absolute difference, using unpaired t-test confirmatively at a significance level of 0.05 significance level. Secondary endpoints include assessment of changes of symptoms, CMR parameters, and CPET after W16, and frequency of major adverse cardiac events after 1 year. Safety data will be analyzed for frequency, severity, and types of adverse events (AEs) for all treatment groups. The proportion of AEs related to the contrast agent gadobutrol will also be analyzed. A calculated sample size is a total of 280 participants (accounting for 22 subjects (8%) drop out), randomized in 1:1 fashion to 140 in the verum and 140 placebo groups.

Conclusion: Myoflame-19 study will examine the efficacy of a myocardial protection therapy in symptomatic participants with post-COVID inflammatory cardiac involvement determined by CMR. The aim of the intervention is to reduce the symptoms and inflammatory myocardial injury, improve exercise tolerance, and preclude the development of cardiac impairment.

1. Introduction

Persisting cardiac symptoms are an increasingly recognized complication of coronavirus disease 2019 (COVID-19) infection, commonly referred to as the postacute sequelae of COVID-19 (PASC) [1]. PASC is associated with increased risk of cardiovascular disease (CVD), deconditioning, reduced quality of life (QoL), and long-term disability [2]. Typical cardiac symptoms include exertional dyspnea, chest tightness, higher resting heart rate, and excessive tachycardia, together manifesting as exercise intolerance. Cardiac symptoms are commonly accompanied with systemic manifestation referred to as PostCOVID syndrome [3,4]. Whereas PASC cardiac symptoms may be due to worsening of pre-existing conditions during severe course of COVID-19 illness (PASC-CVD), in previously well people, there is a new onset of chronic inflammatory heart involvement despite often mild acute illness (PASC-cardiovascular syndrome [CVS]). The underlying pathophysiology entails a complex immunological response to viral infection with dysregulation of humoral and cellular pathways, including autoimmune mechanisms and endothelial injury [5,6]. The heterogeneous symptoms stem from tissue-level hypoperfusion due to dysfunctional small vessel and capillary networks, underscored by a combination of endothelial dysfunction, increased vascular permeability, procoagulability, and mitochondrial dysfunction with impaired tissue oxygen extraction and gas exchange [7]. The myocardial tissue changes include low-grade inflammation and reactive interstitial diffuse fibrosis, with increase in myocardial stiffness, reduced preload, and accelerated deconditioning [8].

The recognition and management of postacute inflammatory cardiac involvement in clinical setting remains a considerable challenge. In PASC-CVD, the presence of structural heart disease initiates the guideline-directed recognition and management. On the contrary, the absence of overt structural heart disease in PASC-CVS precludes any formal cardiac diagnosis and treatment [1,2]. Studies in previously well individuals using cardiovascular magnetic resonance (CMR) imaging reported subclinical findings, including subnormal systolic function, low-grade diffuse myocardial tissue edema, diffuse interstitial fibrosis, non-ischemic epicardial and intramyocardial late gadolinium enhancement (LGE), and small pericardial effusions between thickened pericardial layers (summarized in [1]). These abnormalities could be detected as early as 2 weeks after the infection and can persist for several months-years. The persisting symptoms were found to have a predictive association with female sex and ongoing myocardial inflammation [9].

Cardiopulmonary exercise testing (CPET) studies in patients with PASC have demonstrated markedly reduced exercise tolerance, associated with diminished maximal oxygen uptake (VO_2 max), an earlier anaerobic threshold, accelerated heart rate response, lower workload achieved, lower peak O_2-pulse and wider breathing reserve despite normal pulmonary function tests [7]. Studies that employed concomitant cardiac imaging identified reduced stroke volume augmentation with exercise, attributable to preload failure, as well as chronotropic incompetence [10,11]. There is increasing evidence of ongoing disability and poor outcome in patients with PASC [2,12]; however, there is currently no evidence for a specific treatment in the absence of structural heart disease. Current recommendations include lifestyle adjustment with activity management, commonly known as “pacing,” aiming to reduce tissue oxygen demand and release of toxic tissue metabolites [7,13]. Symptomatic therapy for excessive tachycardia includes standard medications for heart rate control [1]. Clinical trials of immunosuppression in patients with acute severe COVID-19 illness showed an improved short-term outcome [14–16]. The benefits of early initiation of antiremodeling therapy to reduce symptoms of exercise intolerance are well recognized [17–19]. Endothelial dysfunction is a recognized underlying disease process in non-ischemic (i.e., not caused by an infarction-related myocardial injury) cardiac conditions [20]; reducing vascular dysfunction and improving tissue perfusion by losartan led to improved exercise capacity and reduced rate of heart failure (HF) complications [21–25]. Specific myocardial protection therapy directed at reducing postacute cardiac inflammatory involvement before development of myocardial injury and impairment is missing.

1.1. Rationale and hypothesis

The principal hypothesis is that intervention with myocardial protection treatment in a form of combined immunosuppression and

antiremodeling therapy by low-dose prednisolone and losartan, respectively, in participants fulfilling the CMR criteria for post-COVID inflammatory involvement but no overt structural heart disease, reduces cardiac symptoms, and myocardial impairment. The proposed underlying mechanism is by reducing the disease activity by improving endothelial function, tissue perfusion, and cardiac metabolism, thus favorably modifying the underlying disease process. Endothelial function, vascular leak, and tissue hypoxia due to the endothelial dysfunction, but not direct cardiomyocyte damage, are important therapeutic targets in several inflammatory cardiac conditions inducing HF. Losartan has been shown to attenuate a number of processes of potential importance in the treatment of HF, including cardiac dysfunction, oxidative stress, fibrosis, and inflammatory and cell death signaling pathways in HF and conditions leading to it, including hypertension, diabetes, renal impairment, etc [19,24,26,27].

Low-dose short-term steroid regime is safe and well-tolerated and prevents the undesirable side effects associated with the high-dose long-term steroid treatment, including euphoria, hypertension, tachycardia, cushingoid effects, or secondary infections, etc. A low-maintenance dose allows good tolerability, while preserving the remission. Fluid retention due to prednisolone may in fact be beneficial to overcoming the intravascular fluid loss, exacerbating the symptoms of excessive tachycardia. Furthermore, we will minimize the occurrence of undesirable effects in the present study. We will use the lowest effective dose will be used for the minimum treatment period. Post-COVID inflammatory activity in most symptomatic patients is low grade (significant rise in c-reactive protein is rarely observed); however, there is a trend toward chronicity. An indirect rationale is provided by evidence of immunodysregulation and low cortisol [28] suggesting immunosuppressive as well as a (cortisol) exhaustive effect of the underlying disease process. Thus, this trial will provide the necessary evidence for low-dose prednisolone and losartan for the indication of PostCOVID inflammatory heart involvement. Maintenance therapy may help to maintain the reduced disease activity, improve exercise tolerance, and preclude the development of irreversible cardiac impairment.

The choice of CMR parameters as inclusion criteria is based first on the evidence of their accuracy and reproducibility, allowing high sensitivity to detect small changes [29–31]. Second, the CMR inclusion criteria are based on the evidence for detection of changes, which directly relate to the underlying pathophysiology, as well as the fact that left ventricular ejection fraction (LVEF) does not improve spontaneously in those with persistent symptoms [9,32]. Thus, CMR serves as the primary efficacy endpoint by a methodological robust measurement (LVEF by CMR), as well as a pluripotent imaging method informing the relevant pathophysiological insights as inclusion criteria. The composite imaging approach to detect complex subclinical changes intends to advance the present clinical routine of relying on a single measurement, such as the LVEF, which is routinely derived by less sensitive techniques, and which fails to sufficiently inform about the clinical context to effectively guide management in early disease [33,34].

This is a pragmatic study design within a short timeframe and a context of an early disease, where the customary hard endpoints are not unachievable and nonexistent. Most cardiovascular clinical trials using hard clinical endpoints to date examined populations with advanced structural heart disease, primarily relating to the outcomes of atherosclerotic disease including HF, and thus hard clinical endpoints are a pathophysiologically expected phenomenon [35]. On the contrary, the present study is a blueprint of a cardioprotection study, where detection of subclinical changes of an inflammatory heart disease can guide intervention to prevent the development of structural heart disease. Given the aging population defined by accumulation of chronic diseases, effectively not addressed in subclinical stages, this is a pertinent and much needed development toward an efficient trial design with sensitive measures, delivering faster impact for preservation of health and reducing the progression of disease.

2. Methods

2.1. Study design overview

Myoflame-19 is a prospective multicenter, randomized, double-blind, placebo-controlled (phase III) clinical trial of myocardial protection therapy of combined immunosuppressive/antiremodeling treatment for a total of 16 weeks (W16) in participants with COVID-19-related cardiac involvement and no structural heart disease determined by CMR imaging (Graphical Abstract). It is actively recruiting within three German and one Austrian centers. The study is conducted by the principles of the Declaration of Helsinki; Good Clinical Practice and European Clinical Trial Regulation (EU CTR 536/2014). The study protocol and other relevant documentation have been reviewed and approved by the Ethics Committee of University Hospital Frankfurt of Goethe University, relevant national ethics committees, as well as competent authorities (Bundesinstitut für Arzneimittel und Medizinprodukte (German Competent Authority) [BfArM] and Bundesamt für Sicherheit im Gesundheitswesen (Austrian Competent Authority) [BASG]). The study registration identifiers include EudraCT 2022-001682-12; NCT05619653.

Patient identification and screening: Interested participants register via a secure online portal to undergo screening for study eligibility by inclusion and exclusion criteria (see Supplementary Material for details). In brief:

1. Age more or equal 18 years
2. Evidence of COVID-19 infection (> 4 weeks, defined as > 28 days from the date of the clinical diagnosis)
3. PASC syndrome by review of cardiac symptoms
4. Exclusion criteria:
   a. Prior cardiac symptoms (i.e., present before infection) or significant heart conditions, necessitating treatment
   b. Prior medical history and medications for significant comorbidities
   c. Contraindications to contrast-enhanced CMR imaging
   d. Severe acute COVID illness requiring hospitalization
   e. Known allergy to or intolerance of the study medications, including symptomatic hypotension (systolic blood pressure less than 90 mm Hg), not reversible with oral hydration
   f. Any previous or current use of angiotensin-converting enzyme inhibitors, angiotensin Receptor blockers; or heart failure treatment, any previous oral prednisolone, or any other immunosuppressive or biological treatment (within prior 10 weeks)
   g. For female participants: pregnant or breastfeeding women, women of childbearing potential not willing to use highly effective contraception
   h. Known alcohol, drug, or chemical abuse
   i. Participants currently participating in an investigational study or for whom participation is planned
   j. Unable to provide written informed consent

Informed consent and baseline visit: All eligible participants willing to undergo study procedures shall provide written informed consent. A baseline visit with clinical assessments is scheduled (standardized questionaries for symptoms, blood sampling, electrocardiogram [ECG], CPET, CMR). Participants provide confirmatory evidence of COVID-19 infection by an approved method. The Centre for Disease Control definition of Long COVID defines a chronic condition that occurs after severe acute respiratory syndrome coronavirus 2 infection and is present after the acute phase (4 weeks) and for at least 3 months, with persistence of new symptoms not previously experienced. In the clinical reality of repeated infections, the present study patients will have Long COVID resulting from the previous infections with longstanding symptoms, where > 4 weeks serve as a practical demarcation from repeated infections, when eligible to attend a baseline visit. Chest pain,

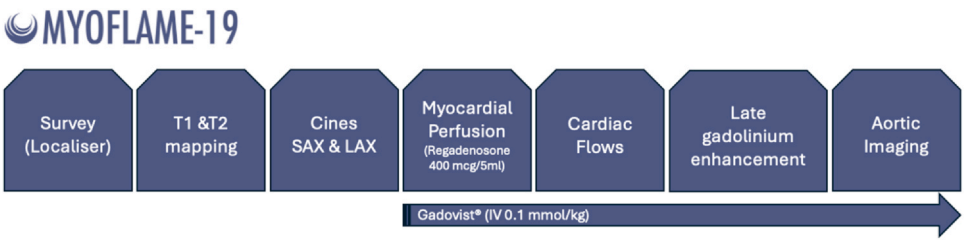

Fig. 1. Myoflame-19 CMR imaging protocol. *CMR* cardiovascular magnetic resonance, *LAX* long axis, *SAX* short axis

dyspnea, palpitations, and syncope are considered cardiac symptoms. Associated systemic symptoms are also collected. Participants fulfilling all inclusion and exclusion criteria, including *CMR criteria for post-COVID inflammatory cardiac involvement and exclusion of structural heart disease at baseline CMR assessment* (Fig. 1), respectively, are randomized equally (1:1) into the verum therapy (prednisolone/losartan) and placebo arm (placebo 1/placebo 2). Investigators and study participants are blinded to the underlying group allocation.

Participants with clinically significant findings in the baseline scan (LVEF < 45%, structural heart disease, etc) mandating a guideline-directed therapy, or blood results indicating a medical emergency are not eligible for the study. They are instructed to see their doctor to arrange diagnostic procedures using routine clinical pathways.

2.2. Study therapy and follow-up visits

The investigational medicinal products (IMPs) in this study include low-dose prednisolone and losartan, or their respective placebos. Before the commencement of the study medication, all randomized participants receive detailed information about the handling of IMPs, concomitant medication and a general advice on lifestyle, and contraception in women of childbearing potential (WOCBP). Study treatment is initiated in the morning and the evening of day 0, after all baseline assessments are completed and the participant has been randomized. Study medication is administered orally according to the same treatment schedule, irrespective of the treatment group. Schedules of prednisolone taper and losartan dose escalation are foreseen for treatment and placebo arm up to a target daily dose of prednisolone of 5 mg and losartan 50 mg, respectively (see Supplementary Material). If the dose increase of losartan is not tolerated, the dose is reduced to the previously tolerated dose.

Remote follow-up visits are scheduled at week (W)2, W6 (with routine blood tests and ECG at the center or local physician, as easiest), W12 after initiation of IMP. The final visit at W16 is conducted on site with repeated assessments for primary and secondary endpoints (blood tests, ECG, CMR, and CPET). The schedule treatment regime and assessments are provided in the Supplementary Material.

Drug accountability: The participants conduct a medication diary and blood pressure measurements, using blood pressure and heart rate monitoring device (Omron X2 Smart). The entries are checked at every visit. Participants are instructed to return all open blisters, as well as any unused medication at on-site visit at W16 for drug accountability check. Detailed treatment dispensing log of study medication is maintained at each study site, inventoried at each monitoring visit. After the final drug accountability, all study IMPs are returned to the pharmacy for destruction.

2.3. Concomitant medications

All female participants are informed about the possible teratogenic effects of losartan in early pregnancy, hence the importance of a highly effective method of contraception. For prevention of pregnancy during the trial period, highly effective methods of contraception are mandated in WOCBP for the duration of the treatment period (listed in the Supplementary Material).

Heart rate-control medications including ivabradine or highly selective beta blockers are encouraged in participants with excessive tachycardia symptoms, if not already taken [1,36]. For example, a starting dose of ivabradine at 2.5 mg twice a day (morning and midday) is recommended as standard therapy for all participants with resting heart rates above 70 bpm, or excessive tachycardia with minimal exertion (> 120/min while walking on flat surfaces) [36]. Participants are encouraged to monitor their resting heart rate profile using commercially available smartwatches.

Concomitant medication permitted during the treatment period includes paracetamol or ibuprofen on per needed basis. With COVID-19 reinfection, short-term antiviral COVID-19 therapy with Paxlovid is recommended [37]. Prior COVID-19 vaccination is not an exclusion criterion. Colchicine, immunosuppressive therapies, or other disease-modifying interventions will not be permitted for the duration of the treatment period. New onset of multivitamins, other supplements, or other experimental therapies are discouraged for the duration of treatment period (W16). Vaccinations during the treatment period will not be permitted. Any new emergency treatments as prescribed by their general practitioner or family doctor will be documented.

Lifestyle advice: The syndrome of PASC is characterized by exercise intolerance and worsening of the symptoms following excessive physical or mental effort owing to the altered tissue lactate production and mitochondrial dysfunction [7]. Therefore, *pacing* is mandated throughout the study; the study participants are instructed to reduce the level of exercise to low intensities (guided by the maximum heart rate of 110/min), to reduce the likelihood of triggering symptoms or worsening with postexercise malaise (PEM). Low-intensity exercises, such as yoga, breathwork exercises, and slow walking, are encouraged, if tolerated, to strengthen respiratory and body musculature. The participants are encouraged to use Long COVID apps to record symptoms and daily activities and monitor disease activity and progress of improvement. Participants are instructed to avoid emotional and mental stress, which are also known triggers of symptoms. To counter the hypovolemic state due to vascular leak, we emphasize the importance of ample hydration (at least 3 L of fluid/day). Less restrictive salt intake or over the counter oral rehydration solutions are important temporary countermeasures with low-cardiac output, symptoms of dizziness or tiredness due to low blood pressure. Healthy, predominantly plant-based diet and consistent sleep routines are encouraged.

2.4. Assessments

2.4.1. Symptoms scores and quality of life

Symptoms scores and QoL will be assessed at baseline, W6, and W16 using standardized questionnaires (Modified Canadian Chest Pain Scale, MRC Dyspnoea Scale; Quality of Life Assessments (RAND 36-item Health Survey Scores, Version 2), all questionnaires are provided in the Supplementary Material.

2.5. Blood tests

About 50 mL of venous blood will be sampled at baseline and W16. Additional routine blood tests for safety assessment will be performed at week 6. Blood samples for standard laboratory tests will be processed

in local blood laboratories. Routine blood tests will include full blood count, blood chemistry, assessments of liver, kidney, and thyroid function, cholesterol levels, HbA1c, D-dimer fibrinogen, and rheumatology. Biobanking samples (full blood, plasma, and serum) will be frozen at −80°C for future processing of emerging cardiovascular biomarkers.

Pregnancy tests will be performed in all women at baseline and W16 either by urine or blood test.

2.6. Cardiovascular magnetic resonance

CMR is an advanced imaging technology providing in-depth, versatile, accurate, and non-invasive means of phenotyping cardiovascular pathophysiology in-vivo [31]. CMR is a gold standard for measurement of cardiac volumes and function. Myocardial tissue mapping and LGE constitute established techniques of cardiovascular tissue characterization, including detection of inflammation, diffuse fibrosis, scarring, and edema, as well as pericardial involvement. Myocardial perfusion imaging with a vasodilatory agent is an established clinical technique for evaluation of myocardial tissue perfusion [38].

Participants undergo CMR imaging at baseline and W16. A study-specific standardized imaging protocol entails a pre-defined set of imaging parameters that are locked and standardized and deployed at all sites for the purpose of Myoflame-19 study. All local imaging teams underwent supervised training in operating procedures pertaining to study-specific image acquisition. Sites are provided with an imaging manual and inducted into scanning procedures. Quality control of the imaging is conducted using remote supervision of scanning procedures.

The CMR protocol entails standardized acquisition in cardiac short-axis (SAX) and long-axis slices for cine imaging, T1 and T2 mapping, myocardial perfusion with a vasodilatory agent Regadenosone, LGE, aortic wall imaging, and vascular flow acquisition (Fig. 1). The imaging parameters are study-specific and optimized for evaluation of non-ischemic inflammatory cardiac conditions, as previously described [9,32,39]. Participants receive intravenous administration of gadolinium-based contrast agent (gadobutrol, Gadovist 0.1 mmol/kg, Bayer AG, Leverkusen, Germany). Myocardial perfusion with Regadenosone (400 mcg/5 mL) to assess myocardial ischemia and microvasculature is performed. Administration of ivabradine may be considered before CMR in participants with resting heart rates ≥75/min, either orally or intravenously, up to a maximum daily dose of 15 mg. Cardiac images are transferred to Central Core Lab (Goethe University, Frankfurt) via upload in electronic case report form (eCRF) and analyzed centrally including the eligibility and endpoint assessment. Cardiac volumes, function, and mass are measured in line with standardized post-processing recommendations [40]. Papillary muscles are included as a part of the LV blood volume (suiteHEART, NeoSoft, suiteHEART, Neosoft LLC, Pewaukee, Wisconsin, U.S.). LV end-diastolic volumes (EDVs) and end-systolic volumes (ESVs) are determined using the rule of disks. Ejection fraction is computed as (EDV − ESV)/EDV. All volumetric indices are normalized to body surface area. Myocardial T1 and T2 relaxation times are measured in the septal myocardium of the midventricular SAX slice [41]. Visual assessment is performed for exclusion of prognostically relevant coronary artery disease [38]. Any LGE pattern suggesting a recognizable specific underlying etiology (e.g., ischemic scar, amyloid, sarcoidosis, viral myocarditis, etc) is an exclusion criterion for the participation in this study. Per protocol (PP), the eligibility is determined by the dedicated core-lab personnel. Whereas patients receive the information about the outcome of eligibility, no details of CMR measurements nor images are shared with the study participants.

2.7. Cardiopulmonary exercise testing

CPET is a standard diagnostic tool for unexplained dyspnea and reduced exercise tolerance. The aim of the assessment is to determine anaerobic threshold. CPET is performed at the baseline and W16 using standardized protocol, including a 12-lead ECG, spirometry, with breathed gas exchange measurement using a modified ramp exercise protocol. CPET will be performed, subject to local availability. Participants may be hesitant or unwilling to undergo CPET due to the fear of triggering PEM, hence participation is optional. Participants will be encouraged to choose their own starting workload, pace, and duration, in line with their current physical state, and to avoid over-exertion. The available datasets analysis will be analyzed by dedicated core-lab study personnel.

2.8. Outcome endpoints (1-year follow-up)

Participants will be followed up after 1 year for collection of the secondary outcome endpoints. These include a major adverse cardiovascular event (MACE), and HF endpoint. MACE is a composite of adverse cardiovascular events (cardiovascular mortality, nonfatal acute coronary syndrome (ACS), and an appropriate device discharge). ACS was defined by a significant rise of hs-TropT in the presence of typical symptoms. HF endpoint is a composite of death due to HF or a documented episode of hospitalization, defined by an episode of hospitalization with symptoms and signs of HF, which is accompanied by a significant N-terminal pro-hormone brain natriuretic peptide (NT-proBNP) level; defined by NT-proBNP level equal or higher that the cut defining the normal range (> 125 pg/dL). A threshold rather than a rise is preferable, as many participants have very low BNP at baseline (due to hypovolemia) and thus a % increase would overestimate HF events. An appropriate device discharge is defined as a documented shock delivered through an implanted cardioverter device that terminated a life-threatening ventricular arrhythmia, i.e., ventricular tachycardia or fibrillation. Nonfatal endpoints, including seeking medical attention for worsening symptoms, new medication, hospitalizations, and documented arrhythmias, will be collected. The first single event per patient will be included in the analysis.

2.9. Adverse events

Any adverse events (AEs) or serious AEs are recorded on the eCRF and managed in line with standard definitions and procedures, using standard pharmacovigilance definitions, which are provided in Supplementary Material. AEs will be documented, recorded, and followed up upon from the time of written informed consent until 4 weeks after the last administration of IMP (W16) or after the last administration of the gadolinium contrast agent, whichever occurs last, considered the AE reporting deadline. An independent Data Safety Monitoring Committee (DSMC) will review serious AEs and any other trial safety issues.

2.10. Endpoints and statistical considerations

2.10.1. Endpoints

Primary endpoint is to determine the efficacy of a combined immunosuppressive and antiremodeling therapy for 16 weeks using an absolute LVEF change to baseline at W16, measured by CMR, compared between the verum and placebo group by absolute treatment difference.

Secondary endpoints are determined by a change from baseline compared between the verum and placebo group in the following clinical parameters.

- CMR measures of cardiac structure (T1 and T2 mapping, LV volumes and mass; myocardial deformation/strain; scar burden by LGE
- Aortic wall imaging and stiffness (pulse wave velocity) by CMR
- CPET
- Symptom scores
- Compliance/tolerance of therapy
- Treatment response:

- Partial response: a normal CMR result is defined as normal T1 and T2, normal gender-age predicted LVEF, non-dilated LV
- Total response: in addition to the above: absence of LGE

- Progression to HF and major adverse cardiac events, compared to placebo after 1 year.

2.11. Data analysis

All primary and secondary efficacy analyses will be performed for the intention-to-treat (ITT) and for the PP population (definitions in Supplementary Material). All safety analyses will be performed for the safety set. ITT analysis will apply the analysis strategy of the treatment policy, while PP analysis will apply while on treatment strategy. All primary and secondary endpoints will also be analyzed in a descriptive manner using summary statistics stratified by treatment and visit. The mean (or median) and proportion of the treatment difference in selected endpoints will be reported at all visits of interest together with the 95% confidence interval (or IQR). All named analyses will be performed on the patient level. Detailed data analyses and sample size considerations are provided in Supplementary Material.

2.12. Data collection

Baseline demographics, ECG, CMR, CPET, physical examination, medical history, trial medication, concomitant medication, blood pressure diary, and any AEs will be documented for all visits. The study data are recorded on paper source documents and transferred on an eCRF. Data are monitored at all sites for completeness and quality by the contract research organization (CRO). A full data-monitoring schedule is established, and an independent data monitor regularly verifies the eCRF against the source data.

2.13. Organization and monitoring

This is an investigator-initiated research study, funded by Bayer AG.

The sponsor of the study is Goethe University Frankfurt, represented by the President and delegated to the representative (V.P./E.N.).

The study is supported by the CRO Alcedis GmbH, Giessen, Germany, which is responsible for overall study management, including preparation of all study material and procedures, in-house and on-site data monitoring, data handling, data quality assurance, safety reporting (A.F.), and statistical reporting (C.W.K.).

A Steering Committee is appointed with Study Chair (C.B.) and independent experts external to the study (B.B. and J.C.K.), and a minimum of four investigators participating in the trial (D.B., A.K., I.V., B.C., and M.D.). The Steering Committee provides clinical and methodological guidance, including overall study design, execution, analysis, and publication of the main study results. The Steering Committee will also act as the Publication Committee.

The DSMC was established in line with the regulatory recommendations. DSMC Chair and independent experts are external to the study and consist of two physicians and a statistician (P.C.T., E.P., and E.H.). Their task is to review all safety events by treatment code and make recommendations to the Steering Committee on further study conduct. In an emergency, they may need to review unblinded study information (on a patient level or treatment group level) during the conduct of the study only if this is considered as needed to fulfill the DSMC tasks.

The study is subject to regulatory oversight by the Ethics Committee of University Hospital Frankfurt, as well as the regional and national competent authorities (BfARm, BASG). The study is registered in the European Clinical Trial Information System.

The study is covered by an insurance policy.

The protocol and the study conduct are compliant with general data protection regulation (EU 2016/679) and regional data protection regulation.

The study drugs (placebo and verum) are purpose-made and dispensed to the participating sites by the Pharmacy of University Hospital Heidelberg (LT).

2.14. Publication and dissemination of the results

The sponsor is responsible for the preparation of a complete, integrated final clinical study report of the study. The investigator/investigator(s) will each receive a copy of this report. Publication(s) will be prepared according to standard guidelines (e.g., Good Publication Practice and Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals) [38].

2.15. Trial network registration

The study is registered with EudraCT 2022-001682-12; NCT05619653.

3. Study limitations and bias

In this prospective randomized controlled-clinical trial, we address an important clinical question, for which there is currently insufficient evidence for an effective diagnostic standard or treatment strategies. Therefore, the results of this trial will help to inform future clinical practice guidelines for “post-COVID inflammatory cardiac involvement, which is unrelated to pre-existing structural heart disease.” It may lead to a new disease entity classified by an International Code of Diseases. To achieve this objective, the trial has been designed to reflect “real-world” medical practice as closely as possible. These consist of guided lifestyle adjustments often not made consistently before the study, including pacing, fluid intake, Ivabradine, the use of long COVID apps, as well as overall better understanding of the underlying disease through education, consistency of measures, as opposed to rapid-fire trial-and-error self-experimentation. This may mean that also patients in placebo group may improve. An important component is (re)build of trust in the medical process and removal of frustration owing to ignorance about the underlying disease and a lack of disease recognition by use of poorly sensitive methods. Although we aim to achieve stable lifestyle routines in both groups for the 16-week treatment period, there are variations between the patients in terms of duration of symptoms, accrued disability, and adherence to the study procedures, as well as support from their general practitioners, often influenced by concomitant social and professional insecurity and processes initiated by the work-related agencies.

Furthermore, the duration of blinded treatment (verum/placebo) for 16 weeks may be too short to unravel the full clinical potential of the therapeutic intervention. Hence the pragmatic combination of, first, the use of imaging endpoints informing on the deeper pathophysiological insights within the 16-week timeframe, and second, the assessment of 1-year outcome after subsequent unblinded open-label treatment. We emphasize the tremendous pressures put on this patients’ population in terms of return to work and getting on with their lives. This is an important consideration, as high level of desperation merges with high rate of self-experimentation, together with unrealistic expectations of quick recovery and misjudgment of the persistent underlying disease processes. Therefore, a longer trial may lead to a higher dropout rate, if no quick improvement is observed. Hence, 16 weeks were chosen as the minimal time to allow for detection of change with compliance to the drug-regime envisaged in the study. Close support of the patients via video calls during the initial weeks of the study medication provides essential reassurance and compliance. Subsequent open-label maintenance therapy helps to maintain the reduced disease activity and sustained improvement of exercise tolerance. The continuation of treatment in the aftermath of the 16-week period is left to the discretion

of the primary care physician in line with the usual ethical mandate for drug-repurposing studies about informing the patient about the availability of the drugs, if wished to be continued. The implementation tends to vary due to regional differences in health systems, understanding of disease mechanisms and readiness for an ongoing support. As physicians are continually informed about the patient progress while on the study medication throughout the 16-week period, there is a common learning curve about the drug initiation and disease management process. As such most patients tend to proceed to the open/off-label medication prescribed by their physicians.

A critical point in implementation of the Myoflame-19 diagnostic CMR criteria is the methodological diversity in everyday CMR imaging practice, due to numerous vendors, software versions, sequence parameters, and their implementations on different scanner types. This is further made complex by an ongoing drive for technological development. Together this precludes a stable universally shared clinical standard. In practice, clinical recognition of myocardial inflammatory injury is best for the infarct-like viral myocarditis [42], which is rare in post-COVID cytokine-induced myocardial injury and consequent autoimmune microvascular disease [8,43–46]. The image acquisition, quality, and interpretation of myocardial mapping remain highly variable and dependent on the experience and doctrines of the individual academic centers, thus inconsistent across different users. The strength of our study design is a unique and uniform imaging acquisition protocol with standardized postprocessing in a core lab. All centers employ identical scanner vendors, software versions, and uniform sequences, with prior steps being undertaken to achieve the uniformity and methodological standardization for all acquisitions within this imaging protocol. All CMR teams have undergone mandatory training of scanning procedures to ensure standardized acquisition for this study, including mapping, cardiac function and structure, and tissue characterization. Our findings are derived using an Frankfurt/Main-MOdified Look Locker Inversion recovery sequence variant with a previously described water-sensitivity, thus, the findings based on this sequence may not be immediately transferable to other T1 mapping sequence types, thus limiting a widespread use in clinical practice with other mapping sequences [39,47]. Thus, translation of the results of Myoflame-19 may only be possible by custom-built implementation of acquisition, postprocessing, and interpretation.

4. Summary

Myoflame-19 study will examine the efficacy of a myocardial protection therapy in symptomatic participants with post-COVID inflammatory cardiac involvement determined by CMR. The aim of the intervention is to reduce the symptoms and inflammatory myocardial injury and thereby preclude development of cardiac impairment and poor health.

4.1. Trial status

Myoflame-19 is currently recruiting in Austria and Germany with four active sites (Vienna, Frankfurt, Kiel, and Greifswald). Further sites in Germany, UK, and the Netherlands are currently undergoing assessments to be considered for inclusion. The number of participants screened and randomized at the time of submission is 563 and 192. This article is concordant with the study protocol version 3.1, dated November 28, 2023.

Clinical trial identifiers

EudraCT 2022-001682-12; NCT05619653.

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Author contributions

V.P. and E.N.: Substantial contributions to the conception or design of the work; V.P., E.N., D.B., A.K., I.V., M.D., and B.C.: the acquisition, analysis, or interpretation of data for the work. All authors: drafting the work or revising it critically for important intellectual content. All authors: final approval of the version to be published. V.P. and E.N.: agreement to be accountable for all aspects of the work.

Ethics approval and consent

The study protocol was reviewed and approved by institutional ethics committees, competent authorities. Written informed consent was obtained from all participants.

Availability of data and materials

Not applicable.

Declaration of competing interests

The authors declare that they have no competing interests. No generative AI tools were used in preparation of this article.

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