A PROSPECTIVE MULTINATIONAL STUDY OF THE NATURAL HISTORY OF PARTICIPANTS WITH BAG3 MUTATION ASSOCIATED DILATED CARDIOMYOPATHY

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Primary:Determine baseline and changes over time in cardiac structure and function in BAG3 associated DCM.Secondary:Assess the progression of prognostic disease biochemical biomarkers in BAG3 associated DCM.

Ethical review	Approved WMO
Status	Pending
Health condition type	Myocardial disorders
Study type	Observational non invasive

Summary

ID

NL-OMON56587

Source
ToetsingOnline

Brief title
C4981001 (9002/0950)

Condition

- Myocardial disorders

Synonym
Cardiovascular disease; Cardiomyopathy

Research involving
Human

Sponsors and support

Primary sponsor: Pfizer

Source(s) of monetary or material Support: By the sponsor as completed in section B7

Intervention

Keyword: BAG3 mutation, Cardiomyopathy, Low-intervention

Outcome measures

Primary outcome

Baseline and change over the course of one year follow up time measures of left ventricular volumes at end systole and diastole including LVEF, LVESVI, LVEDVI and LVMI using imaging over the course of one year follow up time.

Secondary outcome

Baseline, variance, and correlation of circulating biochemical biomarkers hsTNI, hsTNT and NT-proBNP to clinical markers of disease severity over the course of one year follow up time.

Study description

Background summary

A ubiquitously expressed protein, BAG3 is predominantly expressed in the heart where it acts through multiple protein-protein binding domains to couple small and large heat shock proteins to regulate several different cellular processes including protein quality control. BAG3 plays a key role in protein quality control and its loss is related to early and progressive cardiac dysfunction. BAG3 binds and interacts with a myriad of binding partners to promote protein processing and avert apoptosis. Through binding to HSP70, HSPB6 and HSPB8, BAG3 regulates cellular protection during hypoxia/reoxygenation. BAG3 binds BCL2 to inhibit the canonical intrinsic limb of the apoptosis cascade. During cellular stress
BAG3 mediates autophagy up-regulation via interactions with HSPB9 and HSPA1A. Animal models of partial deficiencies of BAG3 demonstrate susceptibility to stress manifesting as myofibrillary disruption, decreased autophagy, increased apoptosis, and left ventricular dysfunction, whereas complete BAG3 deficiency results in rapid cardiovascular decline and early mortality in transgenic animals.

Clinical BAG3 DCM is a rare disorder, occurring in an estimated 2-6% of patients with DCM accounting for an overall prevalence estimated to occur in 1 out of ~25,000 patients in the United States. BAG3 DCM is thought to be due to haploinsufficiency based on the functional loss of a single allele and reduced BAG3 protein expression. Clinically, BAG3 DCM is characterized by an early HF presentation (80% of genotype-positive patients
manifesting HF by age 40). Asymptomatic middle-aged patients with known pathologic BAG3 mutations, have a high incidence of developing HF, 26.1% over ~2 years follow-up. Once symptoms develop, BAG3 DCM patients manifest a poor prognosis, 5.1%/year rate of death or major cardiovascular events (LV device implantation, heart transplant or SCD or equivalent).
Please refer to protocol section 2.2 for more information

Study objective

Primary:
Determine baseline and changes over time in cardiac structure and function in BAG3 associated DCM.
Secondary:
Assess the progression of prognostic disease biochemical biomarkers in BAG3 associated DCM.

Study design

This is a prospective, multinational, multicenter, natural history study to characterize the progression of circulating, imaging, and clinical biomarkers in BAG3 DCM population over time and the corresponding relationship with the clinical outcomes. At least 30 and a maximum of approximately 35 participants with BAG3 DCM and cardiac imaging evidence of left ventricular systolic dysfunction will be enrolled such that 30 evaluable participants complete the study at one year of follow-up. These participants will be stratified to Cohort 1 (New York Heart Association [NYHA] Class I to Class III) or Cohort 2 (NYHA Class IV) according to their NYHA Class at screening and can be initiated simultaneously. The ratio of the number of participants for Cohort 1 versus Cohort 2 must be at least 2:1. That is, no more than one-third of the total number of participants will be in NYHA Class IV and no more than 20% of these NYHA Class IV participants will be on home inotropic therapy. All study participants will be followed for survival and disease progression outcomes for 1 year.

Please refer to protocol section 4 for more information

Study burden and risks

Participants may generate a more in-depth description of BAG3 disease progression which may aid in drug development of future therapies. Considering

the measures taken to minimize risk to participants participating in this study, the potential risks identified in association with cMRI, blood draws, CPET, echocardiography are justified by the anticipated benefits that may be afforded to participants with BAG3 DCM.

Please refer to section "What side effects could you experience", section "What are the pros and cons if you take part in the study?" and Appendix D "Study tests, procedures and assessments and associated risk details" in the Subject Information Sheet and Consent Form for an overview of the risks and side effects.

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. Participants >=18 years (or the minimum country specific age of consent if >18) at Visit 1 (Screen 1). Type of Participant and Disease Characteristics: 2. Participants who are willing and able to comply with all scheduled visits, laboratory tests, and other study procedures. 3. Documented BAG3 pathogenic or likely pathogenic mutation interpreted according to the American College of Medical Genetics Guidelines. 4. NHYA Class I-IV at screening (Stage B-D). 5. LVEF <=50%, except if LVEF 45-50% and NYHA Class I then NT-proBNP must be >=300 ng/dL. LVEF measurement must be within the last 12 month from Echo or cMRI 6. Capable of giving signed informed consent for the study as described in Appendix 1 section 10.1.2, which includes compliance with the requirements and restrictions listed in the ICD and in this protocol.

Exclusion criteria

1. Acute decompensated HF within 1 month prior to enrollment. 2. Any of the following within 3 months prior to screening: myocardial infarction (MI), cardiac surgical procedures (other than for pacemaker/ICD/CRT-defibrillator [CRTD] implantation), acute coronary syndrome or hospitalization for cardiac arrhythmia. 3. History of heart transplantation. 4. eGFR <30 mL/min/1.73 m2 (using the CKD-EPI formula). 5. Malignancy that is active or has been diagnosed within 3 years prior to screening, except surgically curatively resected in situ malignancies or surgically cured early breast cancer, prostate cancer, skin cancer (basal cell carcinoma, squamous cell carcinoma), thyroid cancer, or cervical cancer, or, with prior review by the medical monitor, other early stage surgically curatively resected malignancies with greater than a 20% expected 2 year recurrence rate. 6. Noncardiac condition that limits lifespan to <1 year. 7. Presence of other form(s) of cardiomyopathy contributing to HF (eg, inflammatory or infiltrative cardiomyopathy), clinically significant cardiac anatomic abnormality (eg, LV aneurysm), clinically significant coronary artery disease (eg, coronary revascularization, exercise induced angina) per Investigator judgment or uncorrected, hemodynamically significant (ie, moderate-severe) primary structural valvular disease not due to HF. 8. Any severe concurrent disease or condition (eg, active systemic infection) that, in the judgment of the investigator, would make the participant inappropriate for study participation. 9. Other medical or psychiatric condition including recent (within the past year) or active suicidal ideation/behaviour or laboratory abnormality that may increase the risk of study participation or, in the investigator*s judgment, make the participant inappropriate for the study. 10. Previous administration with an investigational drug within 30 days (or as determined by the local requirement). 11. Likelihood, in the investigator*s opinion, of undergoing cardiac transplantation, left ventricular assist device (LVAD) or other device implantation, or other cardiac surgery within the next 3

months. 12. No more than 3 first-degree members of the same family. 13. Investigator site staff or Pfizer employees directly involved in the conduct of the study, site staff otherwise supervised by the investigator, and their respective family members.

Study design

Design

Study type: Observational non invasive

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

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	31-07-2023
Enrollment:	6
Type:	Anticipated

Ethics review

Approved WMO

Date:	27-12-2023
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

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
CCMO	NL81632.068.22