Official Title of Study:

An Open-Label, Exploratory Study of the Safety and Preliminary Efficacy of Danicamtiv in Stable Ambulatory Participants with Primary Dilated Cardiomyopathy due to either MYH7 or TTN Variants or Other Causalities

NCT Number: NCT04572893

Document Date (Date in which document was last revised): 28 Aug 2023

CLINICAL STUDY PROTOCOL

Protocol Number:	MYK-491-006 (CV028005)
Study Title:	**AN OPEN-LABEL, EXPLORATORY STUDY OF THE SAFETY AND PRELIMINARY EFFICACY OF DANICAMTIV IN STABLE AMBULATORY PARTICIPANTS WITH PRIMARY DILATED CARDIOMYOPATHY DUE TO EITHER MYH7 OR TTN VARIANTS OR OTHER CAUSALITIES**
Brief Study Title:	A Phase 2a Exploratory Study of Danicamtiv in Participants with Primary Dilated Cardiomyopathy
Indication:	Primary Dilated Cardiomyopathy due to MYH7 or TTN Variants or Other Causalities
Phase:	2a
Investigational Medicinal Product:	Danicamtiv (MYK-491; BMS-986434)
Sponsor:	MyoKardia, Inc. 1000 Sierra Point Parkway Brisbane, California 94005 USA
IND Number:	131452
EU CT Number:	2023-505492-68-00
Coordinating Investigator:	[redacted]
Key Sponsor Contacts:	[redacted] Clinical Operations, Study Lead [redacted] [redacted] Clinical Development, Medical Monitor [redacted]
Original Protocol Date:	15 October 2019
Amendment 1	12 August 2020
Amendment 2	11 January 2021
Protocol Clarification Letter	08 Feb 2021
Protocol Clarification Letter	10 June 2021
Protocol Clarification Letter	24 Aug 2021
Amendment 3	11 March 2022

Protocol Clarification Letter	09 May 2022
Protocol Clarification Letter	30 June 2022
Amendment 4	20 December 2022
Administrative Letter 06	01 March 2023
Amendment 5	28 Aug 2023

Confidentiality Statement

OVERALL RATIONALE FOR PROTOCOL AMENDMENT 5:

Overall Rationale for the Amendment

The purpose of this protocol amendment is to update the language around prohibited usage of drug classes, define flexibility around performing unscheduled procedures that support safety monitoring, add guidance of temporary discontinuation of study drug (danicamtiv) in case a short duration of a strong CYP3A4 inhibitor is expected to provide significant benefit for participants, and add a process to resume study drug after temporary discontinuation. Updates were also made to align with European Union (EU) Clinical Trials Regulation (CTR) requirements.

Administrative Letter 06 has also been incorporated into this amendment. Those changes are not detailed in the table below.

Summaries of additional changes are included in the table below to add clarity, consistency in terminology, and accuracy throughout the document. The Protocol Synopsis has been updated to reflect changes made in the protocol body.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 5

Section Number & Title	Description of Changes	Brief Rationale
Title Page Section 14.1	Added Brief Study Title. Replaced European Union Drug Regulating Authorities Clinical Trials (EudraCT) Number with EU CT Number. Added language referring to EU CTR 536/2014 for clinical studies.	Updated to align with requirements set out in Annex 1 of the EU CTR.
Section 4.2: Rationale for Dose and Dosing Schedule Section 6.1.2: Part B Figure 3: Part B Study Schema Section 9.2.2: Part B	Added another Part B starting dose regimen for the case with 10 mg twice daily (BID) and 25 mg BID in Part A. Clarified that 75 mg BID starting dose in Part B is specific for the participants who received Part A doses with 25 mg BID and 50 mg BID which resulted in [redacted]. • If both doses in Part A resulted in a [redacted] of [redacted] with 10 and 25 mg BID, then the Part B dose for that participant is 50 mg BID. • If both doses in Part A resulted in a [redacted] of [redacted] with 25 and 50 mg BID, then the Part B dose for that participant is 75 mg BID.	Participants will receive either 10 mg BID or 50 mg BID in Part A Treatment Period 2 depending on a [redacted] after 25 mg BID at end of Treatment Period 1. The Part B dose selection algorithm was updated to be able to select the next higher dose depending on Part A doses if both doses resulted in minimum [redacted] as defined as [redacted] from the Part A baseline.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 5

Section Number & Title	Description of Changes	Brief Rationale
Section 4.2: Rationale for Dose and Dosing Schedule	Added Part B starting dose for 2 scenarios, in case one dose is [redacted] and one is [redacted] • If 25 mg BID [redacted] and 10 mg BID [redacted] 10 mg BID. • If 25 mg BID [redacted] and 50 mg BID [redacted] 25 mg BID.	To define Part B starting dose for all possible scenario of [redacted] in Part A. Thus far, no participant met these scenarios. The lower dose will be selected for Part B starting dose if participants met the [redacted] as described.
Section 4.2: Rationale for Dose and Dosing Schedule	Added text stating that Part B starting dose can be either one of 5 mg BID, 10 mg BID, 25 mg BID, 50 mg BID, or 75 mg BID.	To summarize Part B starting dose which has been described in the protocol.
Section 6.1.1: Part A Table 3: Schedule of Assessments, Part A	Added text allowing rescreening upon discussion with and documented approval by the Sponsor's Medical Monitor and clarified that repeat genetic testing is not necessary if rescreening is conducted. Added that up to 1 rescreen per participant is permitted.	To accommodate the participants' conditions which may vary depending on the time of assessment, and to allow rescreening in Part A. Additionally, removed repeat of the genetic testing in rescreening since genetic variants implicated in DCM are germline mutations and would not change over the participant's lifetime.
Section 6.1.2: Part B	Added text allowing repeat of rescreening upon discussion with and documented approval by the Sponsor's Medical Monitor.	To accommodate the participants' conditions, which may vary depending on the time of assessment, and allow additional rescreening.
Section 6.2.1: Temporary Treatment Discontinuation (or Treatment Interruption)	Added details for the dose at which treatment should be resumed in consultation with the Sponsor's Medical Monitor.	To accommodate possible changes in study participants which may occur over 2 years of the study duration, such as the participant's health conditions and concomitant medication. Danicamtiv dose for resumption after temporary termination to be determined based on adequate advice and oversight from Medical Monitor and/or safety reviewers.
Section 7.2: Exclusion Criteria	Added exclusion criterion #E17 in Part A and #E13 in Part B to exclude participants with a history of advanced heart failure therapy (ie, a heart transplant or left ventricular assisted device therapy).	To exclude participants whose who may have different safety and tolerability response to danicamtiv due to their significantly different cardiac conditions. Furthermore, assessment and interpretation of PD responses by TTE may be difficult in those participants.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 5		
Section Number & Title	**Description of Changes**	**Brief Rationale**
Section 9.6: Concomitant Therapy	Added information for concomitant use of strong CYP3A4 inhibitors for short duration in Part B if it is expected to provide benefit to study participants. Described potential additional study visits if needed for additional safety monitoring, especially after a change in concomitant medication.	[redacted]
Section 11.4.6: Troponin Levels	Removed the following information regarding troponin increase: "roughly twice the 99th percentile value for the overall population, including equal proportions of both genders."	Removed since the information is irrelevant to the current assay of standard Troponin I.
Section 11.6: Participant Restrictions During the Study	Removed the restriction for study drug to be taken with a full meal BID.	Food requirement was removed in the study Protocol Amendment 3, but the removal was not previously captured. [redacted]
Section 12.1.1: Adverse Event	Revised example of protocol-mandated procedure.	Changed to align with procedures performed in this study.
Section 12.1.2: Serious Adverse Events Section 12.3: Reporting Period and Follow Up	Moved reporting period detail from the serious adverse event (SAE) definition in Section 12.1.2 to Section 12.3. The text was also reorganized.	Reorganized text for clarification of SAE reporting.
Appendix 1: Schedule of Assessments	In Table 3, footnote k, increased time allowed to obtain samples at Visit 2A from within 1 hour predose to 3 hours predose.	Expanded predose pharmacokinetic sampling time window to mitigate operational challenges at sites to conduct required assessments at predose.

PROTOCOL SYNOPSIS

Study Title: An Open-Label, Exploratory Study of the Safety and Preliminary Efficacy of Danicamtiv in Stable Ambulatory Participants with Primary Dilated Cardiomyopathy due to either MYH7 or TTN Variants or Other Causalities

Protocol Number: MYK-491-006 (CV028005)

Study Phase: 2a

Investigational Medicinal Product: Danicamtiv (BMS-986434, MYK-491)

Primary Objective:

- To establish preliminary safety and tolerability of treatment with danicamtiv in participants with myosin heavy chain 7 (MYH7)-dilated cardiomyopathy (DCM), with titin (TTN)-DCM, or DCM by other causalities for Part A.

Secondary Objective:

- To establish the preliminary effect, compared with Baseline, of treatment with danicamtiv on cardiac pharmacodynamics (PD), as determined by transthoracic echocardiography (TTE) in participants with MYH7-DCM, or TTN-DCM, or DCM by other causalities.

Exploratory Objectives:

- To establish the preliminary effect of danicamtiv on overall activity level in participants with MYH7-DCM or TTN-DCM, or DCM of other causalities.
- To determine long-term preliminary safety and tolerability of treatment with danicamtiv in participants with MYH7-DCM or TTN-DCM, or DCM of other causalities for Part B.
- To determine the timeline and durability of effects of danicamtiv on cardiac structure and function in participants with MYH7-DCM or TTN-DCM, or DCM of other causalities utilizing cardiac magnetic resonance (CMR) as well as continuing serial TTE assessments for Part B.
- To explore the exposure-response relationship between danicamtiv exposure and TTE parameters in participants with MYH7-DCM, TTN-DCM, and DCM of other causalities.
- To explore the effect of danicamtiv on soluble biomarkers of cardiac pathophysiology in participants with MYH7-DCM, TTN-DCM, and DCM of other causalities.
- To explore the different effects of danicamtiv on safety and PD between the groups of MYH7-DCM, TTN-DCM, and primary DCM not related to MYH7 or TTN.
- To explore the natural course of cardiac status in participants with MYH7-DCM or TTN-DCM, or DCM of other causalities who participate in the observational study.

Study Design:

This is a 3-cohort, baseline-controlled, sequential, 2-period, open-label study with an optional extension investigating the safety and efficacy of danicamtiv in stable, ambulatory participants with primary DCM due to either MYH7 or TTN variants, or DCM due to other causalities than MYH7 or TTN variants.

Part A

Screening

Eligibility for the study, based on specific MYH7 or TTN variant and presence of DCM-causing variant of the other genes will be assessed centrally by the Sponsor and Coordinating Investigator (Section 7.1). Pre-Screening using a historical genetic report may be conducted prior to Screening visit (VA1.1) where allowed by local regulations (APPENDIX 1).

Participants will undergo 2 to 8 weeks of Screening and qualification assessments over 1 to 2 visits, as necessary (see Part A Schedule of Assessments, APPENDIX 1). Samples for genetic testing will be collected at Screening and assessed at a central genetic laboratory, where available. Genetic testing results will be submitted for central review and approval for eligibility as described in the Central Genetic Review Charter. For the participants who were enrolled based on genetic testing results that were not conducted at the central genetic laboratory, their

genetic status will be confirmed retrospectively via genetic testing at the central genetic laboratory after being enrolled into the study. Screening will include, but not be limited to: medical history, physical examination, safety laboratory tests, triplicate 12-lead electrocardiogram (ECG) and 1 to 2 TTEs. If a qualifying prior TTE, performed within the past 12 months, is available, then another TTE is required at the first Screening visit. The absolute difference of the left ventricular ejection fraction (LVEF) between the qualifying prior TTE and second TTE at Screening must be < 12%. If there is no prior TTE within the past 12 months, then 2 Screening TTEs are required. TTEs must be performed at least 7 days apart during the Screening period, and there should be < 12% difference between the 2 LVEF values.

If a qualifying prior TTE is being used to qualify the participant, a cardiac rhythm monitoring patch will be placed after a TTE at Screening. If 2 Screening TTEs are required, the patch will be placed at the conclusion of the second TTE. Duration of cardiac rhythm monitoring will be at least 5 days and a maximum of 14 days. If a patch becomes detached before 5 days, a new patch should be placed.

Rescreening is acceptable upon discussion with and documented approval by the Sponsor's Medical Monitor. If rescreening is conducted, repeat of prospective genetic testing at Screening is not necessary. Up to one (1) rescreen per participant is permitted.

Open-label Treatment Periods

All enrolled participants will undergo 2 open-label treatment periods with active study drug. Each treatment period will last 5 to 8 days (see Schedule of Assessments, APPENDIX 1), and do not need to have the same duration.

Treatment Period 1 (5 to 8 days):

Visit 2A (Day 1 of Treatment Period 1): Baseline assessments will be completed prior to administration of the first dose of study drug given in the clinic.

A cardiac rhythm monitoring patch will be placed at the conclusion of the visit. Participants will self-administer study drug orally twice daily (BID) at home for up to 8 days. On Day 1, if baseline assessments are completed in the afternoon, then first dose of study drug will only be administered once in the afternoon.

Telehealth Visit (TH) 1A: One to 3 days before the end of Treatment Period 1, the participant will be contacted to ensure compliance with study drug administration, to check for new adverse events (AEs) and concomitant medications, to remind the participant of the next scheduled clinic visit, and to self-administer study drug approximately 7 hours prior to the next clinic visit.

Visit 3A – End of Treatment Period 1: Participants will return to the clinic for assessments of safety, tolerability, study drug plasma concentration, and PD response (see Schedule of Assessments, APPENDIX 1). The Investigator will evaluate for the absence of permanent discontinuation criteria including, but not limited to, the absence of excessive prolongation of QT interval, corrected using Fridericia's formula (QTcF) (Section 7.2). The cardiac sonographer at each local site will measure [redacted] (Section 11.1.1) and promptly communicate the [redacted] from Baseline value (change from [redacted] determined at Visit 2A) to the Study Coordinator and Investigator. This result will determine the dose for Treatment Period 2 (Section 6.1).

Treatment Period 2 (5 to 8 days):

From Visit 3A until Visit 4A: The study drug will be taken orally BID either starting in the evening of Visit 3A or the morning after Visit 3A, depending on the results of the [redacted] from the TTE performed at Visit 3A. Participants should continue taking study drug through Visit 4A (see below under Visit 4A).

Telehealth Visit (TH) 2A: At 1 to 3 days before the end of Treatment Period 2, the participant will be contacted (APPENDIX 1) to ensure compliance with study drug administration, to check for new AEs and concomitant medications, to remind the participant of the next scheduled clinic visit, and to take study drug in the morning of the next visit approximately 7 hours prior to the scheduled time of the visit.

Visit 4A – End of Treatment Period 2: Participants will return for a clinic visit, 5 to 8 days after Visit 3A of Treatment Period 2, for assessments of safety, tolerability, study drug plasma concentration, and PD response (see Schedule of Assessments, APPENDIX 1).

Follow-up:

Telehealth Visit (TH) 3A:

The participant will be contacted 1 to 3 days following the last dose of study drug to assess safety.

Visit 5A: A study clinic visit to assess participant safety will occur 14 days (+ 7 days) following the last dose of study drug regardless of the subject's participation in Part B (see Schedule of Assessments, APPENDIX 1).

Part B

The expected study duration for Part B for each participant is approximately 102 weeks, including a 4-week Rescreening period, if needed. This period does not include a potential hiatus between Parts A and B for some participants. Part B will commence after a participant completes Part A and opts to continue onto Part B. If a participant does not complete Part A or completes outside of the protocol defined window due to reasons other than treatment-emergent adverse event (TEAE) considered as study drug related by the investigator, meeting study discontinuation criteria, or withdrawal of the informed consent, Part B participation will be assessed and approved in discussion with the Sponsor.

If a participant has completed Part A more than 56 days prior to the start of Part B, then a Rescreening visit will be required (see Schedule of Assessments, APPENDIX 1).

If a Rescreening visit is not required prior to Part B start, then Visit 1B can be performed on the same day as Visit 5A and any assessments in Visit 5A that are also required in Visit 1B need to only be performed once. A repeat of rescreening is acceptable after discussion with and documented approval by the Sponsor's Medical Monitor.

A cardiac rhythm monitoring patch will be placed at Visit 1B, Visit 6B, Visit 8B, Visit 10B, and EOT (see Schedule of Assessments, APPENDIX 1).

Individual participant doses for Part B will be based on [redacted] in Part A (Section 4.2). After the initiation of Part B dosing, the [redacted] at V2B and at V3B from the [redacted] at Part B baseline (V1B) will be assessed locally. The dose titration may occur based on these 2 [redacted] changes at Visit 3B (Section 4.2).

High sensitivity troponin T (hsTnT), high sensitivity troponin I (hsTnI), and standard troponin I (TnI) will be evaluated multiple times throughout the study in Parts A and B in conjunction with a 12-lead ECG.

In Part B, TnI (standard) results will be communicated to the study sites by the central laboratory, as they are available, and will be part of an algorithm to evaluate the significance of TnI increase in this patient population. Details of this process are provided in Section 11.4.6.

Additional assessments in Part B include, but are not limited to: N-terminal pro-B-type natriuretic peptide (NT-proBNP) evaluation, activity monitoring, cardiac magnetic resonance (CMR) if considered as suitable condition, 6-Minute Walk Distance (6MWD), New York Heart Association (NYHA) Functional Classification assessments, and Kansas City Cardiomyopathy Questionnaire (23-item version) (KCCQ-23) measurements (see Schedule of Assessments, APPENDIX 1).

If a participant did not opt to participate in Part B, an observational study without study drug treatment is available. A participant still needs to consent to the Part B observation study before receiving any study assessment.

Number of Participants:

Enrollment of total of approximately 40 completed participants (~12 participants with MYH7 variant, ~12 participants with TTN variant, and ~16 participants with primary DCM not with MYH7 or TTN disease-causing variant) is planned. *Note: The ratio of participants with known DCM-causing variants (other than MYH7 or TTN) and non-genetic cause will be approximately 1:1.*

Study Treatment:

In Part A, study drug will consist of 5 and 25 mg [redacted] tablets and 5 mg, 25 mg, and 50 mg [redacted] tablets. In Part B, study drug will consist of 5, 25, 50, and 75 mg [redacted] tablets and [redacted] 5 mg tablets.

Part A:

Study drug will be administered orally BID for at least 5 days and up to 8 days for each Treatment Period. Doses may occur ± 2 hours from scheduled dosing times as long as doses are separated by at least 10 hours and by no more than 14 hours.

Treatment Period 1:

Participants will receive 25 mg BID of study drug. On the last dosing day of Treatment Period 1, a TTE will be performed either in the afternoon of Day 5, 6, 7, or 8, and approximately 7 hours after the morning dose. The [redacted]

change from Baseline observed on that TTE, measured locally at the site by the site sonographer, will determine the dose to be administered in Treatment Period 2.

Treatment Period 2 (doses determined by site measurement of [redacted]:

- If at the end of Treatment Period 1 (Visit 3A), the [redacted] from Baseline (Visit 2A) to Visit 3A is [redacted] to [redacted] the participant will be instructed to skip one dose and then will be down-titrated to 10 mg BID. If a participant is down-titrating, then dosing will start in the morning following the last dose for Treatment Period 1 and will end between 5 to 8 days later.
- If at the end of Treatment Period 1 (Visit 3A), the [redacted] from Baseline (Visit 2A) is [redacted], the participant will be up-titrated to 50 mg BID. If a participant is up-titrating, then dosing will start in the evening on the last dosing day for Treatment Period 1 and will end between 5 to 8 days later.

NOTE: If at the end of Treatment Period 1 (Visit 3A), the [redacted] from Baseline (Visit 2A) is [redacted], then study drug should be permanently discontinued (Section 6.2).

Part B:

Initial individual participant doses will be based on centrally determined [redacted] in Part A, regardless of whether a participant has to be rescreened in Part B:

- If one of the doses in Part A resulted in a [redacted] and [redacted], then that will be the dose for Part B (10, 25, or 50 mg BID)
- If both doses in Part A resulted in a [redacted] and [redacted], then the dose for Part B is the lower of the 2 doses that the participant received in Part A
- If both doses in Part A resulted in a [redacted] with 10 and 25 mg BID, then the Part B dose for that participant is 50 mg BID
- If both doses in Part A resulted in a [redacted] with 25 and 50 mg BID, then the Part B dose for that participant is 75 mg BID
- If both doses in Part A resulted in a [redacted] with 10 and 25 mg BID, then the Part B dose for that participant is 5 mg BID
- If both doses in Part A resulted in a [redacted] with 25 and 50 mg BID, then the Part B dose for that participant is 10 mg BID
- If 25 mg BID dose from Part A [redacted] and 10 mg BID dose from Part A [redacted] 10 mg BID
- If 25 mg BID dose from Part A [redacted] and 50 mg BID dose from Part A [redacted] 25 mg BID

Participants who could not complete Part A or completed TTE assessments outside of the protocol defined window may participate in Part B after investigator discussion with the Sponsor. The reasons of incompletion of Part A should be due to reasons other than treatment-emergent adverse event (TEAE) considered as study drug related by the investigator, meeting study discontinuation criteria, or withdrawal of the informed consent. Part B starting dose for such cases is described in following 2 bullets.

- If [redacted] of both doses were unavailable or performed significantly outside of the assessment window (see Appendix 1. Part A SoA footnote g), then the Part B dose will be 50 mg BID.
- If a [redacted] was only available with 25 mg BID (Treatment Period 1) and a [redacted] was [redacted] and [redacted], then 25mg BID is the dose for Part B. If a [redacted] was [redacted], then the Part B dose is 50 mg BID. If 25 mg BID dose [redacted] 10 mg BID

Part B dose adjustment:

After the initiation of Part B dosing, a TTE will be performed at Visit 2B and Visit 3B to ensure adequate PD responses. [redacted] measured at these times from Part B Baseline (V1B) will dictate dose adjustments as follows:

- If there is a [redacted] of [redacted] on both TTEs at Visits 2B and 3B compared from Part B baseline (V1B), based on local assessments, the dose will be titrated up to the next dose level. If a participant is already receiving the highest dose (75 mg BID), per the Investigator's discretion, the participant will continue the study at 75 mg BID as long as there are no safety concerns (Section 6.2).
- If there is a [redacted] of [redacted] on both TTEs at Visits 2B and 3B compared from Part B baseline (V1B), based on local assessments, the dose will be titrated down to the next dose. If a participant is already receiving the lowest dose (5 mg BID), then the participant will be discontinued from the study (Section 6.2).
- If there is a [redacted] on at least one of TTEs from Visits 2B and 3B, based on local assessments, no dose change is needed.
- If [redacted] at Visit 2B and 3B are [redacted] at one visit and [redacted] at the other, no dose change is needed.

Study Duration:

The expected study duration of Part A for each participant ranges from approximately 4 to 11 weeks, including 2 to 8 weeks for Screening, 9 to 16 days for treatment, and approximately 2 weeks for follow-up.

The expected study duration for Part B for each participant is approximately 102 weeks, including a 4-week Rescreening period, if needed. This period does not include a potential hiatus between Parts A and B for some participants.

The total duration of the study for Parts A and B for each participant is up to 115 weeks.

Inclusion Criteria

Part A:

Each participant in Part A must meet the following criteria to be included in this study.

I1. Able to understand and comply with the study procedures, understand the risks involved in the study, and provide written informed consent according to federal, local, and institutional guidelines before the first study-specific procedure.

I2. Men or women 18 to 80 years of age (inclusive) at the Screening visit.

I3. For MYH7 and TTN cohorts, diagnosis of primary DCM, clinically stable and due to probably disease-causing variant of MYH7 or TTN as defined by (a) through (f) of the following. All study participants, regardless of the cohort, must meet (g) and (h) criteria:

a. Primary DCM participants that have no identified etiology other than variant in MYH7 or TTN (e.g., coronary artery disease or severe valvulopathy), as determined by the Investigator. Participants with a diagnosis of heart failure with reduced ejection fraction should be on Guideline Directed Medical Therapy as tolerated.

NOTE: Presence of coronary artery disease, functional mitral regurgitation, or mild-to-moderate valvular disease may be allowed if not considered the primary cause of the heart failure based on evaluation by the Investigator. Moderate aortic stenosis should be excluded.

b. Pathogenic or likely pathogenic variants submitted in the form of final official genetic laboratory reports will be reviewed centrally by the Sponsor and Coordinating Investigator for eligibility. Some variants designated variant of uncertain significance (VUS) may also be permitted upon central review.

Note: Participants with titin variants in the Z-disk and I-band regions will be excluded from the study (even if regarded as Pathogenic or Likely Pathogenic).

c. DCM is not secondary to long-standing MYH7- or TTN-related hypertrophic cardiomyopathy or left ventricular noncompaction cardiomyopathy, as determined by the Investigator.

NOTE: Hypertrabeculation of the left ventricular myocardium is not, in and of itself, a criterion for exclusion.

d. Participants with DCM related to pathogenic or likely pathogenic variants of TTN must not also have a diagnosis of peripartum DCM (defined by DCM diagnosed initially in the last month of pregnancy or the 6 months following delivery).

e. In participants with DCM related to pathogenic or likely pathogenic variants of TTN, DCM must not be secondary to significant exposure to cardiotoxic chemotherapy agents, as determined by the Investigator.

f. In participants with DCM related to pathogenic or likely pathogenic variants of TTN, DCM must not be due to a history of significant alcohol abuse, as determined by the Investigator.

g. Documented LVEF 15 to 45% (on 2 occasions), including at least once during Screening and confirmed by the Echo Core Laboratory.

- If a participant's most recent prior TTE (within past 12 months) documents a LVEF ≤ 45%, then only a single Screening visit confirming LVEF ≤ 45% by the Echo Core Laboratory is required.
- If no prior documented LVEF ≤ 45% by TTE within the past 12 months is available, then 2 Screening TTEs are needed at least one week (7 days) apart.
- In addition, the absolute difference between the 2 LVEF values qualifying the participant should be < 12%.

h. Participant receives chronic medication for the treatment of heart failure reflecting current guidelines, including at least one of the following, unless not tolerated or contraindicated: β-blocker, angiotensin converting enzyme inhibitor, angiotensin receptor blocker, or angiotensin receptor neprilysin inhibitor. Such treatments should have been given at stable doses for ≥ 2 weeks with no plan to modify during the study.

I4. Sinus rhythm or stable atrial or ventricular pacing or persistent atrial fibrillation that is adequately rate-controlled to allow PD assessments by TTE.

NOTE: Participants with implantable cardioverter defibrillator, pacing, or cardiac resynchronization therapy are eligible if provided device programming is unchanged starting 2 months prior to and throughout the dosing period.

I5. If multiple members of a family meet eligibility criteria, a maximum of 3 eligible participants per family may enroll in the study.

I6. Female participants of childbearing potential (Appendix 6) must not be pregnant or lactating and, if sexually active, must use one of the following highly effective birth control methods from the Screening visit through 3 months after the last dose of study drug:

- combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation or progestogen-only hormonal contraception associated with inhibition of ovulation by oral, implantable, or injectable route of administration
- intrauterine device (IUD)
- intrauterine hormone-releasing system (IUS)
- Female subject is surgically sterile. Surgical sterilization includes documented hysterectomy, bilateral oophorectomy, bilateral salpingectomy, and/or bilateral tubal occlusion or ligation prior to Screening.
- Female participant postmenopausal for 1 year. Female subjects are considered postmenopausal if they have had amenorrhea for at least 1 year or more following cessation of all exogenous hormonal treatments, and follicle-stimulating hormone (FSH) levels are in the postmenopausal range.
- Male partners of female participants must also use a contraceptive (eg, barrier, condom, or vasectomy).

I7. Male participants must use barrier method of contraception (whether or not the participant had vasectomy).

I8. For the cohort of primary DCM due to other causalities than MYH7 and TTN, participant must meet the following criteria in addition to I1, I2, I3 (g) and (h), I4, I5, I6, and I7.

a. The cause of DCM is not related to MYH7 or TTN variants

b. The cause of primary DCM is by variants of the other genes except MYH7 and TTN, or non-genetic cause

Note: The ratio of participants with known DCM-causing variants (other than MYH7 or TTN) and non-genetic cause will be approximately 1:1.

c. DCM is chronic; not due to acute or possibly reversible conditions (eg, hyper/hypothyroidism, infectious cause, tachyarrhythmia, iron overload) according to investigator's determination.

d. DCM is not attributed to pregnancy, alcohol abuse, substance abuse, amyloidosis, sarcoidosis, or any other secondary form of cardiomyopathy per the investigator's determination.

Part B:

Each Part A participant who opts in for Part B must meet the following criteria.

Note 1: If no Rescreening Visit is required, the following criteria must be evaluated by or at Part B Baseline Visit prior to dosing.

Note 2: I4 and I5 only applies to participants in Part B receiving danicamtiv, not the participants in the observational study.

I1. Able to understand and comply with the study procedures, understand the risks involved in the study, and provide written informed consent according to federal, local, and institutional guidelines before the first study-specific procedure.

I2. Participant receiving chronic medication for the treatment of heart failure reflecting current guidelines, including at least one of the following, unless not tolerated or contraindicated: β-blocker, angiotensin converting enzyme inhibitor, angiotensin receptor blocker, or angiotensin receptor neprilysin inhibitor. Such treatments should have been given at stable doses for ≥ 2 weeks prior to the start of Part B.

I3. Sinus rhythm or stable atrial or ventricular pacing or persistent atrial fibrillation that is adequately rate-controlled to allow PD assessments by TTE.

NOTE: Participants with implanted cardioverter defibrillator, pacing, or cardiac resynchronization therapy are eligible if provided device programming is unchanged starting 2 months prior to Part B.

I4. Female participants of childbearing potential (Appendix 6) must not be pregnant or lactating and, if sexually active, must use one of the following highly effective birth control methods after participants signed Part B informed consent through 3 months after the last dose of study drug

- combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation or progestogen-only hormonal contraception associated with inhibition of ovulation by oral, implantable, or injectable route of administration
- intrauterine device (IUD)
- intrauterine hormone-releasing system (IUS)
- Female participant is surgically sterile. Surgical sterilization includes documented hysterectomy, bilateral oophorectomy, bilateral salpingectomy, and/or bilateral tubal occlusion or ligation before and/or at the signing of the Part B informed consent execution.
- Female participant postmenopausal for 1 year. Female subjects are considered postmenopausal if they have had amenorrhea for at least 1 year or more following cessation of all exogenous hormonal treatments, and follicle-stimulating hormone (FSH) levels are in the postmenopausal range.
- Male partners must also use a contraceptive (eg, barrier, condom, or vasectomy).

I5. Male participants must use barrier method of contraception (whether or not the participant had vasectomy).

Part A Exclusion Criteria:

Participants who meet any of the following criteria will be excluded from the study.

E1. Inadequate echocardiographic acoustic windows.

E2. A participant has a QTcF interval > 480 milliseconds not attributable to ventricular pacing or has prolonged QRS duration ≥ 120 milliseconds, average of triplicate ECGs.

E3. a. For MYH7 and TTN cohorts, participants with known pathogenic variant of another gene implicated in DCM at Screening.

b. For the cohort of participants with primary DCM due to other causalities than MYH7 and TTN, known MYH7 or TTN variants implicated in DCM at Screening.

E4. Heart failure with reduced ejection fraction considered to be caused primarily by ischemic heart disease, chronic valvulopathy, or another condition, as determined by the Investigator.

E5. Recent (< 90 days) acute coronary syndrome or angina pectoris.

E6. Coronary revascularization (percutaneous coronary intervention or coronary artery bypass graft) within prior 90 days.

E7. Recent (< 90 days) hospitalization for heart failure, use of intravenous diuretic or chronic intravenous inotropic therapy, or other cardiovascular events (eg, cerebrovascular accident)

E8. Known aortic stenosis of moderate or greater severity.

E9. Presence of disqualifying cardiac rhythms that would preclude echocardiographic assessments, as determined by the Investigator, including: (a) rapid, inadequately rate-controlled atrial fibrillation or (b) frequent premature ventricular contractions that might interfere with reliable echocardiographic measurements of left ventricular function.

E10. Hypersensitivity to danicamtiv or any of the components of the danicamtiv formulation.

E11. Active infection, indicated clinically as determined by the Investigator. In the case of SARS-CoV-2 (COVID-19) infection within 4 weeks prior to and during Screening, symptoms must have completely resolved and based on Investigator assessment in consultation with the Clinical Trial Physician, there are no sequelae that would place the participant at a higher risk of receiving investigational treatment. The methods to assess SARS-CoV-2 (COVID-19) infection include PCR, antigen test and serology tests. Each study site should follow requirements per local institutional or regulatory guidance if any.

E12. History of malignancy of any type within 5 years prior to Screening, with the exception of the following surgically excised cancers occurring more than 2 years prior to Screening: in situ cervical cancer, nonmelanomatous skin cancers, ductal carcinoma in situ, and nonmetastatic prostate cancer.

E13. Severe renal insufficiency (defined as current estimated glomerular filtration rate [eGFR] < 30 mL/min/1.73 m^2 by simplified Modification of Diet in Renal Disease equation [sMDRD]).

E14. Serum potassium < 3.5 or > 5.5 mEq/L.

E15. Any persistent (2 or more) out-of-range laboratory parameters (chemistry, hematology) at Screening, considered by the Investigator and the Medical Monitor to be clinically significant.

E16. History or evidence of any other clinically significant disorder, condition, or disease (including substance abuse) that, in the opinion of the Investigator or the Sponsor Physician would pose a risk to participant safety or interfere with the study evaluation, procedures, completion, or lead to premature withdrawal from the study.

E17. History of advanced heart failure therapy (ie, a heart transplant or left ventricular assisted device [LVAD] therapy).

E18. A life expectancy of < 6 months.

E19. Participated in a clinical trial in which the participant received any investigational drug (or is currently using an investigational device) within 30 days prior to Screening, or at least 5 times the respective elimination half-life (whichever is longer).

E20. WOCBP with a positive pregnancy test.

E21. Is employed by or is a first-degree relative of someone employed by the Sponsor, the Investigator, or his/her staff or family.

E22. Currently placed in hospital or facility due to legal or administrative order.

E23. Not having an implantable cardioverter defibrillator despite meeting the conditions of Class I recommendation defined in the 2022 American Heart Association (AHA)/American College of Cardiology (ACC) heart failure (HF) guidelines (7.4.1) or the 2021 European Society of Cardiology (ESC) HF guideline, depending on the region where participants reside.

E24. Unstable or untreated severe ventricular arrythmia (e.g., ventricular tachycardia or ventricular fibrillation). Participants with severe ventricular arrythmia who have not received an implantable cardioverter defibrillator.

Part B Exclusion Criteria:

Participants who meet any of the following criteria after Part A completion to Part B cannot participate in Part B of the study.

Note1: If no Rescreening Visit is required, the following criteria must be evaluated by or at Part B Baseline Visit prior to dosing.

E1. Recent (< 90 days) acute coronary syndrome or angina pectoris.

E2. Coronary revascularization (percutaneous coronary intervention or coronary artery bypass graft) within prior 90 days.

E3. Recent (< 90 days) hospitalization for heart failure, use of intravenous diuretic or chronic intravenous inotropic therapy or other cardiovascular events (eg, cerebrovascular accident).

E4. Active infection, indicated clinically as determined by the Investigator. In the case of SARS-CoV-2 (COVID-19) infection within 4 weeks prior to Part B Baseline Visit or Rescreening (if required), symptoms must have completely resolved and based on Investigator assessment in consultation with the Clinical Trial Physician, there are no sequelae that would place the participant at a higher risk of receiving investigational treatment. The methods to assess SARS-CoV-2 (COVID-19) infection include PCR, antigen test and serology tests. Each study site should follow requirements per local institutional or regulatory guidance if any.

E5. For participants who need Rescreening, severe renal insufficiency (defined as current eGFR < 30 mL/min/1.73 m^2 by sMDRD).

E6. For participants who need Rescreening, any persistent (2 or more) out-of-range safety laboratory parameters (chemistry, hematology), considered by the Investigator and the Medical Monitor to be clinically significant.

E7. WOCBP with a positive pregnancy test.

E8. History or evidence of any other clinically significant disorder, condition, or disease (including substance abuse) that, in the opinion of the Investigator or the Sponsor Physician, would pose a risk to participant safety or interfere with the study evaluation, procedures, completion, or lead to premature withdrawal from the study

E9. Is employed by or is a first-degree relative of someone employed by the Sponsor, the Investigator, or his/her staff or family.

E10. Currently placed in hospital or facility due to legal or administrative order.

E11. Not have an implantable cardioverter defibrillator despite meeting the conditions of class I recommendation defined in 2022 AHA/ACC HF guidelines (7.4.1) or the 2021 ESC HF guideline, depending on the region where participants reside.

E12. Unstable or untreated severe ventricular arrythmia (e.g., ventricular tachycardia or ventricular fibrillation). Participants with severe ventricular arrythmia who have not received an implantable cardioverter defibrillator

E13. History of advanced heart failure therapy (ie, a heart transplant or LVAD therapy)

Study Endpoints:

Primary: clinical safety and tolerability as assessed by the following:

- Frequency of treatment-emergent adverse events and serious adverse events in Part A
- Frequency of clinically significant abnormalities from vital signs, adverse events, physical examination, ECG recordings, and safety labs in Part A

Secondary: change in the following PD parameters, as assessed by TTE from Baseline corresponding to Parts A and B of the study:

- Left ventricular [redacted]

- Parameters of left ventricular systolic function including but not limited to left ventricular stroke volume (LVSV), LVEF, left ventricular strain (LVGLS and LVGCS), and tissue Doppler imaging (TDI) of mitral valve annulus peak systolic velocity (s')
- Parameters of left ventricular dimensions including left ventricular end-systolic and end-diastolic diameters (LVESD, LVEDD), left ventricular end-systolic and end-diastolic volumes indexed for body surface area (LVEDVi, and LVESVi)
- Parameters of left atrial volume and function including, but not limited to minimum and maximum left atrium (LA) volumes indexed for body surface area (LAmaxVi, LAminVi), left atrial emptying fraction (LAEF), and left atrial function index (LAFI)
- Parameters of left ventricular diastolic function including, but not limited to, TDI of mitral valve annulus peak velocity in diastole (e', lateral, septal), ratio of peak inflow velocities in early and late diastole (E/A), ratio of early mitral peak inflow velocity to early mitral peak annulus velocity (TDI) (E/e') lateral, septal, and average

Exploratory:

- [redacted] will be summarized by the cohort (MYH7, TTN, and other DCM) using descriptive statistics.
- Clinical safety and tolerability as assessed by the following:
  - Frequency of treatment-emergent adverse events and serious adverse events in Part B
  - Frequency of clinically significant abnormalities from vital signs, adverse events, physical examination, ECG recordings, and safety labs in Part B
- Additional exploratory endpoints including concentration-PD effect and soluble biomarkers of cardiac physiopathology may be included.
- Frequency of left ventricular reverse remodeling (LVRR) during Part B, defined by the following criteria (Escobar-Lopez et al. 2021):
  - either left ventricular normalization (LVEF improvement to ≥ 50% with a ≥ 5% LVEF increment on TTE at the last follow-up)
  - or an absolute increase in LVEF by ≥ 10% on TTE at the study visits from TTE at baseline

Sample Size and Statistical Considerations:

The sample size for Part A of approximately 40 completed participants (approximately 12 participants with MYH7 variant, 12 participants with TTN variant, and approximately 16 participants with primary DCM due to causalities other than MYH7 and TTN variants) has been selected empirically to assess the effect size of danicamtiv on the various PD measurements and to provide a preliminary assessment of safety and tolerability in this patient population. There is no target sample size for Part B because it is an optional part of the study.

Treatment-emergent adverse events, ECGs, vital signs, and laboratory values will be analyzed using descriptive statistics. Formal statistical testing will not be performed.

Clinical data will be summarized by cohort, MYH7-DCM, TTN-DCM, and primary DCM by other causalities, and by dose in Part A and Part B. For MYH7 and TTN cohorts, data may be summarized by variant type and the location. For DCM cohort, data will be further evaluated by genetic mutation-positive and genetic mutation-negative variable. If positive genetics are identified, additional analysis may be performed by variant type. Descriptive summary statistics for continuous variables will include the number of participants, mean, standard deviation (SD), median, minimum, and maximum. Categorical variables will be summarized using counts and percentages.

Blood samples to measure the peak danicamtiv plasma concentration will be drawn. Plasma concentration data for danicamtiv will be summarized using descriptive statistics, including mean or geometric mean as appropriate, SD, median, minimum, and maximum values and coefficient of variation % (CV%). No PK analyses will be performed.

TTE data including, but not limited to, LVEF, [redacted], LVSV, and LAFI will be analyzed by cohort and dose using descriptive statistics. Observations by timepoint and change from Baseline (either absolute or percent relative change) at each timepoint will be summarized by cohort and by dose in both Part A and Part B.

Change in [redacted] will be summarized using descriptive statistics.
Compliance Statement: This study will be conducted in accordance with the International Council on Harmonisation (ICH) Good Clinical Practice (GCP) guidelines, US Title 21 Code of Federal Regulations (CFR) Parts 11, 50, 54, 56 and 312; European Union GCP and Good Manufacturing Practices (GMP); and the principles enunciated in the Declaration of Helsinki and all human clinical research regulations where the study is to be conducted.
Additional Items for Consideration: Guidance on COVID-19 risk mitigation is outlined in APPENDIX 5.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

6MWD	6-minute walk distance
ACC	American College of Cardiology
AE	Adverse event
AESI	Adverse events of special interest
AHA	American Heart Association
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
[redacted]	[redacted]
BID	Twice daily
BP	Blood pressure
CFR	Code of Federal Regulations
cGMP	Current Good Manufacturing Practices
CHMP	Committee for Medicinal Products for Human Use
CK-MB	Creatine kinase-MB fraction
CM	cardiomyopathy
C_{max}	Maximum observed plasma concentration
CMR	Cardiac magnetic resonance
COVID-19	Coronavirus disease 19
CV%	Coefficient of variation %
CTR	Clinical Trials Regulation
DCM	Dilated cardiomyopathy
DILI	Drug-induced liver injury
EC	Ethics committee or International Ethics Committee or equivalent
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
E/e	Ratio of early mitral peak inflow velocity to early mitral peak annulus velocity
eGFR	Estimated glomerular filtration rate
ESC	European Society of Cardiology
ET	Early Termination
EU	European Union
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
HF	Heart failure
HfrEF	Heart failure with reduced ejection fraction
HR	Heart rate
HsTnI	High sensitivity troponin I
HsTnT	High sensitivity troponin T
IB	Investigator's Brochure

ICF	Informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IUD	Intrauterine device
IUS	Intrauterine hormone-release system
KCCQ-23	Kansas City Cardiomyopathy Questionnaire (23-item version)
LAEF	Left atrial emptying fraction
LAFI	Left atrial function index
LAmaxVi	Left atrial maximum volume, indexed for BSA
LAminVi	Left atrial minimum volume, indexed for BSA
LAaEF	left atrial active emptying fraction
LArEF	left atrial reservoir emptying fraction
LVAD	left ventricular assisted device
LVEDD	Left ventricular end diastolic diameter
LVEDVi	Left ventricular end diastolic volume, indexed for BSA
LVEF	Left ventricular ejection fraction
LVESD	Left ventricular end systolic diameter
LVESVi	Left ventricular end systolic volume, indexed for BSA
LVFS	Left ventricular fractional shortening
LVGLS	Left ventricular global longitudinal strain
LVGCS	Left ventricular global circumferential strain
LVSV	Left ventricular stroke volume
MedDRA	Medical Dictionary for Regulatory Activities
MYH7	Myosin Heavy Chain 7
NT-proBNP	N-terminal pro-B-type natriuretic peptide
NYHA	New York Heart Association
PCR	Polymerase chain reaction
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
QTcF	QT interval, corrected using Fridericia's formula
s'	Mitral valve annulus peak systolic velocity
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
[redacted]	[redacted]
sMDRD	Simplified Modification of Diet in Renal Disease
SUSAR	Suspected unexpected serious adverse reaction
$t_{1/2}$	Mean terminal half life
TBL	Total bilirubin

TDI	Tissue Doppler imaging
TEAE	Treatment-emergent adverse event
TIBC	Total iron-binding capacity
T_{max}	Time of maximum observed plasma drug concentration
TnI	Troponin I
TSH	Thyroid-stimulating hormone
TTE	Transthoracic echocardiography, transthoracic echocardiogram
TTN	Titin
ULN	Upper limit of normal
US	United States
V1B	Part B baseline
VUS	Variant of uncertain significance

1 INTRODUCTION

Heart failure is a global pandemic, affecting about 26 million people worldwide (including about 6.5 million people in the United States [US]) and its prevalence is increasing due to aging of the population. Despite therapeutic advances made over the past 10 to 20 years, heart failure remains a major source of morbidity and mortality, comparable to cancer, with about 50% of heart failure patients dying within 5 years. Heart failure is also the leading cause of hospitalization in patients aged 65 years or older in the US and represents a major financial burden to society (Braunwald 2013; Yancy et al. 2013; Benjamin et al. 2017). Therefore, it is imperative that new, innovative therapies be developed for this condition.

Dilated cardiomyopathy (DCM) is a disease of the myocardium defined by left ventricular enlargement and myocardial systolic and diastolic dysfunction in the absence of known abnormal loading condition or significant coronary artery disease. Recently, hypokinetic non-dilated cardiomyopathy which is defined as left ventricular or biventricular global systolic dysfunction without dilatation in the absence of the same conditions for previously described DCM, has been considered as a part of DCM (McDonagh et al. 2021; Pinto et al. 2016). While DCM may affect up to 1 in 250 individuals worldwide, in some 20 to 30% of cases, the disorder is mediated by intrinsic variants in single genes in sarcomeric or structural proteins that can ultimately cause contractile dysfunction (Hershberger, Hedges, and Morales 2013).

Myosin heavy chain 7 (MYH7) is a gene that encodes a β-myosin heavy chain protein. Certain variants identified in MYH7 have been shown to result in detrimental alterations in actomyosin that have been implicated in DCM (Ujfalusi et al. 2018).

Titin (TTN) is a gene that encodes the protein titin, which is the largest protein in the human body that provides structure to the contractile elements of the cardiac sarcomere. Variants that truncate the protein have been implicated in the development of DCM (Herman et al. 2012), both alone and in concert with other provoking events, such as pregnancy (Ware, Seidman, and Arany 2016), anthracycline chemotherapy exposure (Linschoten et al. 2017), and chronic alcohol abuse (Ware, Seidman, and Arany 2016). These pathogenic variants are largely concentrated in the region of the protein termed the Aband where myosin is bound and may interfere with myosin heads' ability to interact with actin (Roberts et al. 2015). However, rarer variants within the Z-disk and I-band that affect sarcomere assembly, structure, and integrity have been implicated in DCM as well (Herman et al. 2012).

The Sponsor intends to develop danicamtiv (MYK 491; BMS-986434) for the treatment of heart failure with reduced ejection fraction (HFrEF) and DCM, which together represent about 40% of heart failure. Contemporary medical therapy for systolic heart failure centers on counteracting the effects of maladaptive neurohormonal activation with β adrenergic blockers, diuretics, and modulators of the renin-angiotensin-aldosterone-system (Yancy et al. 2016). Although these drugs are effective and improve clinical outcomes, chronic, well-tolerated therapies that directly target the weakened myocardium and/or address the underlying cause of myocardial dysfunction are lacking.

2 DANICAMTIV

2.1 Overview of Pharmacological Properties and Animal Studies

Danicamtiv is a novel, orally active, small molecule in clinical development for HFrEF and DCM that binds selectively to cardiac myosin and improves cardiac contractility by directly increasing actomyosin cross-bridge formation. Binding of danicamtiv to myosin is reversible and does not inhibit subsequent cross-bridge detachment. In biochemical experiments, as well as in studies conducted in vivo in small and large animals (rats, dogs, and pigs), danicamtiv increased myocardial contractility with minimal impact on cardiac relaxation and without perturbing calcium homeostasis, unlike current standard inotropic drugs. Toxicology studies performed showed that observed toxicities were the result of exaggerated, on-target pharmacological effects consistent with the known mechanism of danicamtiv, without off-target effects (Section 9.4).

Please refer to the Investigator's Brochure (IB) for more detailed information on danicamtiv.

3 BACKGROUND

3.1 Summary of Clinical Experience to Date with Danicamtiv

Four clinical studies with danicamtiv have been completed (3 in healthy participants, 1 in participants with HFrEF/DCM). A summary of the clinical experience to date is provided below. For more details, please refer to the latest IB.

3.1.1 Studies in Healthy Participants

Three clinical studies with danicamtiv have been completed in healthy participants (MYK-491-001, MYK-491-002, [redacted]).

MYK-491-001: A single-ascending dose, double-blind, placebo-controlled, tolerance, pharmacokinetic (PK), and echocardiographic pharmacodynamic (PD) study in healthy participants. A total of 64 participants were enrolled across 8 cohorts. Dose levels studied were [redacted]

The PK profile showed [redacted] Mean time to maximum observed plasma concentration (T_{max}) was [redacted] and mean terminal half-life ($t_{1/2}$) was [redacted]

Danicamtiv was generally well-tolerated at all doses. One participant, who received a single oral dose of 100 mg once daily (QD), experienced 3 short asymptomatic episodes of complete heart block (4 to 8 seconds each) during sleep, captured as a single adverse event (AE). This event was serious due to the need for in-hospital monitoring and was considered treatment-related by the Investigator, but no intervention was required. Three other participants exposed to danicamtiv, experienced brief asymptomatic episodes (2 to 3 beats) of ventricular arrhythmia. Such arrhythmias can occur in normal individuals undergoing continuous monitoring (Min et al. 2010).

[redacted] (25 and 75 mg [redacted]

[redacted] 200 mg QD [redacted]

One participant experienced transient, asymptomatic, non-sustained, ventricular tachycardia lasting for approximately 10 beats and occurring at approximately 36 hours and at approximately 82 hours postdose in a fasted state.

3.1.2 Study in Heart Failure Patients

A single, Phase 1b/2a study with danicamtiv has been completed in heart failure participants.

MYK-491-003: A randomized, double-blind, placebo-controlled, adaptive design evaluation of the safety, tolerability, preliminary PK, and echocardiographic PD of ascending single and multiple oral doses of danicamtiv in participants with stable, moderate HFrEF (ischemic or non-ischemic origin).

In the single-ascending dose (SAD) portion of the study, 12 HFrEF participants received oral doses of danicamtiv (175 to 550 mg). In the multiple-ascending dose (MAD) portion of the study, 40 HFrEF participants were randomized (30 danicamtiv, 10 placebo) and administered danicamtiv (50 to 100 mg twice daily [BID]) or placebo for 7 days; 7 of these 40 participants were enrolled in both the SAD and MAD portions of the study. In both parts of the study, danicamtiv was safe and generally well-tolerated. Mild transient troponin increases were observed with danicamtiv in both SAD and MAD cohorts. These increases were not associated with electrocardiogram (ECG) changes suggestive of ischemia and levels of troponin I and returned to normal or Baseline values by the end of the study. With the exception of one case where the troponin increase was deemed possibly related to myocardial injury and possibly related to study drug, all other troponin increases were asymptomatic. All instances of troponin elevation were transient and resolved without sequelae. In the MAD cohorts, mild asymptomatic, transient increases in troponin, meeting predefined criteria were observed in 4 participants (4/20 = 20%) exposed to danicamtiv versus none on placebo. There were no concomitant associated symptoms or ECG changes suggestive of ischemia (Voors et al. 2020). Of note, mild troponin elevation was also observed with omecamtiv mecarbil, another compound in this class of cardiac myosin activators currently being investigated in a large, Phase 3 cardiovascular outcome trial in HFrEF (Teerlink et al. 2016; Teerlink et al. 2020).

Single-Ascending Dose Portion

[redacted] In general, single

doses of danicamtiv were well-tolerated with exposure concentrations reaching 6000 to 7000 ng/mL. One participant experienced the following AEs beginning 12 to 24 hours after dosing with the highest dose (550 mg) and lasting approximately 24 hours: dyspnea, cardiac discomfort, and elevated troponin levels. The troponin I level reached a maximum of 0.12ng/mL (4 times the upper limit of normal [ULN] for the assay of 0.03 ng/mL). The danicamtiv concentration during the AE was in the range of 4900 ng/mL. There were no concurrent ECG changes, and the participant recovered fully with no residual findings.

Intermittent and mildly elevated levels of troponin occurred in several participants, though only the one described above was symptomatic. Elevated troponin levels than ULN were seen during active treatment with danicamtiv as well as predose and during placebo dosing, but Safety Review Committee-defined criteria for troponin increase were only seen during active danicamtiv dosing. There was no relationship of danicamtiv concentration to the presence of elevated troponin. This pattern of elevated troponin is similar to that reported with omecamtiv mecarbil (Teerlink et al. 2016). The mechanism and significance of the troponin elevations in this class of drugs is currently unknown.

Multiple-Ascending Dose Portion

In the MAD portion of the study, 30 participants received danicamtiv at 50, 75, or 100 mg BID doses and 10 participants received matching placebo for 7 days. In general, danicamtiv was well-tolerated at all doses. There were neither drug-related serious adverse events (SAEs), nor drug-related AEs leading to treatment discontinuation. One SAE of hyperkalemia was reported, which resolved favorably and was not considered related to double-blind treatment. All observed AEs were of mild to moderate severity. There were no cardiac ischemic events or ventricular arrhythmia AEs that were significantly changed from Baseline. Mild, asymptomatic, transient elevations of troponin without concurrent ECG changes were observed in several participants at Baseline and during treatment with active danicamtiv, with no apparent relation to dose or plasma concentration.

At steady-state, the PK data demonstrated a mean T_{max} of approximately 6 hours with a broad peak lasting several hours and a mean terminal $t_{1/2}$ of approximately 22 hours. The preliminary PD responses assessed by echocardiography were related to danicamtiv plasma concentrations as shown in Table 1.

Table 1: Study MYK-491-003: Placebo-corrected Change from Baseline in Selected TTE Parameters by Danicamtiv Plasma Concentration Group (MAD Cohorts)

Parameter	Statistic	Baseline[a] (n = 40)	MYK-491 Plasma Concentration (ng/mL)		
			< 2000 (n = 30)	2000-< 3500 (n = 26)	≥ 3500 (n = 13)
Plasma Concentration (ng/mL)	Mean	-	1169	2716	4448
	SD	-	454	425	855
	Median	-	1220	2740	4290

Table 1: Study MYK-491-003: Placebo-corrected Change from Baseline in Selected TTE Parameters by Danicamtiv Plasma Concentration Group (MAD Cohorts)

Parameter	Statistic	Baseline[a] (n = 40)	MYK-491 Plasma Concentration (ng/mL)		
			< 2000 (n = 30)	2000-< 3500 (n = 26)	≥ 3500 (n = 13)
[redacted]					
LVEF (%)	Mean change[b]	32.4	-0.25	1.12	2.29
	SE[c]	6.002	0.872	0.928	1.158
LVFS (%)	Mean change[b]	18.18	0.46	0.78	0.51
	SE[c]	5.241	0.537	0.574	0.725
LVSV (mL)	Mean change[b]	59.4	3.1	7.8**	5.7*
	SE[c]	12.9	1.8	2.0	2.5
LVESVi (mL/m^2)	Mean change[b]	60.0	-0.9	-1.3	-4.6**
	SE[c]	21.8	1.3	1.4	1.7
LVGLS (%)	Mean change[b]	-11.2	-0.3	-0.9*	-1.0*
	SE[c]	2.3	0.3	0.4	0.4
LVGCS (%)	Mean change[b]	-14.1	-0.4	-2.1**	-3.3**
	SE[c]	4.3	0.6	0.7	0.8

LVEF=left ventricular ejection fraction; LVESVi=left ventricular end systolic volume index; LVFS=left ventricular fractional shortening; LVGCS=left ventricular global circumferential strain; LVGLS=left ventricular global longitudinal strain;

LVSV=left ventricular stroke volume; MAD=multiple-ascending dose; SE=standard error; [redacted] TTE=transthoracic echocardiogram

P-values were computed using an analysis of covariance with fixed effects for group and covariate of baseline assessment and random effects for participant.

* $p<0.05$.

** $p<0.01$.

[a] Absolute arithmetic mean values for the Baseline, where the Baseline was average value of measurements across all the predose values, excluding Screening.

[b] LS mean difference (SE) between each plasma concentration bin (<2000, 2000-<3500 or ≥3500 ng/mL) and placebo (concentration=0) in TTE parameters change from Baseline.

[c] SE=standard error of the LS mean difference.

3.2 Known and Potential Risks and Benefits

There is no expectation of clinical benefit for participants who volunteer to participate in the study. Please see Section 10 for risks.

4 RATIONALE FOR THE STUDY AND FOR DOSE AND DOSING SCHEDULE

4.1 Rationale for the Study

In cases where MYH7 or TTN variants are implicated as the cause of DCM, biochemical studies have shown clear depression in actomyosin function culminating in reduced contractile force (Ujfalusi et al. 2018; Roberts et al. 2015). In further biochemical assays, danicamtiv has been shown to increase actomyosin ATPase rates in a variety of MYH7 variants and specifically [redacted] (internal data on file). This stands in contrast to omecamtiv mecarbil, which was shown in biochemical studies to have a reduced impact on ATPase activity in this particular mutant myosin F764L (Tang et al. 2019).

[redacted]

In cases of DCM related to TTN variants, the vast majority occur in the A-band of the final protein where myosin heads are attached. These variants truncate the final protein product and ostensibly decrease the number of myosin heads available to interact with actin. In human induced pluripotent stem cardiomyocyte tissues possessing known truncating variants of TTN, exposure to a compound closely related with similar activity to danicamtiv demonstrated significant increases in maximal twitch tension (Hinson et al. 2015). Based on this evidence, the hypothesis of this exploratory study is that MYH7-DCM and TTN-DCM patients may be particularly suited to treatment with danicamtiv since it appears to address the very defect exhibited in these patients that results in cardiac dysfunction. It is possible these patients may either demonstrate PD

responses at doses not expected to be effective in the general HFrEF population or may see greater and/or more consistent PD responses at doses shown to be effective in general HFrEF.

Participants enrolled in the study will have primary DCM that is not explained by ischemic heart disease or other reasons such as valvulopathy, and a documented DCM-causing MYH7 or TTN variant. In the amended protocol, danicamtiv will also be assessed in the individuals with primary DCM not related to MYH7 or TTN variants to preliminarily evaluate generalizability of safety and PD responses in the broader DCM population. Clinical relevance of genetic variants in DCM have been studied in several observational studies in DCM patients. Accumulating data suggest different clinical course per etiology and the underlying affected gene (Escobar-Lopez et al, 2021; Anderson et al, 2020; Shah et al, 2021). These studies also revealed different response to HFrEF GDMT by the presence of genetic-causality and the affected gene. A recent natural history study in MYH7-DCM patients observed only 28% of the 106 study participants achieved left ventricular remodeling (LVRR) by HFrEF GDMT during 4.5 years (median, IQR: 1.7-8.0 years) follow up period (de Frutos et al, 2022), although LVRR is generally observed around 50% of DCM patients (Escobar-Lopez et al, 2021). To date, there has been no approved therapy with the same MoA of Danicamtiv for DCM and HFrEF. Preliminary PD effects of danicamtiv in DCM patients by different underlying causality will be explored.

There is precedent in early development of novel heart failure therapies to conduct pilot studies in small numbers of patients with an open-label and baseline-controlled design in order to document a therapeutic effect prior to conducting larger, placebo-controlled trials (Gronda et al. 2014; Thomas, O'Gorman, and Sheridan 1993)

4.2 Rationale for Dose and Dosing Schedule

In Part A, the choice of the initial dose (25 mg BID) and treatment duration (up to 5 to 8 days) have been selected as they are expected to lead to steady-state peak concentrations (1000 to 2000 ng/mL). This concentration range appears to be sub-therapeutic in the general HFrEF participant population based on Study MYK-491-003 MAD, but may be therapeutic in the genetic DCM population. The choice of the scheduling window for treatment duration is to accommodate weekends and holidays; the 2 treatment periods do not need to have the same duration. After Treatment Period 1, a transthoracic echocardiogram (TTE) will be performed for an initial evaluation of the PD response (based on [redacted]) to determine dosing for Treatment Period 2, which will entail either a decrease to 10 mg BID (if participant responded to 25 mg BID and in order to assess possible response to a lower dose) or an increase to 50 mg BID (if participant had no substantial response with 25 mg BID and to assess response to a higher dose).

In Part B, initial individual participant doses will be based on [redacted] in Part A, regardless of whether a participant has to be rescreened in Part B. The Part B starting dose can be either one of 5 mg BID, 10 mg BID, 25 mg BID, 50 mg BID, or 75 mg BID:

- If one of the doses in Part A resulted in a [redacted] and [redacted], then that is the dose for Part B (10, 25, or 50 mg BID)
- If both doses in Part A resulted in a [redacted] and [redacted], then the dose for Part B is the lower of the 2 doses that the participant received in Part A

- If both doses in Part A resulted in a [redacted] of [redacted] with 10 and 25 mg BID, then the Part B dose for that participant is 50 mg BID
- If both doses in Part A resulted in a [redacted] of [redacted] with 25 and 50 mg BID, then the Part B dose for that participant is 75 mg BID
- If both doses in Part A resulted in a [redacted] of [redacted] with 10 and 25 mg BID, then the Part B dose is 5 mg BID
- If both doses in Part A resulted in a [redacted] of [redacted] with 25 and 50 mg BID, then the Part B dose for that participant is 10 mg BID
- If 25 mg BID dose from Part A [redacted] and 10 mg BID dose from Part A [redacted] 10 mg BID
- If 25 mg BID dose from Part A [redacted] and 50 mg BID from Part A [redacted] 25 mg BID

For participants who could not complete Part A or completed TTE assessments outside of the protocol defined window may participate in Part B after investigator discussion with the Sponsor. The reasons of incompletion of Part A should be due to reasons other than treatment-emergent adverse event (TEAE) considered as study drug related by the investigator, meeting study discontinuation criteria, or withdrawal of the informed consent. Part B starting dose for such cases is described in following 2 bullets.

- If [redacted] of both doses were unavailable or performed significantly outside of the assessment window (see Appendix 1. Part A SoA foot note g), then the Part B dose will be 50 mg BID.
- If a [redacted] was only available with 25 mg BID (Treatment Period 1) and a [redacted] was [redacted] and [redacted], then 25 mg BID is the dose for Part B. If a [redacted] was [redacted], then the Part B dose is 50 mg BID. If 25 mg BID dose resulted in a [redacted] then the Part B dose for that participant is 10 mg BID

Part B dose adjustment:

- After the initiation of Part B dosing, TTE will be performed at Visit 2B and Visit 3B to ensure adequate PD responses. The PD responses from these two TTEs compared to Part B baseline (V1B) will yield the following dose titrations at Visit 3B:
- If there is a [redacted] of [redacted] on both TTEs at Visits 2B and 3B compared from V1B, based on local assessments, the dose will be titrated up to the next dose level. If a participant is already receiving the highest dose (75 mg BID), per the Investigator's discretion, the participant will continue the study at 75 mg BID or discontinue the study (Section 6.2.2).
- If there is a [redacted] of [redacted] on both TTEs at Visits 2B and 3B compared from V1B, based on local assessments, the dose will be titrated down to the next dose. If a participant is already receiving the lowest dose (5 mg BID), the participant will be discontinued from the study (Section 6.2.2).
- If there is a [redacted] and [redacted] on at least one of TTEs at Visits 2B or 3B compared from V1B, no dose change is needed.
- If [redacted] at Visit 2B and 3B are [redacted] at one visit and > [redacted] at the other, no dose change is needed.

Results of this study will inform potential subsequent clinical development in a genetic DCM subpopulation.

5 STUDY OBJECTIVES

5.1 Primary Objectives

The primary objective of this study is:

- To establish preliminary safety and tolerability of treatment with danicamtiv in participants with MYH7-DCM or with TTN-DCM, or DCM by other causalities for Part A.

5.2 Secondary Objectives

The secondary objective of this study is:

- To establish the preliminary effect, compared with Baseline, of treatment with danicamtiv on cardiac PD, as determined by TTE in participants with MYH7-DCM or TTN-DCM, or DCM by other causalities.

5.3 Exploratory Objectives

The exploratory objectives of this study are:

- To establish the preliminary effect of danicamtiv on overall activity level in participants with MYH7-DCM or TTN-DCM, or DCM of other causalities.
- To determine long term preliminary safety and tolerability of treatment with danicamtiv in participants with MYH7-DCM or TTN-DCM, or DCM of other causalities Part B.
- To determine the timeline and durability of effects of danicamtiv on cardiac structure and function in participants with MYH7-DCM or TTN-DCM, or DCM of other causalities utilizing cardiac magnetic resonance (CMR) as well as continuing serial TTE assessments for Part B.
- To explore the exposure-response relationship between danicamtiv exposure and TTE parameters in participants with MYH7-DCM, TTN-DCM, and DCM of other causalities.
- To explore the effect of danicamtiv on soluble biomarkers of cardiac physiopathology in participants with MYH7-DCM, TTN-DCM, and DCM by other causalities.
- To explore the different effects of danicamtiv on safety and PD between the groups of MYH7-DCM, TTN-DCM, and primary DCM not related to MYH7 or TTN
- To explore the natural course of cardiac status in participants with MYH7-DCM or TTN-DCM, or DCM of other causalities who participate in the observational study

6 OVERALL STUDY DESIGN AND PLAN

6.1 Study Design

This is a 3-cohort, baseline-controlled, sequential, 2-period, open-label study with an optional extension investigating the safety and efficacy of danicamtiv in stable, ambulatory participants with primary DCM due to either MHY7 or TTN variants, or primary DCM due to other causalities not related to MYH7 or TTN variants. Total enrollment of approximately 40 participants (approximately 12 participants with MYH7 variant, 12 participants with TTN variant, and approximately16 participants with DCM not caused by MYH7 or TTN variant) ages 18 to 80 years is planned.

Note: The ratio of participants with DCM-causing variants (other than MYH7 or TTN) and non-genetic cause will be approximately 1:1.

6.1.1 Part A

Screening

After providing informed consent, the participant's anonymized genetic information will be communicated to the Sponsor at the time of the first Screening visit. Eligibility for the study, based on specific MYH7 or TTN variant, and presence of DCM-causing variant of the other genes will be assessed centrally by the Sponsor and Coordinating Investigator (Section 7.1). Pre-Screening using historical genetic report may be conducted prior to Screening visit (VA1.1) where allowed by local regulations (APPENDIX 1).

Participants will undergo 1 or 2 Screening visits to assess qualification for study participation over within 56 days of the Baseline visit (see Schedule of Assessments Part A, APPENDIX 1). Samples for genetic testing will be collected at Screening and assessed at a central genetic laboratory, where available. Genetic testing results will be submitted for central genetic reviewers for review and approval as described in the Central Genetic Review Charter. For the participants who were enrolled based on genetic testing results that were not conducted at a central genetic laboratory, their genetic status will be confirmed retrospectively via genetic testing at a central genetic laboratory after being enrolled into the study. Screening will include, but not be limited to: medical history, physical examination, safety laboratory tests, 12-lead ECG (triplicate), and 1 to 2 TTEs. If a qualifying prior TTE, performed within the past 12 months, is available, then another TTE is required at the first Screening visit. The absolute difference of the left ventricular ejection fraction (LVEF) between the qualifying prior TTE and the second TTE at Screening must be < 12%. If there is no prior TTE within the past 12 months, then 2 Screening TTEs are required. TTEs must be performed at least 7 days apart during the Screening period, and there should be < 12% difference between the 2 LVEF values.

Abnormal findings from laboratory assessments performed at Visit 1.1A may be repeated once during Screening.

If a qualifying prior TTE is being used to qualify the participant, a cardiac rhythm monitoring patch will be placed after a TTE In Screening. If 2 Screening TTEs are required, the patch will be placed at the conclusion of the second TTE. The duration of cardiac rhythm monitoring will be at least 5 days and a maximum of 14 days. If the patch becomes detached before 5 days, the participant will need to return to the clinic so that another patch is placed.

[redacted]

In addition, the protocol-specified Screening window may be extended due to participant or site scheduling issues, shipment delays (ie, study drug or essential equipment), or other unforeseeable issues (ie, due to the COVID-19 pandemic or natural disasters). The decision to extend the Screening window and/or repeat any assessments will be made on a per participant basis at the discretion of the Sponsor in consultation with the site Investigator.

Guidance on COVID-19 risk mitigation is outlined in APPENDIX 5.

Rescreening is acceptable upon discussion with and documented approval by the Sponsor's Medical Monitor. If rescreening is conducted, repeat of genetic testing at Screening is not necessary. Up to one (1) rescreen per participant is permitted.

A study schema depicting the design of Part A is provided in Figure 2.

Open-label Treatment Periods:

All enrolled participants will undergo 2 open-label treatment periods with active study drug. Both treatment periods will last 5 to 8 days (see Schedule of Assessments, APPENDIX 1) and do not need to have the same duration.

Treatment Period 1 (5 to 8 days):

Visit 2A (Day 1 of Treatment Period 1): Baseline assessments, including a TTE (see Schedule of Assessments, APPENDIX 1), will be completed prior to administration of the first dose of study drug which is to be taken by the Participant prior to leaving the study site. The participant will be given adequate study drug (25 mg BID for up to 8 days) as well as clear study drug administration instructions from the site (every day, BID, at each administration). On Day 1, if baseline assessments are completed in the afternoon, then study drug will only be administered once in the afternoon. A cardiac rhythm monitoring patch will be placed at the conclusion of the visit. Duration of cardiac rhythm monitoring may be between 5 and 14 days. If the patch becomes detached before 5 days, the participant will need to return to the clinic so that another patch is placed prior to leaving the study site.

Telehealth Visit (TH) 1A: 1 to 3 days before the end of Treatment Period 1, the participant will be contacted via telephone, two-way text message, or e-mail (APPENDIX 1) to ensure compliance with study drug administration, to check for new AEs and concomitant medications, to remind the participant of the next scheduled clinic visit, and to take study drug in the morning of the next visit approximately 7 hours prior to the scheduled time of the visit.

Visit 3A – End of Treatment Period 1 (Day 5 or up to Day 8): Participants will return for a clinic visit in the afternoon on Day 5, 6, 7, or 8, approximately 7 hours after the morning dose, for assessments of safety, tolerability, study drug plasma concentration, and evaluation of the PD response. A TTE and other study assessments including, but not limited to, 12-lead ECG and cardiac rhythm monitoring will be completed (see Schedule of Assessments, APPENDIX 1). The Investigator will evaluate for the absence of permanent discontinuation criteria including, but not limited to, the absence of excessive prolongation of QTcF (Section 6.2.2) to confirm that the participant can continue with the study. The cardiac sonographer at each local site will carefully measure [redacted] (Section 11.1.1) and promptly communicate the [redacted] from Baseline value (change from [redacted] determined at Visit 2A) to the Study Coordinator and Investigator. This result will determine the dose for Treatment Period 2, either 50 mg BID beginning that evening or 10 mg BID beginning the following morning (Section 6.1).

The Investigator and/or Study Coordinator will inspect the cardiac rhythm monitoring patch. If the adhesive appears intact, the existing patch should be left in place. If the adhesive appears to be failing or the patch has become detached, then a new patch should be applied at this time.

Treatment Period 2 (5 to 8 days):

From Visit 3A until Visit 4A: Danicamtiv must be taken BID either starting in the evening of Visit 3A or the morning after Visit 3A, depending on the results of the [redacted] from the TTE performed at Visit 3A. Participants should continue taking study drug through Visit 4A (see below under Visit 4A).

Telehealth Visit (TH) 2A: 1 to 3 days before the end of Treatment Period 2 (Visit 4A), the participant should be contacted via telephone, two-way text messaging, or e-mail (APPENDIX 1) to ensure compliance with study drug administration, to check for new AEs and concomitant medications, to remind the participant of the next scheduled clinic visit, and to take study drug in the morning of the next visit approximately 7 hours prior to the scheduled time of the visit.

Visit 4A – End of Treatment Period 2 (5 to 8 days after Visit 3A): Participants will return to the clinic for assessments of safety, tolerability, study drug plasma concentration, and evaluation of the PD response.

The last dose of study drug will be taken in the morning, approximately 7 hours before the clinic visit 5 to 8 days after Visit 3A. A TTE and other study assessments including, but not limited to, laboratory and plasma concentration blood samples, 12-lead ECG (triplicate), and cardiac rhythm monitoring will be completed (see Schedule of Assessments, APPENDIX 1).

Early Termination Visit: If, after enrollment and receipt of any danicamtiv treatment, a decision is made that the participant should discontinue, an Early Termination Visit should be conducted as soon as feasible to ensure participant safety.

Part A Completion vs Part B Start:

After Visit 4A in Part A, each participant will have the option to continue onto Part B or to only complete the remaining Part A study visits. If a participant opts to continue onto Part B, the participant will need to sign the Part B ICF (Section 6.1.2). If a participant does not opt to continue onto Part B of the study, then refer to the Part A Follow-up below.

Part A Follow-up:

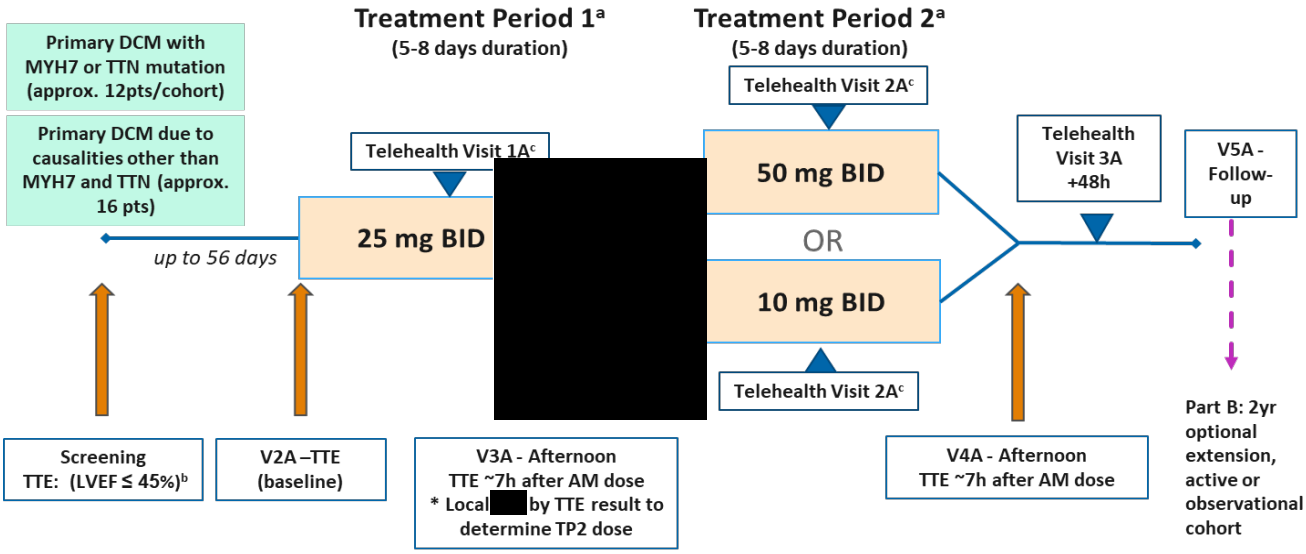
Telehealth Visit (TH) 3A:

The participant should be contacted (APPENDIX 1) 1 to 3 days following the last dose of study drug to assess safety.

Visit 5A – A study clinic visit to assess participant safety will occur 14 days (+ 7 days) following the last dose of study drug regardless of the participant's participation in Part B (see Schedule of Assessments, APPENDIX 1).

Guidance on COVID-19 risk mitigation is outlined in APPENDIX 5.

Figure 2: Part A Study Schema



BID = twice daily; DCM = dilated cardiomyopathy; LVEF = left ventricular ejection fraction; MYH7 = myosin heavy chain 7; [redacted]; TTE = transthoracic echocardiogram; TTN = Titin; V = visit

[a] Each Part A Treatment Period will be between 5-8 days and the 2 periods need not be the same duration.

[b] Participant screening may include a preliminary consent to review existing genetic testing results and 1 to 3 visits to confirm eligibility with 2 TTEs (1 may be historic within the last 12 months).

[c] Participant should be contacted 1 to 3 days prior to Visit 3A and Visit 4A (telehealth) to check for any new or worsening adverse events and review concomitant medications, ensure compliance with study drug, and to remind participant to take study treatment on the morning of Visit 3A and Visit 4A (visits with a TTE scheduled in the afternoon 5-8 days after Visit 2A and 3A, and approximately 7 hours after dosing).

[d] If [redacted], then study drug should be discontinued permanently (Section 6.2).

6.1.2 Part B

A study schema depicting the design of Part B is provided in Figure 3.

The expected study duration for Part B for each participant is approximately 102 weeks, including a 4-week Rescreening period, if needed. This period does not include a potential hiatus between Parts A and B for some participants.

Part B will commence after a participant completes Part A and consents to continue onto Part B. If a participant does not complete Part A or completed outside of the protocol defined window due to reasons other than treatment-emergent adverse event (TEAE) considered as study drug related by the investigator, meeting study discontinuation criteria, or withdrawal of the informed consent, Part B participation will be assessed and approved in discussion with the Sponsor.

If a participant has completed Part A more than 56 days prior to the start of Part B, then a Rescreening visit is required (see Schedule of Assessments, APPENDIX 1).

If a Rescreening visit is not required prior to Part B start, then Visit 1B can be performed on the same day as Visit 5A and any assessments in Visit 5A that are also required in Visit 1B need to only

be performed once. A repeat of rescreening is acceptable after discussion with and documented approval by the Sponsor Medical Monitor.

A cardiac rhythm monitoring patch will be placed at Visit 1B, Visit 6B, Visit 8B, Visit 10B, and EOT (see Schedule of Assessments, APPENDIX 1) and will be mailed back to the site by the participant after 2 weeks or when it spontaneously detaches after at least 5 days of monitoring. If the patch becomes detached prior to 5 days since application, a new patch should be placed as soon as possible at the site.

Individual participant doses for Part B will be based on [redacted] in Part A (Section 4.2), regardless of whether a participant requires rescreening for Part B. After the initiation of Part B dosing, a TTE will be performed at Visit 2B and Visit 3B to ensure adequate PD responses, based on local assessments, with the potential for dose titration at Visit 3B (Section 4.2). Visit 2B, 3B, 4B, 6B, 8B, 10B and EOT should be planned to perform a TTE and blood draw for study drug plasma concentration, etc. at approximately 7 hours after the morning dose.

High sensitivity troponin T (hsTnT), high sensitivity Troponin I (hsTnI), and standard troponin I (TnI), will be evaluated multiple times throughout the study in Parts A and B in conjunction with a 12-lead ECG.

During Part B, TnI (standard) results will be communicated to the study sites by the central laboratory, as they are available, and will be part of an algorithm to evaluate the significance of TnI increase in this participant population. Details of this process are provided in Section 11.4.6.

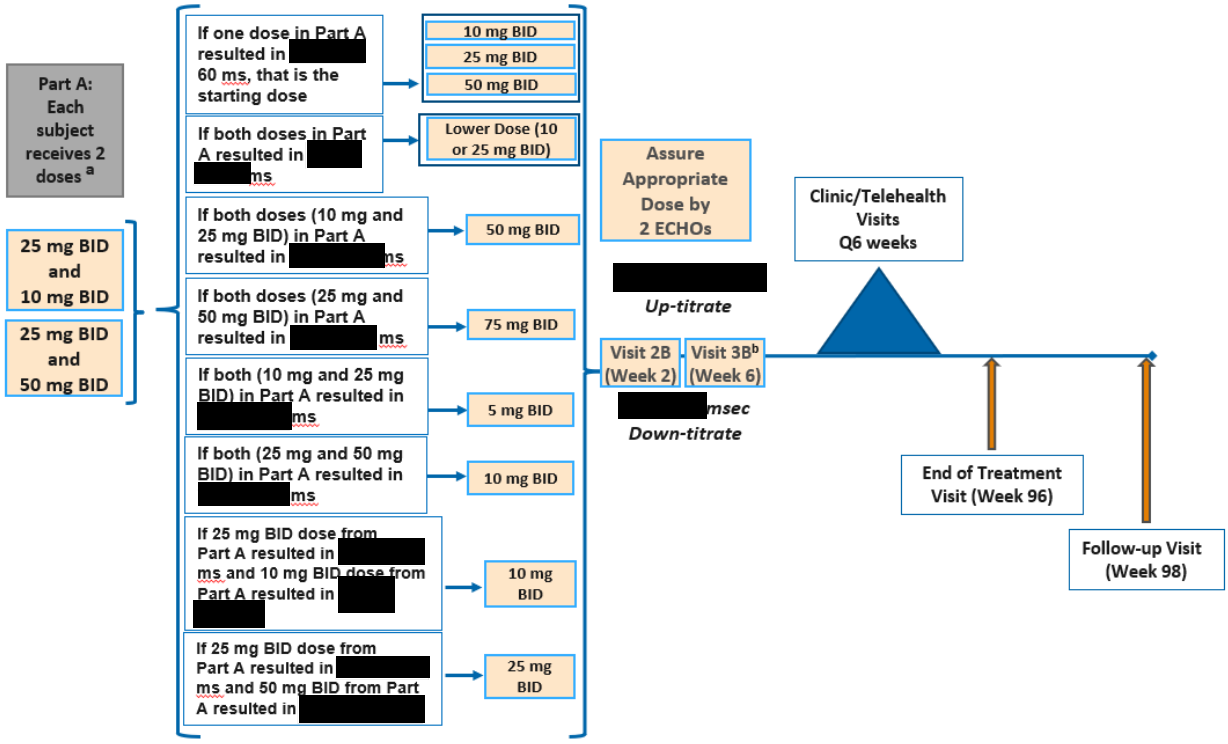
In addition to routine safety evaluations, additional assessments in Part B will include, but not be limited to, N-terminal pro-B-type natriuretic peptide (NT-proBNP) evaluation, activity monitoring, CMR (for suitable study participant), 6-Minute Walk Distance (6MWD), New York Heart Association (NYHA) Functional Classification assessments, and Kansas City Cardiomyopathy Questionnaire (23-item version) (KCCQ-23) measurements (see Schedule of Assessments, APPENDIX 1).

Early Termination Visit: If, after enrollment and receipt of any danicamtiv treatment, a decision is made that the participant should discontinue, then an Early Termination Visit should be conducted as soon as feasible to ensure participant safety.

End of Study / Follow-up Visit: A study clinic visit to assess safety will be made 4 weeks (± 1 week) following the last dose of study drug (see Schedule of Assessments, APPENDIX 1).

Participants who do not opt in for Part B have the option of participating in an observational study without study drug administration (Part B observational study). Limited study assessments at smaller number of study visits will be performed after participants consent to this observational study (see Schedule of Assessments, APPENDIX 1).

Figure 3: Part B Study Schema



[a] For participants who did not complete Part A due to reasons other than treatment-emergent adverse event (TEAE) considered as study drug related by the investigator, meeting study discontinuation criteria, or withdrawal of the informed consent, Part B participation may be assessed and approved in discussion with the Sponsor. Part B initial dose for this case can be found in Sections 4.2 and 9.2.2.

[b] Dose change may occur at Visit 3B.

6.2 Treatment Discontinuation

6.2.1 Temporary Treatment Discontinuation (or Treatment Interruption)

In case permanent discontinuation criteria in Section 6.2.2 are not met, temporary treatment discontinuation (skipping one or several doses of study drug*; doses may be skipped for additional days in agreement between Sponsor's Medical Monitor and the Investigator*) may be considered for the following situations:

- Participant experiences an AE/SAE and upon Investigator's opinion that a temporary treatment discontinuation should be applied. Every effort should be made to resume study drug after careful consideration by the Investigator and if the participant does not meet any permanent discontinuation criteria. The study drug may be resumed at the same or lower dose after discussion with the Sponsor's Medical Monitor.
- Part B only – participant has confirmed TnI levels which exceed 0.1 ng/mL. Treatment will be temporarily discontinued until a decision is reached by the Coordinating Investigator, the

consulting Safety Reviewer, and the Sponsor's Medical Monitor, as described in Section 11.4.6.

- For other reasons upon Investigator's consideration
- By the Investigator in cases of TnI increase > 0.1 ng/mL above Baseline as mentioned previously (Section 11.4.6) or from AE/SAE or other reason. In cases of TnI increase > 0.1 ng/mL with appropriate confirmation, treatment with danicamtiv will be discontinued until a decision is reached by the Coordinating Investigator, the consulting Safety Reviewer, and the Sponsor's Medical Monitor, as described in Section 11.4.6. If a decision was not permanent discontinuation, the study drug will be resumed at the same or lower dose recommended by the Coordinating Investigator, the consulting Safety Reviewer, and the Sponsor's Medical Monitor.

6.2.2 Permanent Treatment Discontinuation

Permanent discontinuation of study drug should be applied for the following situations:

- Part A – participant has a [redacted] at Visit 3A (End of Treatment Period 1) based on local site assessment (Section 11.1.1)
- Part B – participant has a [redacted] of [redacted] at both Visit 2B and Visit 3B compared from Part B baseline [redacted], based on local site assessment, and is already receiving the lowest dose (5 mg BID). (Section 7.3.2 and 9.2.2)
- Part B – a participant has a [redacted] of [redacted] at both Visits 2B and 3B compared from Part B baseline [redacted] based on local assessment, and is already receiving the highest dose (75 mg BID). Per the Investigator's discretion, the participant will continue the study at 75 mg BID (Section 7.3.2 and 9.2.2)
- Participant has drug-related coronary ischemia, as determined by the Investigator

  NOTE: The whole context (clinical symptoms, ECG, and cardiac biomarkers, such as troponin, creatine kinase-MB fraction [CK-MB], cardiac imaging, and coronary angiograms, if applicable) should be taken into account by the Investigator in making that determination since participants enrolled in the study are likely to have an abnormal ECG and/or elevated and/or fluctuating troponin at Baseline in relation to their heart failure condition.

- Participant has a drug-related SAE
- A participant has a QTcF interval > 500 milliseconds (corrected using Fridericia's formula), average of triplicate ECGs) not attributable to ventricular pacing or prolonged QRS duration (≥ 120 milliseconds).
- Participant fulfills the criteria for potential drug-induced liver injury (Hy's Law), including:
- Aminotransferases (alanine aminotransferase [ALT] or aspartate aminotransferase [AST]) are > 3 times ULN with an associated elevation of total bilirubin (TBL) > 2 times ULN without evidence of hemolysis, or
- ALT or AST activity that is > 5 times ULN, or
- TBL > 3 times ULN
- Participant request
- If in the Investigator's opinion, continuation of administration of study treatment would be detrimental to participant's safety or well-being

- At the specific request from the Sponsor

Investigators are strongly encouraged to discuss with the monitoring team and/or the Sponsor in case a treatment discontinuation (temporary or permanent) is being considered.

In case of early permanent treatment discontinuation, an Early Termination Visit should be scheduled as early as possible to perform End of Study assessments, including, but not limited to, evaluations of clinical safety and tolerability, as well as a TTE (APPENDIX 1).

6.2.3 Data Reviews

All collected data will be reviewed by the Coordinating Investigator and the Sponsor's Medical Monitor after 4 participants have completed Part A in each of the 3 cohorts (MYH7 and TTN variants or other causalities). This review is primarily to assess safety, given the potential for an outsized clinical response in this mechanism of disease. The magnitude of clinical response will also be evaluated during these reviews – one for each cohort. Additional reviews may be conducted by the Sponsor at any time during Part A. During these reviews, enrollment may continue uninterrupted. If no safety signal is detected, complete data will be formally reviewed when all participants have completed dosing in Part A.

For Part B, safety reviews will be performed by the Coordinating Investigator, the Sponsor's Medical Monitor, and the consultant safety reviewer on regular basis (approximately every 3 to 6 months) to ensure there are no safety concerns. Discontinuation of participants and dose adjustments may be considered based on the safety data.

6.2.4 Discontinuation of Study

The Sponsor reserves the right to terminate the study at any time for any reason including, but not limited, safety, lack of efficacy, or for strategic reasons.

6.3 Study Duration

The durations listed below are for each individual participant:

Part A: The expected study duration for Part A ranges from approximately 4 to 11 weeks, including 2 to 8 weeks for Screening, approximately 9 to 16 days (*Note: Day 16 only applies to the case when the dose was down-titrated in Treatment Period 2.*) for treatment, and approximately 2 weeks for follow-up.

Part B: The expected study duration for Part B is approximately 102 weeks, including a 4-week Rescreening period, if needed. This period does not include a potential hiatus between Parts A and B for some participants.

The total duration of the study for Parts A and B is up to 115 weeks.

The end of study is defined as the last participant last visit (LSLV) date of Part B.

7 SELECTION OF STUDY POPULATION

7.1 Inclusion Criteria

Part A:

Each participant in Part A must meet the following criteria to be included in this study.

Informed Consent:

I1. Able to understand and comply with the study procedures, understand the risks involved in the study, and provide written informed consent according to federal, local, and institutional guidelines before the first study-specific procedure.

Age:

I2. Men or women 18 to 80 years of age (inclusive) at the Screening visit.

Type of Participant and Disease Characteristics:

I3. For MYH7 and TTN cohorts, diagnosis of primary DCM, clinically stable and due to probably disease-causing variant of MYH7 or TTN as defined by (a) through (f) of the following. All study participants must meet (g) and (h) criteria:

a. Primary DCM participants that have no identified etiology other than variant in MYH7 or TTN (e.g., coronary artery disease or severe valvulopathy), as determined by the Investigator. Participants with a diagnosis of heart failure with reduced ejection fraction should be on Guideline Directed Medical Therapy as tolerated.

NOTE: Presence of coronary artery disease, functional mitral regurgitation, or mild-to-moderate valvular disease may be allowed if not considered the primary cause of the heart failure based on evaluation by the Investigator. Moderate aortic stenosis should be excluded.

b. Pathogenic or likely pathogenic variants submitted in the form of final official genetic laboratory reports will be reviewed centrally by the Sponsor and the Coordinating Investigator for eligibility. Some variants designated variant of uncertain significance (VUS) may also be permitted upon central review.

Note: Participant s with titin variants in the Z-disk and I-band regions will be excluded from the study (even if regarded as Pathogenic or Likely Pathogenic).

c. DCM is not secondary to long-standing MYH7- or TTN-related hypertrophic cardiomyopathy or left ventricular noncompaction cardiomyopathy, as determined by the Investigator.

NOTE: Hypertrabeculation of the left ventricular myocardium is not, in and of itself, a criterion for exclusion.

d. Participants with DCM related to pathogenic or likely pathogenic variants of TTN must not also have a diagnosis of peripartum DCM (defined by DCM diagnosed initially in the last month of pregnancy or the 6 months following delivery).

e. In participants with DCM related to pathogenic or likely pathogenic variants of TTN, DCM must not be secondary to significant exposure to cardiotoxic chemotherapy agents, as determined by the Investigator.

f. In participants with DCM related to pathogenic or likely pathogenic variants of TTN, DCM must not be due to a history of significant alcohol abuse, as determined by the Investigator.

g. Documented LVEF 15 to 45% (on 2 occasions), including at least once during Screening and confirmed by the Echo Core Laboratory.

- If a participant's most recent prior TTE (within past 12 months) documents a LVEF ≤ 45%, then only a single Screening visit confirming LVEF ≤ 45% by the Echo Core Laboratory is required.
- If no prior documented LVEF ≤ 45% by TTE within the past 12 months is available, then 2 Screening TTEs are needed at least one week (7 days) apart.
- In addition, the absolute difference between the 2 LVEF values qualifying the participant should be < 12%.

h. Participant receives chronic medication for the treatment of heart failure reflecting current guidelines, including at least one of the following, unless not tolerated or contraindicated: β-blocker, angiotensin converting enzyme inhibitor, angiotensin receptor blocker, or angiotensin receptor neprilysin inhibitor. Such treatments should have been given at stable doses for ≥ 2 weeks with no plan to modify during the study.

I4. Sinus rhythm or stable atrial or ventricular pacing or persistent atrial fibrillation that is adequately rate-controlled to allow PD assessments by TTE.

NOTE: Participants with implanted cardioverter defibrillator, pacing, or cardiac resynchronization therapy are eligible if provided device programming is unchanged starting 2 months prior to and throughout the dosing period.

I5. If multiple members of a family meet eligibility criteria, a maximum of 3 eligible participants per family may enroll in the study.

I6. Female participants of childbearing potential (Appendix 6) must not be pregnant or lactating and, if sexually active, must use one of the following highly effective birth control methods from the Screening visit through 3 months after the last dose of study drug

- combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation or progestogen-only hormonal contraception associated with inhibition of ovulation by oral, implantable, or injectable route of administration
- intrauterine device (IUD)
- intrauterine hormone-releasing system (IUS)
- Female participant is surgically sterile. Surgical sterilization includes documented hysterectomy, bilateral oophorectomy, bilateral salpingectomy, and/or bilateral tubal occlusion or ligation prior to Screening.

- Female participant postmenopausal for 1 year. Female subjects are considered postmenopausal if they have had amenorrhea for at least 1 year or more following cessation of all exogenous hormonal treatments, and follicle-stimulating hormone (FSH) levels are in the postmenopausal range.
- Male partners must also use a contraceptive (eg, barrier, condom, or vasectomy).

I7. Male participants must use barrier method of contraception (whether or not the participant had vasectomy).

I8. For the cohort of primary DCM due to causalities other than MYH7 and TTN, participant must meet the following criteria in addition to I1, I2, I3-g & h, I4, I5, I6 and I7.

a. The cause of DCM is not related to MYH7 or TTN variants.

b. The cause of primary DCM is by variants of other genes except MYH7 and TTN, or non-genetic cause

Note: The ratio of participants with known DCM-causing variants (other than MYH7 or TTN) and non-genetic cause will be approximately 1:1.

c. DCM is chronic; not due to acute or possibly reversible conditions (eg, hyper/hypothyroidism, infectious cause, tachyarrhythmia, iron overload) according to investigator's determination.

d. DCM is not attributed to pregnancy, alcohol abuse, substance abuse, amyloidosis, sarcoidosis, or any other secondary form of cardiomyopathy per the investigator's determination.

Part B:

Each Part A participant who opts in for Part B must meet the following criteria.

Note 1: If no Rescreening Visit is required, the following criteria must be evaluated by or at Part B Baseline Visit prior to dosing.

Note 2: I4 and I5 only applies to participants in Part B receiving danicamtiv, not the participants in the observational study.

I1. Able to understand and comply with the study procedures, understand the risks involved in the study, and provide written informed consent according to federal, local, and institutional guidelines before the first study-specific procedure.

I2. Participant receiving chronic medication for the treatment of heart failure reflecting current guidelines, including at least one of the following, unless not tolerated or contraindicated: β-blocker, angiotensin converting enzyme inhibitor, angiotensin receptor blocker, or angiotensin receptor neprilysin inhibitor. Such treatments should have been given at stable doses for ≥ 2 weeks prior to the start of Part B.

I3. Sinus rhythm or stable atrial or ventricular pacing or persistent atrial fibrillation that is adequately rate-controlled to allow PD assessments by TTE.

NOTE: Participants with implanted cardioverter defibrillator, pacing, or cardiac resynchronization therapy are eligible if provided device programming is unchanged starting 2 months prior to Part B.

I4. Female participants of childbearing potential (Appendix 6) must not be pregnant or lactating and, if sexually active, must use one of the following highly effective birth control methods after participants signed Part B informed consent through 3 months after the last dose of study drug

- combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation or progestogen-only hormonal contraception associated with inhibition of ovulation by oral, implantable, or injectable route of administration
- intrauterine device (IUD)
- intrauterine hormone-releasing system (IUS)
- Female participant is surgically sterile. Surgical sterilization includes documented hysterectomy, bilateral oophorectomy, bilateral salpingectomy, and/or bilateral tubal occlusion or ligation before and/or at the signing of the Part B informed consent execution.
- Female participant postmenopausal for 1 year. Female subjects are considered postmenopausal if they have had amenorrhea for at least 1 year or more following cessation of all exogenous hormonal treatments, and follicle-stimulating hormone (FSH) levels are in the postmenopausal range.
- Male partners must also use a contraceptive (eg, barrier, condom, or vasectomy).

I5. Male participants must use barrier method of contraception (whether or not the participant had vasectomy).

7.2 Exclusion Criteria

Part A:

Participants who meet any of the following criteria will be excluded from the study.

E1. Inadequate echocardiographic acoustic windows.

E2. A participant has a QTcF interval > 480 milliseconds not attributable to ventricular pacing or prolonged QRS duration ≥ 120 milliseconds, average of triplicate ECGs.

E3. a. For MYH7 and TTN cohorts, participants with known pathogenic variant of another gene implicated in DCM at Screening.

b. For the cohort of participants with primary DCM due to other causalities than MYH7 and TTN, known MYH7 or TTN variants implicated in DCM at Screening.

E4. HFrEF considered to be caused primarily by ischemic heart disease, chronic valvulopathy, or another condition, as determined by the Investigator.

E5. Recent (< 90 days) acute coronary syndrome or angina pectoris.

E6. Coronary revascularization (percutaneous coronary intervention or coronary artery bypass graft) within prior 90 days.

E7. Recent (< 90 days) hospitalization for heart failure, use of intravenous diuretic or chronic intravenous inotropic therapy, or other cardiovascular event (eg, cerebrovascular accident).

E8. Known aortic stenosis of moderate or greater severity.

E9. Presence of disqualifying cardiac rhythms that would preclude echocardiographic assessments, as determined by the Investigator, including: (a) rapid, inadequately rate-controlled atrial fibrillation or (b) frequent premature ventricular contractions that might interfere with reliable echocardiographic measurements of left ventricular function.

E10. Hypersensitivity to danicamtiv or any of the components of the danicamtiv formulation.

E11. Active infection, indicated clinically as determined by the Investigator. In the case of SARS-CoV-2 (COVID-19) infection within 4 weeks prior to and during Screening, symptoms must have completely resolved and based on Investigator assessment in consultation with the Clinical Trial Physician, there are no sequelae that would place the participant at a higher risk of receiving investigational treatment. The methods to assess SARS-CoV-2 (COVID-19) infection include PCR, antigen test and serology tests. Each study site should follow requirements per local institutional or regulatory guidance if any.

E12. History of malignancy of any type within 5 years prior to Screening, with the exception of the following surgically excised cancers occurring more than 2 years prior to Screening: in situ cervical cancer, nonmelanomatous skin cancers, ductal carcinoma in situ, and nonmetastatic prostate cancer.

E13. Severe renal insufficiency (defined as current estimated glomerular filtration rate [eGFR] < 30 mL/min/1.73 m^2 by simplified Modification of Diet in Renal Disease equation [sMDRD]).

E14. Serum potassium < 3.5 or > 5.5 mEq/L.

E15. Any persistent (2 or more) out-of-range laboratory parameters (chemistry, hematology) at Screening, considered by the Investigator and the Medical Monitor to be clinically significant.

E16. History or evidence of any other clinically significant disorder, condition, or disease (including substance abuse) that, in the opinion of the Investigator or the Sponsor Physician would pose a risk to participant safety or interfere with the study evaluation, procedures, completion, or lead to premature withdrawal from the study.

E17. History of advanced heart failure therapy (ie, a heart transplant or left ventricular assisted device [LVAD] therapy).

E18. A life expectancy of < 6 months.

Prior/Concurrent Clinical Study Experience:

E19. Participated in a clinical trial in which the participant received any investigational drug (or is currently using an investigational device) within 30 days prior to Screening, or at least 5 times the respective elimination half-life (whichever is longer).

Other Exclusions:

E20. WOCBP with a positive pregnancy test.

E21. Is employed by or is a first-degree relative of someone employed by the Sponsor, the Investigator, or his/her staff or family.

E22. Currently placed in hospital or facility due to legal or administrative order.

E23. Not having an implantable cardioverter defibrillator despite meeting the conditions of class I recommendation defined in 2022 AHA/ACC HF guidelines (7.4.1) or the 2021 ESC HF guideline, depending on the region where participants reside.

E24. Unstable or untreated severe ventricular arrythmia (e.g., ventricular tachycardia or ventricular fibrillation). Participants with severe ventricular arrythmia who have not received an implantable cardioverter defibrillator.

Part B:

Participants who meet any of the following criteria after Part A completion to Part B cannot participate in Part B of the study.

Note 1: If no Rescreening Visit is required, the following criteria must be evaluated by or at Part B Baseline Visit prior to dosing.

E1. Recent (< 90 days) acute coronary syndrome or angina pectoris.

E2. Coronary revascularization (percutaneous coronary intervention or coronary artery bypass graft) within prior 90 days.

E3. Recent (< 90 days) hospitalization for heart failure, use of intravenous diuretic or chronic intravenous inotropic therapy or other cardiovascular event (eg, cerebrovascular accident).

E4. Active infection, indicated clinically as determined by the Investigator. In the case of SARS-CoV-2 (COVID-19) infection within 4 weeks prior to Part B Baseline Visit or Rescreening (if required), symptoms must have completely resolved and based on Investigator assessment in consultation with the Clinical Trial Physician, there are no sequelae that would place the participant at a higher risk of receiving investigational treatment. The methods to assess SARS-CoV-2 (COVID-19) infection include PCR, antigen test and serology tests. Each study site should follow requirements per local institutional or regulatory guidance if any.

E5. For participants who need Rescreening, severe renal insufficiency (defined as current eGFR < 30 mL/min/1.73 m2 by simplified sMDRD).

E6. For participants who need Rescreening, any persistent (2 or more) out-of-range safety laboratory parameters (chemistry, hematology), considered by the Investigator and the Medical Monitor to be clinically significant.

E7. WOCBP participants with a positive pregnancy test.

E8. History or evidence of any other clinically significant disorder, condition, or disease (including substance abuse) that, in the opinion of the Investigator or the Sponsor Physician, would pose a risk to participant safety or interfere with the study evaluation, procedures, completion, or lead to premature withdrawal from the study.

E9. Is employed by or is a first-degree relative of someone employed by the Sponsor, the Investigator, or his/her staff or family.

E10. Currently placed in hospital or facility due to legal or administrative order.

E11. Not have an implantable cardioverter defibrillator despite meeting the conditions of class I recommendation defined in 2022 AHA/ACC HF guidelines (7.4.1) or the 2021 ESC HF guideline, depending on the region where participants reside.

E12. Unstable or untreated severe ventricular arrythmia (e.g., ventricular tachycardia or ventricular fibrillation). Participants with severe ventricular arrythmia who have not received an implantable cardioverter defibrillator

E13. History of advanced heart failure therapy (ie, a heart transplant or LVAD therapy).

7.3 Withdrawal and Replacement of Participants

The Investigator will make every reasonable attempt to retain participants through completion of the study.

7.3.1 Withdrawal from the Study

Participants may withdraw from participation in the study at any time and for any reason. The degree to which a participant withdraws can vary, and efforts will be made to collect important safety data if feasible and the participant agrees.

Participants can:

- Withdraw from treatment and agree to participate in the Early Termination Visit
- Withdraw from treatment and all follow up

See Section 6.2 for Permanent Treatment Discontinuation.

In all cases, the reason(s) for study withdrawal will be recorded in the source document and on the appropriate electronic case report form (eCRF).

7.3.2 Follow-up Procedures After Early Withdrawal from Study

The Investigator will make every effort to complete the protocol-specified follow-up procedures as specified in the Early Termination Visit in APPENDIX 1, including the follow-up of any unresolved AEs until the AE is resolved or stabilized.

In the case of early permanent treatment discontinuation, an Early Termination Visit should be scheduled as early as possible (same day, next day, or as best as possible) to perform End of Study assessments, including but not limited to evaluations of clinical safety and tolerability, as well as a TTE (APPENDIX 1).

7.3.3 Replacement of Participants

Participants who withdraw/are withdrawn permanently due to a drug-related AE may not be replaced. Participants who discontinue Part A of the study after receiving study drug for reasons other than drug-related AEs or participants who are not evaluable for concentration-PD at steady state may be replaced at the discretion of the Sponsor in consultation with the Investigator. Participants that discontinue the study during Part B will not be replaced.

8 RANDOMIZATION AND BLINDING PROCEDURES

This is an open-label and non-randomized study.

9 STUDY TREATMENT

The study drug is defined as danicamtiv (MYK-491).

9.1 Investigational Medicinal Product

Danicamtiv drug substance is a [redacted] with a molecular weight of 435.4 g/mol. Danicamtiv is [redacted]

Danicamtiv will be provided as [redacted] (Part A and Part B) [redacted] (Part B) tablets. Danicamtiv tablets are manufactured according to current Good Manufacturing Practice (cGMP) regulations.

9.1.1 Supply of Investigational Medical Product

The clinical study material for the MYK-491-006 study will be provided by the Sponsor.

Part A:

The Sponsor will provide:

- [redacted] 5 mg tablets (to support 10 mg BID and 25 mg BID doses) and [redacted] 25 mg tablets (to support the 50 mg BID doses). The tablets will be blistered and carded; each blister card will contain either only 5 mg or only 25 mg tablets. There will be no mixed strength blister cards. Each blister card will be labeled as required by local regulations and will be "open" in labeling (label will identify the contents of the blister card).
- [redacted] tablets supplied in high-density polyethylene bottles with induction seals and child-resistant caps – each one of 3 strengths: 5 mg (to support the 10 mg BID dose), 25 mg, and 50 mg.

Part B:

The Sponsor will provide:

- [redacted] 5 mg tablets in blister cards (to support the 5 mg and 10 mg BID doses).

- [redacted] tablets supplied in high-density polyethylene bottles with induction seals and child-resistant caps of 4 strengths: 5 mg (to support the 5 mg BID and 10 mg BID doses), 25 mg, 50 mg, and 75 mg.

9.1.2 Storage and Handling Procedures

Danicamtiv must be stored in accordance with the labeled storage conditions in the packaging supplied by the Sponsor. At the investigational site, danicamtiv will be stored in a secure area with access limited to authorized study personnel.

9.1.3 Packaging and Labeling

Danicamtiv will be shipped in appropriately labeled containers. All study drug will be labeled according to applicable local regulatory guidelines.

9.2 Investigational Medicinal Product, Administration, and Schedule

Each dose of study drug should be ingested with a full meal.

9.2.1 Part A:

In Treatment Period 1, participants will receive 25 mg BID (every 12 hours) of danicamtiv. Doses may occur ± 2 hours from scheduled dosing times as long as doses are:

- separated by at least 10 hours and by no more than 14 hours, and
- given for at least 5 days and up to 8 days, ie, with treatment starting on the morning (or afternoon if baseline assessments completed in the afternoon) of Day 1 and last dose taken in the morning, at the earliest on Day 5 and at the latest on Day 8 (corresponding to a total of 8 to 15 doses for Period 1).

On the last dosing day of Treatment Period 1 (Visit 3A), a TTE will be performed in the afternoon of Day 5, 6, 7, or 8, approximately 7 hours after the morning dose. The [redacted], observed between the Baseline (Visit 2A) TTE and the Visit 3A TTE, measured locally at the site by the site sonographer, will determine the dose to be administered in Treatment Period 2.

Treatment Period 2 (doses determined by site measurement of [redacted]):

- If at the end of Treatment Period 1 (Visit 3A), the [redacted] from Baseline (Visit 2A) to Visit 3A is [redacted] to [redacted], the participant will be instructed to skip one dose and then will be down-titrated to 10 mg BID. Thus, if a participant is down-titrating, then dosing for Treatment Period 2 will begin the morning of the day after the last dose for Treatment Period 1, and end between 5 to 8 days later, ie, last dose in Treatment Period 2 will be taken in the morning.
- If at the end of Treatment Period 1 (Visit 3A), the [redacted] from Baseline (Visit 2A) is [redacted] the participant will be up-titrated to 50 mg BID. If a participant is up-titrating, then dosing will start in the evening on the last dosing day for Treatment Period 1 (Visit 3A).

NOTE: If at the end of Treatment Period 1 (Visit 3A), the [redacted] from Baseline (Visit 2A) is [redacted], then study drug should be permanently discontinued (Section 6.2).

9.2.2 Part B:

Initial individual participant doses will be based on [redacted] in Part A, regardless of whether a participant has to be rescreened in Part B. The Part B starting dose can be either one of 5 mg BID, 10 mg BID, 25 mg BID, 50 mg BID, or 75 mg BID:

- If one of the doses in Part A resulted in a [redacted] and [redacted], then that will be the dose for Part B (10, 25, or 50 mg BID)
- If both doses in Part A resulted in a [redacted] and [redacted], then the dose for Part B is the lower of the 2 doses that the participant received in Part A
- If both doses in Part A resulted in a [redacted] of [redacted] with 10 and 25 mg BID, then the Part B dose for that participant is 50 mg BID
- If both doses in Part A resulted in a [redacted] of [redacted] with 25 and 50 mg BID, then the Part B dose for that participant is 75 mg BID
- If both doses in Part A resulted in a [redacted] of [redacted] with 10 and 25 mg BID, then the Part B dose for that participant is 5 mg BID
- If both doses in Part A resulted in a [redacted] of [redacted] with 25 and 50 mg BID, then the Part B dose for that participant is 10 mg BID
- If 25 mg BID dose from Part A [redacted] and 10 mg BID from Part A [redacted] 10 mg BID
- If 25 mg BID dose from Part A [redacted] and 50 mg BID dose from Part A [redacted] 25 mg BID

For participants who could not complete Part A or completed TTE assessments outside of the protocol defined window may participate in Part B after investigator discussion with the Sponsor. The reasons of incompletion of Part A should be due to reasons other than treatment-emergent adverse event (TEAE) considered as study drug related by the investigator, meeting study discontinuation criteria, or withdrawal of the informed consent. Part B starting dose for such cases is described in following 2 bullets.

- If [redacted] of both doses were unavailable or performed significantly outside of the assessment window (see Appendix 1. Part A SoA foot note g), then the Part B dose will be 50mg BID.
- If a [redacted] was only available with 25 mg BID (Treatment Period 1) and a [redacted] was [redacted] and [redacted], then 25mg BID is the dose for Part B. If a [redacted] was [redacted], then the Part B dose is 50 mg BID. If 25 mg BID dose resulted in a [redacted], then the Part B dose for that participant is 10 mg BID.

Part B dose adjustment:

After the initiation of Part B dosing, a TTE will be performed at Visit 2B and Visit 3B (2 weeks and 6 weeks after start of Part B dosing, respectively) to ensure adequate PD responses. [redacted] measured at these times from V1B will dictate dose adjustments as follows:

- If there is a [redacted] of [redacted] on both TTEs at Visits 2B and 3B compared from V1B, based on local assessment, the dose will be titrated up to the next dose level. If a participant is already receiving the highest dose (75 mg BID), per the Investigator's discretion, the participant will continue the study at 75 mg BID or discontinue from the study (Section 6.2).

- If there is a [redacted] of [redacted] on both TTEs from Visits 2B and 3B compared from V1B, based on local assessments, the dose will be titrated down to the next dose. If a participant is already receiving the lowest dose (5 mg BID), then the participant will be discontinued from the study (Section 6.2).
- If there is a [redacted] and [redacted] on at least one of TTEs from Visits 2B and 3B compared from V1B, based on local assessments, no dose change is needed.
- If [redacted] at Visit 2B and 3B are [redacted] at one visit and [redacted] at the other, no dose change is needed.

9.3 Treatment Compliance

Danicamtiv compliance will be monitored during clinic visits when the drug is returned to the site (with count of remaining unused tablets). In addition, in between the clinic visits, participants will be contacted for Telehealth Visits (telephone, 2-way text messaging, or e-mail) to ensure compliance with study treatment. Periodic assessment of danicamtiv plasma concentrations will also ensure compliance. During Part B of the study, an investigational product diary will be used to ensure compliance.

9.4 Guidelines for the Management of an Exaggerated Pharmacological Effect

Based on the nonclinical pharmacological characteristics, exaggerated effects of danicamtiv may lead to myocardial ischemia. Plasma peak concentration (C_{max}) is anticipated to be achieved at approximately 4 to 6 hours postdose. After reaching C_{max}, plasma concentrations declined in a mono-exponential manner with $t_{1/2}$ of approximately 22 to 25 hours. The clinical signs and symptoms, which may include chest pain, lightheadedness, diaphoresis, and ECG changes should start to abate over a short period of time. Any participant with signs and/or symptoms suggestive of cardiac ischemia should be immediately evaluated by the Investigator for the potential diagnosis of cardiac ischemia. The entire context including clinical symptoms, ECGs and serial cardiac biomarkers (eg, troponin, CK-MB), and cardiac imaging (including coronary angiography, if applicable) should be taken into account by the Investigator, in making that determination, since participants enrolled in the study are likely to have abnormal ECGs and possibly elevated or fluctuating troponin levels at Baseline in relation to their heart failure condition. If evidence of cardiac ischemia is present, then the participant should receive standard therapy for ischemia as appropriate, including supplemental oxygen and nitrates. [redacted] In addition, the exaggerated pharmacological effect may increase myocardial oxygen demand, so agents that may increase myocardial oxygen demand further should be administered with caution.

9.5 Overdose

There is no antidote for danicamtiv. Participants who receive a greater dose than planned should be supported as appropriate. If there is an exaggerated pharmacologic effect, the participants should be supported as described in Section 9.4.

Symptomatic and asymptomatic overdose is an adverse event of special interest (AESI; Section 12.1.3). If a participant experiences an overdose, the Investigator will report the overdose within 24 hours, even if there are no associated signs or symptoms. Follow up on the participant's condition will be conducted.

9.6 Concomitant Therapy

During the study, participants should continue to take medications for the treatment of heart failure and other medical conditions at the same doses and as close to the same times as usual, in order to maintain as best as possible similar preload and afterload conditions throughout the study and to minimize confounding factors for the assessment of the effects of danicamtiv.

All prescription and over-the-counter medications must be reviewed by the Investigator and should be recorded in the eCRF. Over-the-counter medications may be taken at stable doses throughout the study (at Investigator's discretion), and in amounts no greater than as directed per the label. Questions concerning enrollment or medications should be discussed with the Medical Monitor. Coadministration of danicamtiv with strong CYP3A4 inhibitors and strong CYP3A4 inducers should be avoided. [redacted] Use of biotin supplements should be avoided throughout the study. Multivitamins that contain biotin (vitamins B7, B8, or H) should be withheld for at least 24 hours prior to each study visit. Other investigational therapies must be discontinued at least 30 days prior to Screening or 5 half-lives (whichever is longer).

COVID-19 vaccine is not prohibited. If possible, participants should avoid receiving the vaccine within 14 days prior to Screening visit and Baseline visits (both study Parts A and B), and during study Part A.

If the participant has an AE requiring treatment (including the ingestion of acetaminophen or ibuprofen), the medication should be recorded in the appropriate section of the eCRF, including time of the administration (start/stop), date, dose, and indication.

10 RISKS AND PRECAUTIONS

10.1 General

In previous clinical studies, single doses of danicamtiv administered to healthy participants and heart failure participants in the dose ranges planned for this study were well -tolerated (Section 3.1).

In Study MYK-491-003, multiple doses of danicamtiv were administered for 7 days to heart failure participants, with doses of up to100 mg BID, greater than those tested in the current study (5 to 75 mg BID). This multiple-dose initial experience in heart failure has been taken into account for the selection of doses in the current MYK-491-006 trial (Section 4.2).

Based on the clinical experience accumulated with danicamtiv in about 120 participants (healthy participants and heart failure participants with 7-day dosing, ranging in heart failure patients from 50 to 100 mg BID, being generally well-tolerated), together with the favorable clinical experience observed with another agent from the same class in a large, cardiovascular outcome, Phase 3 study of ~8 000 HFrEF patients (Teerlink et al. 2021), the Sponsor considers it safe to administer danicamtiv at doses ranging from 5 to 75 mg BID for up to approximately 100 weeks in this study. The dose selected for Part B will be based on participants' response to doses they will have been exposed to in Part A, as well as the additional TTEs performed at Visits 2B and 3B, which will be used for dose titration.

Throughout the study, there will be regular interactions with participants, including serial assessments of clinical safety and tolerability, ECG, and laboratory evaluations. The Sponsor will closely monitor clinical safety (AEs and SAEs), as reported by Investigators. Treatment discontinuation criteria are described above (Section 6.2).

10.2 Pregnancy

10.2.1 Avoidance of Pregnancy

Women of childbearing potential are allowed to participate if they are not currently pregnant and/or breastfeeding and agree to not become pregnant for up to 3 months after the last dose of study drug. Women must use highly effective methods of birth control as listed in Section 10.2.3. Women of nonchildbearing potential are defined as women who are permanently (surgically) sterilized or are postmenopausal. Permanent sterilization includes documented hysterectomy, bilateral oophorectomy, bilateral salpingectomy, and/or bilateral tubal occlusion or ligation prior to Screening. Women are considered postmenopausal if they have had amenorrhea for at least 1 year following cessation of all exogenous hormonal treatments and FSH levels are in the postmenopausal range. Determination of WONCBP should be performed at Part A Screening and to be recorded in eCRF. Pregnancy tests (urine or blood determined by local requirements [eg, only serum is acceptable in the United Kingdom]) should be performed on WOCBP. Pregnant or lactating women are excluded from study participation.

10.2.2 Restrictions for Male Participants

There is no information about effects that danicamtiv could have on the development of the fetus in humans. Therefore, it is important that the partners of male participants do not become pregnant during the study and for a total period of 3 months after the male participant has taken the last dose of study drug. As a precaution, all male participants should avoid fathering a child by using appropriate methods of birth control, as listed in Section 10.2.3, for the duration of the study and for 3 months after the last dose of study drug to ensure a fetus is not potentially exposed to study drug in the ejaculate.

Due to the risk of danicamtiv being secreted in the ejaculate, male participants should be advised not to donate sperm during the study and for 3 months after the last dose of study drug.

In addition, male participants with partners capable of becoming pregnant should use barrier methods for the duration of the study and for 3 months after the last dose of study drug, including male participants who have had vasectomies.

10.2.3 Acceptable Forms of Contraception

Highly effective methods of birth control are defined as those that result in a low failure rate (< 1% per year) when used consistently and correctly. From the time of Screening through 3 months after the last dose of study drug, participants should practice true abstinence or use effective means of contraception as follows:

- Hormonal contraception associated with inhibition of ovulation, IUD, or IUS plus barrier (eg, male using condom or female using diaphragm or cervical cap)
- Vasectomy plus barrier
- Female is surgically sterile or is postmenopausal for 1 year. Permanent sterilization includes documented hysterectomy, bilateral oophorectomy, bilateral salpingectomy, and/or bilateral tubal occlusion or ligation prior to Screening. Females are considered postmenopausal if they have had amenorrhea for at least 1 year or more following cessation of all exogenous hormonal treatments, and FSH levels are in the postmenopausal range.
- Male partners of postmenopausal females

10.2.4 Reporting and Follow-up of Pregnancies

All pregnancies in female participants and female partners of male participants receiving at least 1 dose of study drug will be reported if they occur anytime from first dose to 3 months after the last dose of study drug. The Investigator is responsible for informing the Sponsor of the pregnancy. The participant will be asked to provide information on the outcome of the pregnancy, including premature termination, for 6 months after birth. Spontaneous miscarriages and congenital abnormalities will be collected as SAEs (Section 12.3).

11 STUDY ASSESSMENTS AND PROCEDURES

The Investigator is responsible for ensuring that all staff involved in the study are familiar and comply with the content of this section.

Procedures to be performed during the study are detailed in APPENDIX 1.

11.1 Pharmacodynamic Assessments

11.1.1 Transthoracic Echocardiography

The PD effect of danicamtiv will be evaluated throughout this study by serial TTE examination in accordance with an echo analysis protocol. TTE examination will be performed by the certified sonographers at each study site in accordance with an TTE site instruction manual. Sonographers in the study will complete TTE protocol training and submit an example of a study to the echo core laboratory for evaluation. The echo core laboratory will certify that the sonographer is able to perform the TTEs at a level satisfactory for obtaining the required protocol data.

The participants should be at rest for 10 minutes before the TTEs are obtained.

Transthoracic echocardiograms at all timepoints will be evaluated centrally by a core laboratory for research purposes. At Screening, each site will provide the protocol required images to the Echo Core Laboratory for echo eligibility assessments.

Measurement of [redacted] should be assessed locally at each site on Visit 2A, Visit 3A, Visit 1B, Visit 2B, and Visit 3B. This result should be reported in real time to the Investigator who will determine dosing for Treatment Period 2 at Visit V3A and dose titration, if needed, at Visit 3B (Section 6.1). For acquisition of [redacted] measurement, please refer to the TTE site instruction Manual.

The use of contrast is not recommended for this study and should only be used to optimize image quality in subjects that exhibit technically limited echo windows. If a participant is screened using contrast, then contrast must be administered for all subsequent study related TTE examinations, with the full protocol being obtained with and without contrast.

If echo contrast is used, the sonographer should first obtain the full set of protocol required images without contrast, and then provide additional images after contrast is administered at the end of the study. The full set of images must be transferred to the echo core laboratory and the use of contrast must be noted on the transmittal form.

Key TTE measurements will include, but not be limited to:

- Change in left ventricular [redacted]
- Change in left ventricular systolic function parameters
  - Left ventricular stroke volume (LVSV)
  - LVEF
  - Left ventricular strain parameters: global longitudinal (LVGLS) and circumferential strain (LVGCS)
  - Tissue Doppler imaging (TDI) of mitral valve annulus peak systolic velocity (s')
- Change in left ventricular dimensions:
  - Left ventricular end-systolic and end-diastolic diameters (LVESD, LVEDD)
  - Left ventricular end-systolic and end-diastolic volumes indexed for body surface area (LVEDVi, LVESVi)
- Change in left atrial volume and function:
  - Minimum and maximum LA volumes indexed for body surface area (LAminVi, LAmaxVi)
  - Left atrial emptying fraction (LAEF)
  - Left atrial function index (LAFI)
- Change in left ventricular diastolic function:
  - TDI of mitral valve annulus peak velocity in diastole (e', lateral, septal)
  - Ratio of peak inflow velocities in early and late diastole (E/A)
  - Ratio of early mitral peak inflow velocity to early mitral peak annulus velocity (TDI) (E/e') lateral, septal and average

These parameters will be PD assessments at the timepoints indicated in APPENDIX 1 (with a window of ± 1 hour).

11.1.2 Cardiac Magnetic Resonance Imaging

Part A: CMR will not be obtained in Part A.

Part B: CMR will be obtained in suitable participants (as determined by the investigator) at sites able to perform the examinations at V1B, week 48 (V8B), and week 96 (EOT).

The CMR image acquisition will be performed at each study site and transferred data will be analyzed at the CMR core lab as indicated in the instruction manual and the analysis manual, respectively. Subsequent examinations in those participants will be obtained at one-year intervals (within 4 weeks of each year anniversary on study). Each examination will follow a standard imaging protocol to include, but not be limited to, the following parameters:

- Change in left ventricular systolic function parameters
  - LVSV by phase contrast imaging of LV outflow
  - LVEF by volumetric assessment of short axis stack images
  - LVGLS and LVGCS
- Change in left ventricular dimensions:
  - LVEDVi and LVESVi
- Change in left atrial volume and function:
  - LaminVi and LamaxVi
  - LAEF
  - left atrial reservoir emptying fraction (LarEF
  - left atrial active emptying fraction (LaaEF)

CMR data at all timepoints will be evaluated by a CMR core lab. CMR technologists and devices at sites will undergo training per the specifications of the CMR core lab where they will then be certified to perform CMR for this study.

11.1.3 6-Minute Walk Distance (6MWD)

Part A: The 6MWD will not be conducted in Part A.

Part B: The distance that a participant can walk in 6 minutes (6MWD) will be assessed at Baseline (prior to dosing; within 2 weeks of beginning Part B) per the study-specific 6MWD manual and qualified course at the study sites. Thereafter, the same assessment at the same course will be obtained at approximately 24-week intervals throughout Part B.

Personnel responsible for conducting the 6MWD at the study sites will undergo training and certification by a vendor provided by the Sponsor

11.2 Efficacy Assessments

11.2.1 Exploratory Assessments

11.2.1.1 New York Heart Association Functional Classification

The NYHA Functional Classification of heart failure assigns participants to 1 of 4 categories based on the participant's symptoms (Table 2). Heart failure classification will be assessed by the Investigator as indicated in APPENDIX 1.

Table 2: New York Heart Association Functional Classification of Heart Failure

Class	Patient Symptoms
I	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea (shortness of breath).
II	Slight limitation of physical activity. Comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea (shortness of breath).
III	Marked limitation of physical activity. Comfortable at rest. Less-than ordinary-activity causes fatigue, palpitation, or dyspnea.
IV	Unable to carry on any physical activity without discomfort. Symptoms of heart failure at rest. If any physical activity is undertaken, discomfort increases.

Source: http://www.heart.org/HEARTORG/Conditions/HeartFailure/AboutHeartFailure/Classes-of-Heart-Failure_UCM_306328_Article.jsp#.VrtuzPkrKUl

11.2.1.2 Kansas City Cardiomyopathy Questionnaire (23-item Version)

The Kansas City Cardiomyopathy Questionnaire (23-item version) is a patient reported questionnaire that measures the impact of participants' cardiovascular disease or its treatment on 6 distinct domains using a 2-week recall: symptoms/signs, physical limitations, quality of life, social limitations, self-efficacy, and symptom stability (Green et al, 2000). In addition to the individual domains, 2 summary scores can be calculated from the KCCQ-23: the overall summary score (includes the total symptom, physical limitation, social limitations and quality of life scores) and the clinical summary score (combines the total symptom and physical limitation scales). Scores range from 0 to 100, with higher scores reflecting better health status. The KCCQ-23 will be administered to participants as indicated in APPENDIX 1. The KCCQ-23 assessments completed at visits (except at Screening) should be completed prior to any other study procedure taking place, where possible, and prior to any meaningful discussion about the study or study treatment with investigative site staff.

11.3 Plasma Concentration, Pharmacogenetic, and Biomarker Assessments

11.3.1 Plasma Concentration Assessments

Blood samples will be collected for plasma concentration assessments as indicated in APPENDIX 1. It is important that sampling occur as close as possible to the scheduled time. Unscheduled or additional samples may be collected, if appropriate in the opinion of the Investigator and/or

Sponsor. If an unscheduled TTE or visit to evaluate possible ischemia is performed by the Investigator, a plasma sample should also be collected at this timepoint.

11.3.2 Genetic/Genotype/Pharmacogenetic/Biomarker Assessment

Beside genetic testing for variants associated with cardiomyopathies that is mandatory, all participants will have the option to provide consent for blood to be drawn for potential future analysis of circulating biomarkers or genetic markers in relation to efficacy, safety, PD, or plasma concentration, as determined by future studies through DNA genotyping, direct sequencing, or other genetic testing modalities, unless there are local regulations prohibiting these analyses. If genetic or pharmacogenetic studies are conducted, genetic information will not be returned to participants. Pharmacogenetic samples could be used as a source of DNA for genotyping or sequencing of cardiomyopathy genes.

11.4 Safety Assessments

Safety will be assessed throughout the study as indicated in APPENDIX 1. Safety assessments include medical history, physical examinations, [redacted] as determined by TTE, triplicate 12-lead ECGs, vital signs, observed and participant-reported AEs, serum troponin concentrations, and safety laboratory tests.

The Sponsor will closely monitor safety on an ongoing basis.

Any abnormal findings judged by the Investigator to be clinically important (new or worsened from Baseline) will be recorded as an AE which will be reviewed by the Sponsor.

11.4.1 Medical History

A complete medical history will be recorded at the Screening visit, which will include evaluation (past or present) of the cardiovascular and heart failure medical history as well as the following: general, head and neck, eyes, ears, nose, throat, chest/respiratory, gastrointestinal/liver, gynecological/urogenital, musculoskeletal/extremities, skin, neurological/psychiatric, endocrine/metabolic, hematologic/lymphatic, allergies/drug sensitivities, past surgeries, substance abuse, or any other diseases or disorders as well as participation in clinical studies (study drug and/or device or other therapy).

11.4.2 Vital Signs

Vital signs will be assessed throughout the study as indicated in APPENDIX 1 and will include temperature, HR, and blood pressure (BP). HR and BP shall be the mean of 3 measurements taken with the participant in a supine position after resting for at least 5 minutes.

11.4.3 Physical Examination

Height (cm) and weight (kg) will be measured at Screening and timepoints indicated in APPENDIX 1.

A complete physical examination will be conducted including a neurological examination (gross motor and deep tendon reflexes), and assessment of the following: general appearance, skin, head and neck, mouth, lymph nodes, thyroid, abdomen, musculoskeletal, cardiovascular, neurological,

and respiratory systems. At all other timepoints, an abbreviated physical examination (pulmonary, cardiac, abdominal, and other systems related to symptoms) will be conducted.

11.4.4 Electrocardiograms (12-Lead ECG)

The triplicate 12-lead ECG should be obtained as indicated in APPENDIX 1. The Investigator may add extra 12-lead ECG assessments if there are any abnormal findings or if the Investigator considers it is required for any other safety reason. If the participant has a new troponin abnormality (Section 11.4.6) or any signs or symptoms suggestive of possible cardiac ischemia, additional ECGs should be obtained. These assessments should be recorded as unscheduled assessments. All study ECGs will be read locally and sent to an ECG core laboratory.

The Investigator will judge the overall interpretation as (a) normal, (b) abnormal without clinical significance, or (c) abnormal with clinical significance. If clinically significant, the abnormality will be recorded. In addition, at each visit, the Investigator or sub-investigator should compare the available ECGs at the visit to those from the prior visit. If there are signs of ischemia, dosing should be withheld until there is full understanding of the possible ischemic changes.

In addition, at Visit 3A and Visits in Part B, the Investigator should evaluate the triplicate 12-lead ECGs and confirm lack of QTcF prolongation (Section 6.2) to continue treatment with study drug. The Investigator will review the ECG and correlate abnormal findings with any other clinical findings, participant's medical history, and laboratory data to determine the clinical importance of the finding.

11.4.5 Extended Cardiac Rhythm Monitoring

Part A: If using historical LVEF to qualify a participant, a cardiac rhythm monitoring patch will be placed at the first Screening visit (Visit 1.1A). If using 2 Screening TTEs, the patch will be placed at the time of the second Screening visit (Visit 1.2A). A new patch will be placed at the start of Treatment Period 1, after dosing.

Part B: A cardiac rhythm monitoring patch will be placed at Visits 1B, 6B, 8B, 10B, and EOT.

The duration of monitoring will range from 5-14 days. If the patch becomes detached prior to 5 days, a new patch should be placed as soon as possible. Once the patch detaches (after at least 5 days), participants will be instructed to mail the patch back to the site.

11.4.6 Troponin Levels

In Part A, hsTnT, TnI, and hsTnI samples will be collected at timepoints as indicated in APPENDIX 1. Samples will be analyzed at a central laboratory at all clinic visits after Part A Screening (Visits 1.1A to Visit 5A). There are no discontinuation criteria related to troponin levels in Part A.

In Part B, TnI (standard and high-sensitivity) and hsTnT samples will be collected as described in APPENDIX 1 and analyzed by the central laboratory.

In Part B, troponin increase will be defined as:

1) If TnI (standard) level is below ULN at Baseline (value obtained at Visit 1B) and subsequently increases to more than 0.05 ng/mL on any assay after start of dosing

2) If the TnI (standard) level is above the ULN at Baseline and then subsequently rises by more than 0.05 ng/mL above the participant's Baseline value (obtained at Visit 1B) on any assay after start of dosing.

If either of these conditions are met from start of Visit 1B to Visit 6B (week 24) and the absolute TnI (standard) level is below 0.1 ng/mL, the totality of the clinical data will be reviewed by the Coordinating Investigator, the consulting Safety Reviewer, and the Sponsor's Medical Monitor periodically to determine if any signs of ischemia are seen. During this time, the participant will continue to take danicamtiv at the same dose. Subsequent telehealth visits will be transitioned to in-person clinic visits with 12-lead ECGs and troponin tests until troponin levels are stable or declining.

If the TnI (standard) level exceeds 0.1 ng/mL, at any time, the participant will be asked to return for repeat evaluation as soon as possible. If this level of TnI (standard) is confirmed, treatment with danicamtiv will be temporarily discontinued and an ad hoc review by the Coordinating Investigator, the consulting Safety Reviewer, and the Sponsor's Medical Monitor will be triggered.

Abnormal and/or rising troponin values (as per Investigator's judgment and considering potential Baseline troponin elevation frequently observed in heart failure) should lead to the participant being clinically evaluated for possible myocardial ischemia. Also, if the participant has any signs or symptoms suggestive of possible cardiac ischemia, additional serial troponin (and other safety labs, including CK-MB samples) should be obtained and subsequent dosing should be withheld until there is full understanding of the possible ischemic event. The Investigator will evaluate the entire clinical context (eg, signs, symptoms, new ECG changes, new troponin, and CK–MB abnormalities) and correlate with any other relevant clinical findings, participant's medical history, and laboratory data to determine the clinical significance of the findings.

If the Investigator assessment is that an AE has occurred, the event should also be reported as an AE accordingly (Section 12).

11.4.7 Adverse Events

Please see Section 12 for information on evaluating, recording, and reporting AEs.

11.4.8 Safety Laboratory Tests (Other Than Troponin)

Samples will be drawn for safety laboratory tests at the timepoints indicated in APPENDIX 1. At Screening, assessments will be made by the central laboratory. If the Investigator has any questions regarding eligibility, the Sponsor should be contacted.

Screening laboratory testing will include thyroid-stimulating hormone (TSH) and iron (Fe)/total iron-binding capacity (TIBC)/ferritin to exclude uncontrolled thyroid functions and Fe overload.

11.5 Missed Evaluations

Evaluations should occur within the assessment window specified by the protocol. If an evaluation is missed, it should be performed as close as possible to the original time.

11.6 Participant Restrictions During the Study

Starting at Screening and throughout the study, participants should be instructed to maintain a stable lifestyle. This includes but is not limited to:

- Concomitant medications: every effort should be taken to maintain stable doses of concomitant medications, and to take such medications at consistent times during the day; for cardiovascular drugs, this will allow to minimize variability in cardiac loading conditions.
- Activity levels:
  - In Part A, from 72 hours prior to the first dose through the Follow-up visit, participants should not engage in unaccustomed intensive exercise.
  - In Part B, participants should follow their customary exercise regimen and not engage in unaccustomed intensive exercise. Any planned increase in the amount of regular physical exercise should be discussed with the Investigator prior to commencing.
- Meals/food:
  - Abstain from grapefruit or grapefruit juice, Seville oranges, and quinine (eg, tonic water).
- Fluid intake: maintain usual daily fluid intake and avoid excessive alcohol consumption.

In addition, starting at Screening, participants will be required to abstain from blood or plasma donation until 3 months after the final study visit.

Contraception requirements are discussed in Section 10.2.

If participants are participating in Part B observational study, this restriction will not apply.

12 EVALUATION, RECORDING, AND REPORTING OF ADVERSE EVENTS

12.1 Definitions

12.1.1 Adverse Event

An AE is any untoward medical occurrence, or the deterioration of a preexisting medical condition (other than the condition that is being treated by the study) associated with the use of a study drug in humans, whether or not it is considered related to the study drug. An AE (also referred to as an adverse experience) can, therefore, be any unfavorable and unintended sign (eg, tachycardia, enlarged liver, clinically important abnormal laboratory result or diagnostic procedure), participant-reported symptom (eg, nausea, chest pain), or evidence of any disease activity temporally associated with the use of a study drug, whether or not related to the study drug.

In clinical studies, an AE can include an undesirable medical condition occurring at any time after the participant has signed informed consent, including run-in or washout periods, even if no specific treatment has been administered.

Preexisting medical conditions (other than natural progression of the disease being studied) judged by the Investigator or participant to have worsened in severity or frequency or changed in character during the protocol-specified AE reporting period will be reported as AEs or SAEs as appropriate.

Imaging-based assessments of decrease in contractility are not considered AEs unless associated with symptoms or signs of clinical concern on the part of the Investigator. Such events should be categorized as an AE defined in terms of those symptoms or signs.

An AE or SAE can also be a complication that occurs as a result of protocol-mandated procedures (eg, procedures such as blood draws).

For the Sponsor to collect additional information about clinically important laboratory results or diagnostic tests (eg, blood, ECG, imaging), at a minimum, the following abnormalities should be captured on the AE eCRF:

- Any test result that meets the definition of an AE.
- Any clinically important test abnormality that suggests a disease and/or organ toxicity that has worsened or is new (eg, > 3 times deviation from the upper or lower limit of the analyzing laboratory reference range, or as otherwise specified in the protocol).
- Any test abnormality that requires the participant to have study drug discontinued or interrupted or in the clinical judgment of the Investigator.
- Any test abnormality that requires the participant to receive specific corrective therapy, close observation, more frequent follow-up assessment, or further diagnostic investigation.

The term AE is used generally to include any AE whether serious or nonserious.

12.1.2 Serious Adverse Events

An SAE is an AE that fulfills one or more of the following criteria:

- Results in death
- Is immediately life-threatening (places the participant at immediate risk of death from the event as it occurred)
- Requires in-participant hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity or substantial disruption of the ability to conduct normal life functions
- Results in a congenital abnormality or birth defect
- Is an important medical event that may not result in death, be life-threatening, or require hospitalization, but may be considered an SAE when, based upon appropriate medical judgment, it may require medical or surgical intervention to prevent 1 of the outcomes listed above

12.1.3 Adverse Events of Special Interest

Overdose (asymptomatic and symptomatic) and increased troponin are considered AESI; AESIs are required to be reported by the Investigator to the Sponsor within 24 hours, irrespective of regulatory seriousness criteria.

Increased troponin will be captured as an AESI under the following conditions: if the participant's TnI (standard) level reaches a level greater than 0.1 ng/mL on any assay after the start of dosing.

12.2 Events NOT Meeting the Definition of an Adverse Event

If an event is not an AE, then it cannot be an SAE, even if the event outcome meets the definition for seriousness defined by the criteria in Section 12.1.2. Instances where an event is not an AE include:

- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or hospital admission/extension for convenience).
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition.
- Anticipated day-to-day fluctuations of preexisting disease(s) or condition(s) that are present or detected at the start of the study that do not worsen.
- Hospitalization for a preexisting condition, provided all of the following criteria are met:
  - The participant has not experienced an adverse event.
  - The hospitalization was planned prior to the study or was scheduled during the study when elective surgery or procedure became necessary because of the expected normal progression of the disease.

12.3 Reporting Period and Follow Up

All AEs will be reported throughout the duration of the study. The duration of the study is defined from the time the participant provides informed consent until the End of Study Visit for the participant. Preexisting medical conditions that increase in severity from the first dose of study drug will be reported as AEs.

Any AEs that are unresolved at the participant's last visit in the study are to be followed by the Investigator until resolved or stabilized and are considered irreversible, or the participant has died/lost to follow up. Deaths and new SAEs are to be reported even after end of study if they occurred within 30 days after the last study drug administration for each participant. If death or new SAEs are considered related to study drug or study procedures by the investigator, they must be reported even after this term. All SAEs will be entered into the safety database and handled in the same manner as SAEs reported during the treatment-emergent period; that is, causality will be assessed by both Investigator and Sponsor and if the SAE is deemed a suspected unexpected serious adverse reaction (SUSAR) (related and unexpected), will be submitted to regulators (as applicable) in an expedited fashion.

The Sponsor retains the right to request additional information for any participant with ongoing AE(s)/SAE(s) at the end of the study, if deemed necessary.

All SAEs (and AESIs, regardless of seriousness), regardless of causality, will be reported by the Investigator or designee to the Sponsor or its designee immediately, without undue delay, under no circumstances later than 24 hours after learning of the event. All follow-up information for previously reported SAEs will also be reported to the Sponsor or its designee within 24 hours of knowledge.

12.3.1 Recording and Assessing Adverse Events

12.3.1.1 Description

All AEs spontaneously reported by the participant or reported in response to the open question from the study personnel: *"Have you had any health problems since you were last asked?"* or revealed by observation will be collected and recorded in the eCRF.

When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms (eg, anemia, not low hemoglobin). However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

Death is an outcome and not the name of the event. Every effort should be made to determine the cause of death.

12.3.1.2 Relationship to Study Treatment

The Investigator should assess causality by answering either "yes" or "no" to the question *"Is there a reasonable possibility that the event may have been caused by the IMP/study medication?"*

The following factors can be used in consideration of causality assessment:

- De-challenge/re-challenge: Did the event abate after study drug was reduced or interrupted? Did the event reappear after study drug was reintroduced?
- Temporal relationship and time to onset plausibility
- Confounding risk factors
- Amount and duration of study drug exposure
- Concomitant medications

Adverse Drug Reaction (ADR): An ADR is any untoward medical occurrence, or the deterioration of a preexisting medical condition associated with the use of a study drug in humans, when the Investigator/Sponsor has a reason to assess it as at least possibly related to the study drug. An ADR can, therefore, be any unfavorable and unintended sign (e.g., tachycardia, enlarged liver, clinically important abnormal laboratory result, or diagnostic procedure), participant-reported symptom (e.g., nausea, chest pain), or evidence of any disease activity temporally associated with the use of a study drug which, is assessed by investigator/sponsor as related to the study drug.

Serious Adverse Reaction (SAR): An SAR is an ADR that fulfills one or more of the following criteria in the opinion of the Investigator or the Sponsor:

- Results in death
- Is immediately life-threatening (places the participant at immediate risk of death from the event as it occurred)
- Requires in-participant hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity or substantial disruption of the ability to conduct normal life functions
- Results in a congenital abnormality or birth defect
- Is an important medical event

12.3.1.3 Severity

The Investigator will assess the intensity of each AE and SAE reported during the study and assign it to one of the following categories:

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event causing sufficient discomfort and interferes with normal everyday activities.
- Severe: An event preventing normal everyday activities. An AE that is assessed as severe should not be confused with a SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.
- An AE is defined as serious when it meets the regulatory definitions as outlined in Section 12.1.2. An SAE can also be severe but not all severe AEs are SAEs.

Note: It is important to distinguish between category (AE vs. SAE) and intensity (mild, moderate, or severe) of AEs.

Severity is a measure of intensity, whereas seriousness is defined by the criteria stated above.

An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea but not an SAE. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be an SAE.

12.3.1.4 Pregnancy

Pregnancy in a female participant or if the partner of a male participant becomes pregnant during the study or for a period of 3 months after the male participant has taken the last dose of study drug, is not an SAE, but must be reported within the same timelines as an SAE. Pregnancies will be followed until final outcome and live births will be followed for 6 months after birth. Pregnancy reporting instructions are provided in the Investigator Site File.
Spontaneous miscarriages and congenital abnormalities will be collected as SAEs (see Section 10.2.4).

12.3.1.5 COVID-19 Vaccine

Any AEs or suspected ADRs to the COVID-19 vaccine should be reported through the appropriate regulatory system(s). However, if an AE is considered to be the result of an interaction with the study drug in the trial then the safety assessment and reporting protocols should be followed (see Section 12.3). If the event is serious and considered related to both the COVID-19 vaccine and the study drug then it becomes a SAR. Expectedness will be assessed and SUSAR reporting will be initiated if the SAR is unexpected.

13 STATISTICAL METHODS

13.1 Determination of Sample Size

The sample size for Part A of approximately 40 completed participants (approximately 12 participants with MYH7 variant, approximately 12 participants with TTN variant, and

approximately 16 participants with DCM not related to MYH7 or TTN variant) has been selected empirically to assess the effect size of danicamtiv on the various PD measurements and to provide a preliminary assessment of safety and tolerability in this patient population. There is no target sample size for Part B because it is an optional part of the study.

13.2 Study Endpoints

13.2.1 Primary Endpoint

Primary endpoints are clinical safety and tolerability as assessed by the following:

- Frequency of AEs and SAEs in Part A
- Frequency of clinically significant abnormalities from vital signs, AEs, physical examination, ECG recordings, and safety labs in Part A

13.2.2 Secondary Endpoints

Change in the following PD parameters, as assessed by TTE from Baseline corresponding to Parts A and B of the study:

- Left ventricular [redacted]
- Parameters of left ventricular systolic function including, but not limited to, LVSV, LVEF, left ventricular strain (LVGLS and LVGCS), and TDI of mitral valve annulus peak systolic velocity (s')
- Parameters of left ventricular dimensions including LVESD, LVEDD, LVEDVi, and LVESVi
- Parameters of left atrial volume and function including, but not limited, to LAmaxVi, LAminVi, LAEF, and LAFI
- Parameters of left ventricular diastolic function including, but not limited to, TDI of mitral valve annulus peak velocity in diastole (e', lateral, septal), ratio of peak inflow velocities in early and late diastole (E/A), ratio of early mitral peak inflow velocity to early mitral peak annulus velocity (TDI) (E/e') lateral, septal, and average.

13.2.3 Exploratory Endpoints

The following are exploratory endpoints:

- [redacted] will be summarized by the cohort (MYH7, TTN, and other DCM) using descriptive statistics
- Clinical safety and tolerability as assessed by the following:
  - Frequency of treatment-emergent adverse events and serious adverse events in Part B
  - Frequency of clinically significant abnormalities from vital signs, adverse events, physical examination, ECG recordings, and safety labs in Part B
- Additional exploratory endpoints, including concentration-PD effect and soluble biomarkers of cardiac physiopathology may be included
- Frequency of left ventricular reverse remodeling (LVRR) during Part B, defined by the following criteria (Escobar-Lopez et al, 2021) by TTE and CMR (if any):
  - either LVEF normalization (LVEF improvement to ≥ 50% with a ≥ 5% LVEF increment from baseline)
  - or an absolute increase in LVEF by ≥ 10% at the study visits from baseline.

- Frequency of improvements in LVEF during Part A, defined by the following criteria:
  - either LVEF normalization (LVEF improvement to ≥ 50% with a ≥ 5% LVEF increment from baseline to each post-dose TTE)
  - or an absolute increase in LVEF by ≥ 10% from baseline to each post-dose TTE

13.3 Statistical Analysis

Before database lock, a statistical analysis plan (SAP) for clinical data will be finalized that will contain full details of all planned analyses. Additional reviews may be conducted by the Sponsor at any time during Part A. The analyses presented here represent an outline of the intended methodology.

13.3.1 Analysis Populations

Three analysis populations are defined in this study: the Safety population, the PD Analysis population, and the PK population.

The Safety population is defined as participants who are enrolled and receive any amount of study drug (danicamtiv), including participants who prematurely withdraw from the study. Except as noted, all safety analyses, including demographic and baseline characteristics, will be performed based on the Safety population. The PD (Pharmacodynamic) population is defined as participants who receive any amount of study drug (danicamtiv), have any interpretable PD data, and have no critical or major protocol deviations related to the study drug (eg, incomplete ingestion of the drug, vomiting up to 8 hours after drug administration). The PD analyses will be performed based on the PD population.

The PK (Pharmacokinetic) population is defined as participants who receive any amount of danicamtiv, have detectable plasma concentration data, and have no major or critical protocol deviations related to the study drug (e.g., incomplete ingestion of the drug, vomiting up to 8 hours after drug administration). Plasma concentration data for danicamtiv will be summarized for the PK population.

13.3.2 General Considerations

Clinical data will be summarized by cohort (MYH7, TTN, and DCM by other causalities), and by dose in each Part, and combined. For MYH7 and TTN cohorts, data may be summarized by variant type and the location. For DCM cohort, data will be further evaluated by genetic mutation positive and genetic mutation negative variable. If positive genetics are identified, additional analysis may be performed by variant type. Depending on reports from central genetic testing laboratory, participant reallocation to adequate cohort and additional analysis may be performed. Descriptive summary statistics for continuous variables will include the number of participants, mean, standard deviation (SD), median, minimum, and maximum. Categorical variables will be summarized using counts and percentages.

13.3.3 Participant Disposition

The number and percentage of participants who complete or discontinue the study, as well as reasons for early discontinuation, will be presented separately for Part A and Part B.

13.3.4 Demographics and Baseline Characteristics

Demographic and Baseline characteristics will be summarized descriptively.

13.3.5 Pharmacokinetic Analyses

Plasma concentration data for danicamtiv will be summarized using descriptive statistics, including mean or geometric mean as appropriate, SD, median, minimum and maximum values, and coefficient of variation % (CV%). No PK analyses will be performed.

13.3.6 Pharmacodynamic Analyses

Transthoracic echocardiography data including, but not limited to, [redacted], parameters of LV and LA structure and function, in addition to assessments of LV diastolic function will be analyzed by variant cohort using descriptive statistics. Observations by timepoint and change from Baseline (either absolute or percent relative change) at each timepoint will be summarized by cohort and by dose in both Part A and Part B.

The parameters assessed at each timepoint and change from Baseline, which corresponds each Part of the study, will be summarized in the table. The data will be also presented in the figure and listings.

13.3.7 Safety Analyses

All safety analyses, except [redacted] as determined by TTE, will be performed on the Safety Analysis population. Analyses of [redacted] as determined by TTE, will be performed on the PD Analysis population.

The safety analysis will focus on the treatment-emergent period, which is defined as the time from the first administration of study drug to 14 days after the last administration of study drug.

13.3.7.1 Adverse Events

Adverse events will be mapped to system organ classes and preferred terms using the Medical Dictionary for Regulatory Activities (MedDRA). Adverse events will be monitored during the study, and the data analyzed with respect to overall incidence as well as severity and potential relationship of AEs to study drug. AEs with onset on or after the first dose of study drug to 14 days after the last administration of study drug will be considered treatment-emergent AEs (TEAEs). AEs with an onset before the first dose of study drug that increase in severity on or after the first dose of study drug will also be monitored. Treatment-emergent AEs will be summarized by variant cohort, MedDRA system organ class and preferred term, and by severity and relationship to study drug. All TEAEs, all treatment-emergent SAEs, and all TEAEs leading to study withdrawal or treatment discontinuation, if any, will be presented in data listings.

13.3.7.2 12-lead Electrocardiogram

The triplicate 12-lead ECG data will be utilized to measure RR, PR, QRS, and QT intervals in milliseconds, rounded to the nearest integer. HR will be calculated by the instrument per the device algorithm and rounded to the nearest integer. QT will be corrected for HR using Fridericia's formula.

Changes in ECG wave morphologies and intervals from the Baseline tracing will be analyzed and reported.

13.3.7.3 Other Safety Analyses

Safety laboratory data including hematology, chemistry, and vital signs will be evaluated by timepoint for the Safety Analysis population using descriptive statistics. Changes from Baseline at each post-Baseline timepoint will also be assessed. Listings of participants with laboratory and/or vital sign values that are observed to be out of the reference range will be produced. Abnormal physical examination results will be listed. Concomitant medications will be summarized.

13.3.8 Exploratory Analyses

[redacted] will be summarized by variant cohort using descriptive statistics.

Additional exploratory analyses may be performed. Detailed planned exploratory analyses will be specified in the SAP.

14 STUDY COMPLIANCE AND ETHICAL CONSIDERATIONS

14.1 Compliance Statement

This study will be conducted in compliance with the protocol and in accordance with the International Council for Harmonisation (ICH) Good Clinical Practice (GCP) guidelines; US Title 21 Code of Federal Regulations (CFR) Parts 11, 50, 54, 56, and 312; European Union (EU) GCP; cGMP; EU Clinical Trials Regulation (CTR) 536/2014 for clinical studies (if applicable); the principles enunciated in the Declaration of Helsinki; and all human clinical research regulations in the countries where the study is to be conducted.

14.2 Informed Consent

The ICF used for the study must comply with the Declaration of Helsinki, US 21 CFR Part 50, ICH GCP guidelines, and any other local regulations. The Investigator, or a person delegated by the Investigator, must explain the medical aspects of the study including the nature of the study and the treatment, orally and in writing, in such a manner that the potential participant is aware of potential benefits and risks. Potential participants must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. Participants must give informed consent in writing.

Prior to participation in any study-related procedures, participants must sign and date an Ethics Committee (EC)-approved written ICF in a language the participant can understand. The informed consent process must be conducted, documented in the source document (including the date), and the form must be signed before the participant undergoes any study-specific- procedures.

The language in the written information about the study should be as nontechnical as practical and should be understandable to the potential participant. Before informed consent is obtained, the Investigator should provide the potential participant ample time and opportunity to inquire about the study and to decide whether or not to participate.

All questions about the study should be answered to the satisfaction of the participant. The written ICF should be signed and personally dated by the participant and by the person who conducted the informed consent discussion. All participants will receive a copy of his/her signed and dated ICF.

14.3 Ethics Committee

The term EC used in this document refers to an Institutional Review Board (IRB) or Independent Ethics Committee (IEC) or equivalent. The EC must review and, if appropriate, approve the following documents, as applicable:

- Study protocol and amendment(s)
- Written ICF(s) and consent form updates
- Participant recruitment procedures/documents (eg, advertisements)
- Written information to be provided to participants
- IB and available safety information (Note: ECs do not approve IBs but are responsible for acknowledging receipt)
- Information about payments and compensation available to participants

The EC approval must be in writing, clearly identifying the study (by protocol date and/or version), the documents reviewed (including informed consent), and the date of the review. The Investigator has the responsibility to provide the Sponsor with the written EC approval prior to initiating any study-related procedures.

The Investigator also has the responsibility to inform the EC of the following according to the EC's policy:

- All SUSARs
- Any new information that may affect adversely the safety of the participants or the conduct of the trial
- Protocol deviations
- A synopsis of the study report upon study completion

Documentation of subsequent reviews of the study must also be forwarded to the Sponsor.

15 ADMINISTRATIVE PROCEDURES

15.1 Sponsor's Responsibilities

The Sponsor reserves the right to terminate the study at any time for any reason. The Sponsor and the Investigators will assure that adequate consideration is given to the protection of the participants' interests. The Sponsor retains the right to terminate the study and remove all study materials from a clinical site at any time. Specific circumstances that may precipitate such termination include:

- Request by Health Authority to terminate the study
- Unsatisfactory participant enrollment with regard to quality or quantity
- Significant or numerous deviations from study protocol requirements, such as failures to perform required evaluations on participants, maintain adequate study records or inaccurate, incomplete, or late data recording on a recurrent basis

- The incident or severity of AEs in this or other studies indicating potential health hazard caused by the study drug

15.1.1 Participant Confidentiality

The processing of personal data in pursuit of this study will be limited to those data that are reasonably necessary to investigate the utility of the study drugs used in this study. These data will be processed with adequate precautions to ensure confidentiality according to applicable laws.

The Sponsor ensures that the personal data are:

- Collected for a specified and legitimate purpose
- Processed fairly and lawfully
- Accurate and up to date

Explicit consent for the processing of personal data will be obtained prospectively from the participating participant.

The Sponsor, whose responsibilities require access to personal data, agrees to keep the identity of participants confidential. This confidentiality will be maintained throughout the complete data processing.

Participants will be entitled to request confirmation of the existence of personal data held by the Sponsor and will have the right to rectify erroneous or inaccurate data up until database lock.

15.1.2 Study Supplies

The Sponsor will supply or ensure the coordination of sufficient quantities of the following materials to each clinical site:

- Activity monitor
- Cardiac rhythm monitoring patch
- Danicamtiv (MYK-491) tablets
- ECG equipment
- IB for danicamtiv
- Laboratory manual
- Laboratory test kits
- Pharmacy manual

15.1.3 Investigator Training

A site-specific study initiation meeting and/or an Investigator Meeting will be held to ensure the center staff understands the protocol, study requirements, and data capture processes. This training will take place before the first participant is enrolled. The clinical site will be provided with information regarding GCP and regulations specific to the conduct of the clinical studies. The clinical site will be responsible for ensuring that new team members are adequately trained, and the training is documented.

15.1.4 Ongoing Communication of Safety Information During the Study

The Sponsor will provide the Investigator with documentation of SAEs from the study and other studies with danicamtiv that are unexpected, as appropriate. The Investigator must forward this documentation to the EC as described in Section 14.3.

The Sponsor will also notify the Investigator about any other significant safety findings that could alter the safety profile of the study drug from what is described in the protocol and significantly affect the safety of participants, affect the conduct of the study, or alter the EC's opinion about the continuation of the study.

15.1.5 Study Monitoring

The Sponsor will monitor this clinical study through remote data checks and monitoring visits to check the adequacy of clinical site staff and facilities, and to ensure adherence to the protocol, study procedures, and applicable regulations. The clinical site monitor will also assess proper eCRF completion and source document retention. The Investigator and clinical site staff are expected to provide adequate space for monitoring visits and to allocate sufficient time to permit adequate review of the study's progress. The Investigator will permit study-related monitoring, audits, EC review, and regulatory inspection(s), providing direct access to source data/documents and study-related facilities (eg, pharmacy, diagnostic laboratories).

15.1.6 Study Auditing and Inspecting

The Sponsor may audit the study conduct, compliance with the protocol, and accuracy of the data.

The Investigator(s)/institution(s) will permit study-related monitoring, audits, and inspections by the Sponsor, EC, government regulatory authority(ies), and the Sponsor's quality assurance personnel or its designees by providing direct access to source data/documents after appropriate notification from the Sponsor.

15.2 Investigator's Responsibilities

15.2.1 Study Data Definition

"Study Data" refers to all participant clinical data, primary and summary, laboratory data, and associated imaging data that are generated in connection with the performance of conducting the study, and required to be compiled in CRFs and/or submitted to the Sponsor as a deliverable under the Protocol. Such "Study Data" shall include data collected or prepared by Institution or Investigator in determining whether a study participant satisfies the enrollment criteria for the study or in the performance of the study. These data may be contained in CRFs or electronic data records, as well as any other documents or materials created for the study (e.g., TTE, CMR, or other types of medical images, ECG, or other types of tracings/printouts, or data summaries) and all recorded original observations and notations of clinical activities.

15.2.2 Screening Log

The Investigator must keep a record that lists all participants who signed an ICF and the reason for non-inclusion if the potential participant does not ultimately enroll and not receive study drug.

15.2.3 Danicamtiv Accountability

The Investigator must ensure that the study drug at the investigational site is kept secured and accounted for with access limited to only those individuals authorized by the Investigator. The Investigator, his/her designee, or pharmacist must also maintain adequate records of distribution, dispensing, and all study drug to be able to reconcile the study drug records (accountability or dispensing logs) at the end of the study.. The study medication records must be readily available for inspection by the (unblinded) site monitor and/or auditor. In general, no study medication can be returned to Sponsor/clinical site or disposed of at the clinical site until the clinical site monitor has verified the accuracy of the study medication records at the clinical site and indicated whether the medication should be destroyed at the clinical site or returned to Sponsor/designee

15.2.4 Reporting and Recording of Study Data

Data will be captured and compiled using procedures developed by the Sponsor or designee. All requested study data must be clearly recorded on the eCRF and other forms as required. Whenever possible, the reason for missing data in the source document must be recorded. Only individuals who are identified on the study personnel responsibility/signature log and who have received appropriate training on the electronic data capture (EDC) system may enter or correct data in the eCRF. Incomplete or inconsistent data on the eCRF will result in data queries that require resolution by the Investigator or designee. Corrections to the eCRF, including the reason for change, will be documented.

Participant source data must be maintained as original records or a certified copy (copy of original information that has been verified, as indicated by a dated signature, as an exact copy having all the same attributes and information as the original). The Investigator and affiliated institution should take measures to prevent accidental or premature destruction of documents. Data collected on the eCRF must match the source documents.

An eCRF must be completed for each participant who signs the ICF. All entries into the eCRF are ultimately the responsibility of the Investigator. The Investigator is responsible for ensuring accurate, authentic, and complete records for each participant.

An electronic copy of the eCRF casebooks will be sent to the clinical site for retention with other study documents after full completion of the study.

15.2.5 Source Data and Source Documents

The nature and location of all source documents will be identified to ensure that all sources of original data required to complete the eCRF are known to the Sponsor and clinical site staff. The source documents are to be accessible for verification by the clinical site monitor.

Source documents should at minimum include the following information for each participant:

- Participant identification and contact information (name, date of birth, sex, address, phone)
- Documentation verifying participant eligibility (i.e., medical history, physical examination)
- Informed consent process documentation and ICF
- Record of all visits and other contacts

- Record of all AEs and other safety parameters and all event attributes
- Record of all concomitant therapy (including start/stop dates, indication for use, dose)
- Date of study completion and reason for early discontinuation, if applicable

The author of an entry in the source documents should be identifiable as well as the date of the entry. Direct access to source documentation must be allowed for the purpose of verifying that the data recorded in the eCRF are consistent with the original source data. The Investigator will provide certified copies of the participant's medical records in the event the clinical site's policy does not permit direct access to the electronic medical records.

15.2.6 Participant Identification Information

To permit easy identification of the individual participant during and after the study, the Investigator is responsible for keeping an updated log that contains the participant identification information. This document will be reviewed by the clinical site monitor for completeness. However, to ensure the participant's confidentiality, the document will be maintained at the clinical site and no copy will be made.

15.2.7 Protocol Deviations

Unless there is a safety concern, there should be no deviations or violations of the study protocol. In the event of a safety concern, the Investigator or designee must document and explain the reason for any deviation from the approved protocol. The Investigator may implement a deviation from, or a change to, the protocol to eliminate an immediate hazard to participants, without prior EC approval. If required, immediately after the implemented deviation or change, the Investigator must submit a report explaining the reasons for the protocol deviation to the EC and the Sponsor. If a protocol deviation results in inadequate participant data, the Sponsor may determine that the participant should be replaced. The Medical Monitor will notify the study monitor of the decision.

15.2.8 Blood Sample Collection/Storage

Blood samples that are collected as part of routine medical care or as part of protocol procedures may be stored and analyzed for danicamtiv plasma concentration or biomarker analyses. All participants will be asked to provide consent for blood to be drawn for potential future analyses in relation to efficacy, safety, PD, or plasma concentration, unless there are local regulations prohibiting such analyses.

Samples will be used (if allowed per local regulations) in compliance with guidelines defined by the US Food and Drug Administration (FDA) *Guidance on Informed Consent for In Vitro Diagnostic Device Studies Using Leftover Human Specimens that are Not Individually Identifiable* (issued 25 April 2006) and the European Medicines Agency (EMA) *Reflection Paper on Pharmacogenomic Samples, Testing and Data Handling (EMA/Committee for Medicinal Products for Human Use* [CHMP] 2007).

15.2.9 Records Retention

The Sponsor will inform the Investigator in writing when it is acceptable to dispose of any study records. To enable evaluation and/or audits from regulatory authorities or the Sponsor, the Investigator agrees to keep records, including the identity of all participants (eg, participant

identification code list and all source documents), all original signed ICFs, copies of all eCRFs, original laboratory reports, detailed records of study drug disposition, and all essential documents for the conduct of a clinical study. To comply with international regulations, the records should be retained by the Investigator for at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or until at least 2 years have elapsed since the formal discontinuation of clinical development of the study drug. However, the Investigator may need to retain these documents for a longer period, if required by the local regulatory requirements or by an agreement with the Sponsor.

15.3 Clinical Trial Insurance

Clinical trial insurance has been undertaken according to the laws of the countries where the study will be conducted. An insurance certificate will be made available to the participating clinical sites upon request.

15.4 Protocol Amendments and Study Administrative Letters

Study procedures will not be changed without the mutual agreement of the Investigator and the Sponsor.

If there are any substantial changes to the study protocol, then these changes will be documented in a study protocol amendment and, where required, in a new version of the study protocol.

The amendment should be approved by the EC and the appropriate regulatory authority(ies), before implementation, as appropriate. Local requirements should be followed for revised protocols.

If a protocol amendment requires a change to the ICF, the EC will need to approve the revised ICF before the revised form is used.

If there are nonsubstantial changes, such as clarification of statement or corrections to obvious errors/typographical errors/inconsistencies in the protocol, or change to logistical or administrative aspects, then the Sponsor may issue an Administrative Letter. If local regulations require, any administrative change will be communicated to or approved by the EC.

16 DATA QUALITY ASSURANCE

Quality assurance and quality control systems will be implemented and maintained with Standard Operating Procedures by the Sponsor, as appropriate, to ensure that this clinical study is conducted and data are generated, documented (recorded), and reported in compliance with the protocol, ICH E6 *Good Clinical Practice: Consolidated Guidance*, and the applicable regulatory requirements.

17 ADMINISTRATIVE CONSIDERATIONS

17.1 Use of Computerized Systems

This study will require the use of the following electronic data collection methods:

- EDC system to capture protocol-required participant data: the clinical site will enter data from source documents onto eCRFs for each study timepoint using a web-based interface. Study

monitors and data management personnel will use this system to review data and generate queries and reports as needed.

- Cardiac clinical data management systems will be used to analyze echocardiographic data from digital equipment used by clinical site personnel to collect participant data.

In addition, other central data management systems/databases and software may be used to collect and analyze study data:

- Laboratory Information Systems or proprietary systems will be used by laboratories for storing and/or analyzing bioanalytical laboratory data collected throughout the study.
- Statistical software will be used for the statistical analysis of the study data as outlined in the SAP.

Information on the above systems will be provided to the Investigator, clinical site personnel, and other personnel, as appropriate. Measures will be taken to ensure data security and accuracy, including, but not limited to, user training, granting of user accounts and privileges to trained and authorized personnel in a role-based manner, username/password/electronic signature requirements enforcement, programmed and manual edit checks as outlined in data validation specifications, computer generated audit trails, centralized data management, and routine study monitoring. The systems used will be compliant with US 21 CFR Part 11 and Annex 11 to the Rule Governing Medicinal Products in the EU, and the data collected will be archived (at minimum) for the period specified by applicable regulatory requirements.

17.2 Study Records

The Investigator and affiliated institution shall maintain the study documents and records as specified in "Essential Documents for the Conduct of a Clinical Trial" (ICH E6, *Good Clinical Practice*, Section 8), and as required by the applicable regulatory requirement(s). This includes, but is not limited to, the protocol, eCRFs, AE reports, participant source data (original records or certified copies), correspondence with health authorities and EC, consent forms, Investigator's curriculum vitae, monitor visit logs, laboratory reference ranges and laboratory certification or quality control procedures, and laboratory director curriculum vitae.

The eCRF must be completed at the time of, or shortly after the participant's visit or upon receipt of test results. Information will be provided to clinical site staff on the proper way to complete the eCRF.

A copy of each participant's eCRF will be maintained by the Investigator.

18 PUBLICATION

The data and results of the study will be owned solely by the Sponsor and shall be confidential information of the Sponsor, participant to the Investigator's publication rights, all as outlined in the agreement between the Investigator/institution and the Sponsor regarding the conduct of the clinical study (the "Clinical Study Agreement"). It is understood by the Investigator that the Sponsor may use the information developed in this study in connection with the development of the Sponsor's proprietary study drug and, therefore, may disclose such information as necessary or useful to other clinical Investigators or regulatory agencies. To allow for the use of the

information derived from the study, the Investigator understands that he/she has an obligation to provide and disclose all study results and all data developed during this study to the Sponsor.

Any publication or presentation of the results or data of this clinical study by the Investigator may only be made in strict compliance with the provision of the Clinical Study Agreement. The Investigator understands that it is not the Sponsor's intention to prevent publication of the data generated in the study; rather, the Sponsor reserves the right to control the form and timing of such publication for commercial reasons and desires to confirm the scientific accuracy of such information prior to such publication or presentation.

19 REFERENCE LIST

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APPENDIX 1 SCHEDULE OF ASSESSMENTS

Table 3: Schedule of Assessments, Part A

Period	Pre-Screen	Screening		Treatment Period 1 (25 mg BID)			Treatment Period 2 (10 or 50 mg BID)		Follow-Up		Early Term
Visit Day		**Day -56 to -1 (Screening 1)[t]**	**If needed (Screening 2)**	**Day 1 (Baseline)**	**1-3 days before V3A**	**Afternoon of Day 5, 6, 7, or 8 (End Tx 1)**	**1-3 days before V4A**	**Afternoon, 5-8 days after V3A (End Tx 2)**	**1-3 days after V4A**	**14 days + 7d after V4A[a]**	
Visit Number	**V0A**	**V1.1A**	**V1.2A**	**V2A**	**TH1A**	**V3A**	**TH2A**	**V4A/ EOT (Part A)**	**TH3A**	**V5A/ EOS (Part A)[a]**	**ETA**
Telehealth Visit					**X[s]**		**X[s]**		**X**		
Informed consent		X									
Medical history (General and CV)		X									
Documentation of MYH7- or TTN-DCM Variant	X[b]	X									
Pregnancy Test[c]		X		X - predose						X	
FSH Level[w]		X									
Physical Examination[d]		X		X				X		X	
Height		X									
Weight		X		X		X		X		X	X
Vital Signs		X		X		X		X		X	X
TTE[e]		X[r]	X–	X - predose		X[f,g](7h post-AM dose)		X[g](7h post-AM dose)			X
12-lead ECG[h]		X		X - predose		X[u]		X		X	X
[redacted]											
Cardiac Monitoring Patch[j]		X	←	→							

Table 3: Schedule of Assessments, Part A

Period	Pre-Screen	Screening		Treatment Period 1 (25 mg BID)			Treatment Period 2 (10 or 50 mg BID)		Follow-Up		Early Term
Visit Day		**Day -56 to -1 (Screening 1)[t]**	**If needed (Screening 2)**	**Day 1 (Baseline)**	**1-3 days before V3A**	**Afternoon of Day 5, 6, 7, or 8 (End Tx 1)**	**1-3 days before V4A**	**Afternoon, 5-8 days after V3A (End Tx 2)**	**1-3 days after V4A**	**14 days + 7d after V4A[a]**	
Visit Number	**V0A**	**V1.1A**	**V1.2A**	**V2A**	**TH1A**	**V3A**	**TH2A**	**V4A/ EOT (Part A)**	**TH3A**	**V5A/ EOS (Part A)[a]**	**ETA**
Telehealth Visit					**X[s]**		**X[s]**		**X**		
Evaluation of Patch						X					
NYHA Functional Classification				X				X		X	
KCCQ-23[x]				X				X		X	
Adverse Events[v]		◄									►
Prior/concomitant Therapy		◄									►
Danicamtiv Plasma PK Sample[k]				X[l] -predose		X (7h post-AM dose)		X (7h post-AM dose)			X
hsTnT/TnI/hs-TnI[m] (Central)		X		X[l]		X		X		X	X
NT-proBNP (Central)		X		X[l]		X		X		X	X
Chemistry, Hematology (Central)		X[n]		X[l]		X		X		X	X
Blood sample for Pharmacogenetic Testing[o]				X[l]							
Blood sample for Genetic Cardiomyopathy Testing[y]		X									
Non-genetic Biomarker Sample		X		X		X		X		X	X

Table 3: Schedule of Assessments, Part A

Period	Pre-Screen	Screening		Treatment Period 1 (25 mg BID)			Treatment Period 2 (10 or 50 mg BID)		Follow-Up		Early Term
Visit Day		Day -56 to -1 (Screening 1)[t]	If needed (Screening 2)	Day 1 (Baseline)	1-3 days before V3A	Afternoon of Day 5, 6, 7, or 8 (End Tx 1)	1-3 days before V4A	Afternoon, 5-8 days after V3A (End Tx 2)	1-3 days after V4A	14 days + 7d after V4A[a]	
Visit Number	V0A	V1.1A	V1.2A	V2A	TH1A	V3A	TH2A	V4A/ EOT (Part A)	TH3A	V5A/ EOS (Part A)[a]	ETA
Telehealth Visit					X[s]		X[s]		X		
Tx Period 1 Study Drug Administration[p]				←	—	→					
Tx Period 2 Study Drug Administration[p]							←	→			
Study Drug Compliance Check[q]					X	X	X	X			

AE = adverse event; CV = cardiovascular; DCM = dilated cardiomyopathy; ECG = electrocardiogram; EOS = end of study; ET = early termination Part A FSH = follicle-stimulating hormone; hsTnI = high sensitivity troponin I; hsTnT = high sensitivity troponin T; IMP = investigational medicinal product; KCCQ-23 = Kansas City Cardiomyopathy Questionnaire (23-item version); MYH7 = Myosin Heavy Chain 7; NT-proBNP = N-terminal pro b-type natriuretic peptide; NYHA = New York Heart Association; PK = pharmacokinetic; SAE = serious adverse event; TH = telehealth; TTE = transthoracic echocardiography; TTN = titin; TX = treatment; V = visit.

[a] If a Rescreening visit is not required prior to Part B start, then Visit 1B can be performed on the same day as Visit 5A and any assessments in Visit 5A that are also required in Visit 1B need to only be performed once.

[b] Where allowed by local regulations, participants may consent to share results of previous genetic testing. These results will be shared with the Sponsor for assessing potential eligibility prior to Visit 1A (Screening).

[c] Pregnancy tests, urine or serum, is based on the policy of the local institution or regulating Health Authority (eg, requirement for serum-based testing in the United Kingdom) should be performed on all females of child-bearing potential at Screening, Day 1, and Follow-up.

[d] At Screening, a complete physical examination will be conducted including a neurological examination (gross motor and deep tendon reflexes), height and weight, and assessment of the following: general appearance, skin, head and neck, mouth, lymph nodes, thyroid, abdomen, musculoskeletal, cardiovascular, neurological, and respiratory systems. All other timepoints can be abbreviated physical examination (pulmonary, cardiac, abdominal, and other systems related to any symptoms).

[e] Participant should be at rest for at least 10 minutes prior to performance of any TTE. At least one full TTE must be performed at Screening. Eligibility to be determined by criteria in Section 7.1.

[f] TTE at Visit 3A will be reviewed locally in real time to determine dosing of study drug for Treatment Period 2.

[g] TTE at Visit 3A and Visit 4A should be performed 7 hours (±1 hour) after ingestion of morning study drug dose.

[h] Triplicate 12-lead ECG evaluations (all obtained within a 20-minute window) will be performed in the supine position after 10 minutes of rest. The predose ECG on Day 1 should be performed before dosing. Additional ECGs (unscheduled assessments) should be obtained in cases of suspected ischemia.

[redacted]

[j] Cardiac rhythm monitoring patch will be placed at the first Screening visit (Visit 1.1A) if using historical LVEF to qualify. If using 2 Screening TTEs, the patch will be placed at the time of the 2nd Screening visit (Visit 1.2A). The duration of initial monitoring may range from a minimum of 5 days to a maximum of 14 days. If the patch should become detached prior to 5 days, a new patch should be placed as soon as possible. A new patch will be placed at the start of each Treatment Period, after dosing. The patch will be inspected by the Investigator at each encounter with the participant. If adhesive appears intact, the existing patch should be left in place. If the patch adhesive appears to be failing, a new patch should be placed at that time.

[k] Plasma samples will be obtained within 3 hours predose at Visit 2A. At Visit 3A and Visit 4A, plasma concentration will be obtained at 7 hours (±1 hour) following the last dose (taken in the morning) of each Treatment Period. An unscheduled or additional plasma sample may be collected if appropriate in the opinion of the Investigator and/or Sponsor (eg, in the case of an AE/SAE) (Section 11.3.1).

[l] Predose laboratory samples may be obtained on the day prior to Visit 2A.

[m] All samples will be analyzed at a central laboratory. If the participant has any signs or symptoms suggestive of possible cardiac ischemia, additional troponin samples may be obtained as well as a simultaneous plasma concentration sample (Section 11.3.1).

[n] Abnormal findings from laboratory assessments performed at Visit 1A may be repeated once during Screening after corrective treatment (eg, hemolysis of sample, abnormal potassium levels). Screening laboratory tests will include TSH and Fe/TIBC/ferritin to exclude uncontrolled thyroid functions and Fe overload.

[o] All Participants have the option to provide consent for blood to be drawn for potential future analysis of pharmacogenetics, as permitted by local regulation. Additional samples for pharmacogenetic testing will be collected if needed (eg., samples determined as not adequate for DNA extraction) anytime during the study after participants provided consent for additional sample collection.

[p] Participants will be dosed BID (every 12 hours). Doses may occur ± 2 hours from scheduled dosing times as long as doses are separated by at least 10 hours and by no more than 14 hours. For Treatment Period 1, the initial dose (Visit 2A) should be given after all assessments (cardiac rhythm monitoring patch application excepted) are completed. On Day 1, if baseline assessments are completed in the afternoon then study drug will only be administered once in the afternoon. The last dose for Treatment Period 1 (Visit 3A) and the last dose for Treatment Period 2 (Visit 4A) should be taken the morning of each visit and approximately 7 hours prior to the afternoon visits for Visit 3A and 4A.

[q] Study drug compliance check will entail tablet count at Visit 3A and Visit 4A. At Telehealth Visit 1A and Telehealth Visit 2A, participant will be contacted and interviewed. Acceptable methods of contact include, but are not limited to, telephone, two-way text messaging, and email.

[r] If a participant's most recent prior TTE (within the past 12 months) documents a LVEF ≤ 45%, then only a single Screening visit confirming LVEF ≤ 45% by the Echo Core Laboratory is required. If no prior documented LVEF ≤ 45% by TTE within the past 12 months is available, then 2 Screening TTEs are needed at least one week (7 days) apart. The absolute difference between the 2 LVEF values qualifying the participant should be < 12%.

[s] One to 3 days before the end of each Treatment Period, the participant will be contacted to assess any symptoms, ensure compliance with study drug, and to remind the participant about next visit (Visits 3A and 4A) and to take study drug in the morning of Visits 3A and 4A, about 7 h prior to the scheduled time of each visit.

[t] Visit 3A (D5 to D8) and Visit 4A (5 to 8 days after Visit 3A, ie. Day 9 up to Day 15). This scheduling window is to accommodate weekends and holidays.

[u] Triplicate 12-lead ECG obtained at Visit 3A will be reviewed by the Investigator to confirm lack of QTcF prolongation in order to continue with study drug treatment (Section 6.2) before being sent to the ECG core laboratory.

[v] Changes in baseline conditions from once the ICF is signed will be recorded as an AE. All changes, unless otherwise specified, that occur after the administration of study drug will be considered treatment emergent AEs.

[w] FSH level assessment done at Screening is only for women of non-childbearing potential.

[x] Should be done before any other assessments.

[y] If rescreening is conducted, repeat of genetic testing at Screening is not necessary. Up to 1 rescreen per participant is permitted.

Table 4: Schedule of Assessments, Part B (Active Cohort)

	End of Part A	Part B, Year 1										
Visit Day	**14 days + 7d after V4A**	**Day -28 to -1 (Rescreening, if needed)**	**Day 1 (Baseline)**	**Week 2**	**Week 6**	**Week 12**	**Week 18**	**Week 24**	**Week 30**	**Week 36**	**Week 42**	**Week 48**
Visit Number	**V5A[a]**	**V0B[l]**	**V1B[a]**	**V2B**	**V3B**	**V4B**	**V5B**	**V6B**	**TH1B**	**V7B**	**TH2B**	**V8B**
Visit Windows		**-28 days**		**± 2 days**	**± 7 days**	**± 7 days**	**± 7 days**	**± 7 days**	**± 7 days**	**± 7 days**	**± 7 days**	**± 7 days**
Telehealth Visit									**X**		**X**	
Informed Consent		X	X (if needed)									
Medical History		X	X (if needed)									
Vital Signs		X	X	X	X	X	X	X	X[i]	X	X[i]	X
Weight		X	X	X	X	X		X				X
Complete Physical Exam		X										
Symptom-directed Physical Exam			X	X	X	X	X	X		X		X
TTE			X[d]	X[c,e]	X[c,e]	X[c]		X[c]				X[c]
12-lead ECG	X	X	X	X	X	X	X	X	X[i]	X	X[i]	X
Cardiac Rhythm Monitoring[f]			X					X				X
Activity Monitor[g]			X					X				X
CMR[h]			X[d]									X
6MWD (in clinic)			X[d]					X				X
NYHA Functional Classification	X		X		X	X	X	X		X		X
KCCQ-23	X		X		X	X	X	X	X	X	X	X
hsTnT/TnI/hs-TnI (Central)[b]	X		X	X[j]	X[j]	X[j]	X[j]	X[j]	X[j]	X	X[j]	X

Table 4: Schedule of Assessments, Part B (Active Cohort)

	End of Part A	Part B, Year 1										
Visit Day	**14 days + 7d after V4A**	**Day -28 to -1 (Rescreening, if needed)**	**Day 1 (Baseline)**	**Week 2**	**Week 6**	**Week 12**	**Week 18**	**Week 24**	**Week 30**	**Week 36**	**Week 42**	**Week 48**
Visit Number	**V5A[a]**	**V0B[l]**	**V1B[a]**	**V2B**	**V3B**	**V4B**	**V5B**	**V6B**	**TH1B**	**V7B**	**TH2B**	**V8B**
Visit Windows		**-28 days**		**± 2 days**	**± 7 days**	**± 7 days**	**± 7 days**	**± 7 days**	**± 7 days**	**± 7 days**	**± 7 days**	**± 7 days**
Telehealth Visit									**X**		**X**	
NT-proBNP (Central)	X		X	X	X	X	X	X	X[j]	X	X[j]	X
Chemistry, Hematology (Central)	X	X[o]	X	X	X	X	X	X		X		X
Pregnancy Test[k]	X	X						X				X
Danicamtiv Plasma PK Sample			X (pre-dose_	X[c]	X[c]	X[c]	X	X[c]		X		X[c]
Non-genetic Biomarker Sample	X		X	X	X	X		X		X		X
Study Drug Administration			←	—	—	—	—	—	—	—	—	→
Adverse Events[m]	←	—	—	—	—	—	—	—	—	—	—	→
Concomitant Medications	←	—	—	—	—	—	—	—	—	—	—	→
Study Drug Compliance Check[n]			←	—	—	—	—	—	—	—	—	→

Table 4: Schedule of Assessments, Part B (Active Cohort)

	Part B, Year 2								
Visit Day	**Week 54**	**Week 60**	**Week 66**	**Week 72**	**Week 78**	**Week 84**	**Week 96**	**Follow-up (Week 98)**	**Early Termination**
Visit Number	**TH3B**	**V9B**	**TH4B**	**V10B**	**TH5B**	**TH6B**	**EOT**	**EOS-B/ F/U**	**ETB**
Visit Windows	**± 7 days**	**± 7 days**	**± 7 days**	**±- 7 days**	**± 14 days**	**± 14 days**	**± 14 days**	**+2 weeks**	
Telehealth Visit	**X**		**X**		**X**	**X**			
Informed Consent									
Medical History									
Vital Signs		X		X			X	X	X
Complete Physical Exam							X	X	X
Symptom-directed Physical Exam		X		X					
Weight							X		X
TTE				X[c]			X[c]	X	X[c]
12-lead ECG		X		X			X	X	X
Cardiac Rhythm Monitoring[f]				X			X		
Activity Monitor[g]				X			X		
CMR[h]							X		
6MWD				X			X		
NYHA Functional Classification		X		X			X	X	X
KCCQ-23	X	X	X	X	X	X	X	X	X
hsTnT/TnI/hs-TnI (Central)[b]		X		X			X	X	X
NT-proBNP (Central)		X		X			X	X	X
Chemistry, Hematology (Central)		X		X			X	X	X
Non-genetic biomarker Samples		X		X			X	X	X
Pregnancy Test[k]				X			X		X
Danicamtiv Plasma PK Sample				X[c]			X[c]		

Table 4: Schedule of Assessments, Part B (Active Cohort)

	Part B, Year 2								
Visit Day	**Week 54**	**Week 60**	**Week 66**	**Week 72**	**Week 78**	**Week 84**	**Week 96**	**Follow-up (Week 98)**	**Early Termination**
Visit Number	**TH3B**	**V9B**	**TH4B**	**V10B**	**TH5B**	**TH6B**	**EOT**	**EOS-B/ F/U**	**ETB**
Visit Windows	**± 7 days**	**± 7 days**	**± 7 days**	**±- 7 days**	**± 14 days**	**± 14 days**	**± 14 days**	**+ 2 weeks**	
Telehealth Visit	**X**		**X**		**X**	**X**			
Study Drug Administration	←	—	—	—	—	—	→		
Adverse Events[m]	←	—	—	—	—	—	—	—	→
Concomitant Medications	←	—	—	—	—	—	—	—	→
Study Drug Compliance Check[n]	←	—	—	—	—	—	→		

AEs = adverse events; CMR = cardiac magnetic resonance; ECG = electrocardiogram; EOS-B/F/U = end of study-Part B follow-up; EOT = end of treatment; ETB = early termination Part B; hsTnI = high sensitivity troponin I; hsTnT = high sensitivity troponin T; ICF = informed consent form; IMP = investigational medicinal product; KCCQ-23 = Kansas City Cardiomyopathy Questionnaire (23-item version); NT-proBNP = N-terminal pro b-type natriuretic peptide; NYHA = New York Heart Association; PK = pharmacokinetic; TH = telehealth**;** TTE = transthoracic echocardiography; ULN = upper limit of normal

[a] If a Rescreening visit is not required prior to Part B start, then Visit 1B can be performed on the same day as Visit 5A and any assessments in Visit 5A that are also required in Visit 1B need only be performed once. If Visits 5A and 1B are not performed on the same day, Part B Medical History assessment to be done on study participants who require Rescreening Visit for Part B (V0B) or sign the Part B ICF at V1B and are less than or equal to 56 days from completion of Part A.

[b] If TnI (standard) is elevated, telehealth visits should be converted to clinic visits; see footnote j.

[c] Perform a TTE and dani plasma PK sample collection at approximately 7 hours (± 1 hour) after the morning dose on every visit after Day 1.

[d] Can be done within 7 days of the initial starting dose in Part B

[e] [redacted]

[f] Cardiac rhythm monitoring patch will be placed at Visit 1B, 6B, 8B, 10B, and EOT. The duration of initial monitoring is for a maximum of 14 days. If the patch should become detached prior to 5 days, a new patch should be placed as soon as possible. Once patch detaches after at least 5 days, participants will be instructed to mail the patch back to the site.

[g] [redacted]

[h] CMR to be scheduled prior to dosing (prior to Visit 5A/Visit 1B if combining visits) and then within 4 weeks of each 1 year anniversary on study. CMR will be obtained only in suitable participants.

[i] A 12-lead ECG and vital signs will be performed if TnI (standard) is elevated by more than 0.05ng/mL (see footnote h).

[j] If TnI (standard) level is below ULN at Baseline and subsequently increases to more than 0.05 ng/mL, or if TnI level is above ULN at Baseline and then subsequently increases by more than 0.05 ng/mL above the participant's Baseline value (obtained at Visit 1B in Part B) until Visit 6B (Week 24), the totality of the clinical data will be reviewed by a panel of experts periodically to determine if any signs of ischemia are seen. During this time, the participant will continue danicamtiv at the same dose; subsequent telehealth visits will become in-person clinic visits with 12-lead ECGs, vital signs, and collection of TnI, hsTnI, TnT, and NT-proBNP until troponin levels are stable or declining. If TnI (standard) level exceeds 0.1 ng/mL at any time, the participant will be requested to return for repeat evaluation as soon as possible. If this level of TnI (standard) is confirmed, treatment with danicamtiv will be temporarily discontinued and an ad hoc expert review will be triggered. If TnI (standard and high sensitivity) and hsTnT are collected at visits TH1B and TH2B, then NT-proBNP should also be collected in the same blood draws.

[k] Pregnancy tests, urine or blood, is based on the policy of the local institution or regulating Health Authority (eg, requirement for serum-based testing in the United Kingdom).

[l] Rescreening visit to be performed only if timeframe between completion of Part A to start of Part B is greater than 56 days.

[m] Changes in baseline conditions from once the ICF is signed will be recorded as an AE. All changes, unless otherwise specified, that occur after the administration of study drug will be considered treatment-emergent AEs.

[n] Study drug compliance check will entail table count at all Part B visits including telehealth visits. Acceptable methods of contact include, but are not limited to, telephone, two-way text messaging and email.

[o] Screening laboratory tests will include TSH and Fe/TIBC/ferritin to exclude uncontrolled thyroid functions and Fe overload.

Table 5: Schedule of Assessments, Part B (Observational Cohort)

	Part A						
Visit Day	**14 days + 7d after V4A**	**Day -28 to -1 (Rescreening, if needed)**	**Day 1 (Baseline)**	**Week 12**	**Week 24**	**Week 48**	**Week 96**
Visit Number	**V5A**	**V0O[b]**	**V1O[c]**	**V2O**	**V3O**	**V4O**	**V5O**
Visit Windows		**-28 days**		**± 14 days**	**± 14 days**	**± 14 days**	**± 14 days**
Telehealth Visit							
Informed Consent		X	X (if needed)				
Medical History		X	X (if needed)				
Vital Signs		X	X	X	X	X	X
Weight		X	X		X	X	X
Symptom-directed Physical Exam			X		X	X	X
TTE			X[a]	X	X	X	X
12-lead ECG	X		X	X	X	X	X
6MWD (in clinic)			X		X	X	X
NYHA Functional Classification	X		X	X	X	X	X
KCCQ-23	X		X	X	X	X	X
hsTnT/TnI/hs-TnI (Central)	X		X	X	X	X	X
NT-proBNP (Central)	X		X	X	X	X	X
Chemistry, Hematology (Central)	X	X	X		X	X	X
Non-genetic Biomarker Sample	X		X		X	X	X
Adverse Events	←						→
Concomitant Medications			X	X	X	X	X

6MWD = 6-minute walk distance; ECG = electrocardiogram; hsTnT = high sensitivity troponin T; KCCQ-23 = Kansas City Cardiomyopathy Questionnaire (23-item version); NT-proBNP = N-terminal pro b-type natriuretic peptide; NYHA = New York Heart Association; TnI = standard troponin I; TTE = transthoracic echocardiography; V = visit.

[a] Can be done within 7 days of V1O.

[b] Rescreening visit to be performed only if timeframe between completion of Part A to start of Part B is greater than 56 days.

[c] If a Rescreening visit is not required prior to Part B start, then Visit 1O can be performed on the same day as Visit 5A and any assessments in Visit 5A that are also required in Visit 1O need only be performed once. If Visits 5A and 1O are not performed on the same day, Part B Medical History assessment to be done on study participants who require Rescreening Visit for Part B (V0O) or sign the Part B ICF at V1O and are less than or equal to 56 days from completion of Part A.

APPENDIX 2 LABORATORY ASSESSMENTS

Table 6: Safety Laboratory Parameters

Hematology[a]	Serum Chemistry[a]
• CBC, including differential count • Platelet count	• Sodium • Potassium • Chloride • Bicarbonate • Total protein • Albumin • Calcium • Magnesium • Creatinine • ALP • ALT • AST • Total bilirubin • Glucose • CK • BUN or urea (per local standards) • LDH • Inorganic phosphorus • Total cholesterol • eGFR • Uric acid • Amylase • Lipase

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CBC = complete blood cell count; CK = creatine kinase; eGRF = estimated glomerular filtration rate; LDH = lactic acid dehydrogenase

[a] All samples will be assayed in the central laboratory at all timepoints except when deemed necessary by Investigator's judgement

Troponins and NT-proBNP will also be assessed (APPENDIX 1).

The following nonsafety laboratory parameters will be measured in this study:

- FSH
- Pregnancy, assessed in urine or blood, based on the policy of the local institution or regulating Health Authority (eg, requirement for serum-based testing in the United Kingdom and Germany)
- TSH, Fe/TIBC/ferritin for Screening

APPENDIX 3 POTENTIAL DRUG-INDUCED LIVER INJURY REPORTING AND ADDITIONAL ASSESSMENTS REPORTING

To facilitate appropriate monitoring for signals of drug-induced liver injury (DILI), cases of concurrent AST/ALT and TBL elevation according to the criteria specified in Section 6.2 (3 times ULN for AST/ALT and 2 times ULN for TBL in participants with no underlying liver disease and eligibility criteria requiring normal liver function at Baseline) require the following:

- The event is to be reported to the Sponsor as an SAE within 24 hours of discovery or notification of the event (i.e., before additional etiologic investigations have been concluded).
- The appropriate eCRFs (eg, adverse event eCRFs) that capture information necessary to facilitate the evaluation of treatment-emergent liver abnormalities are to be completed and sent to the Sponsor.

Other events of hepatotoxicity and potential DILI are to be reported as SAEs if they meet the criteria for an SAE defined in Section 12.1.2.

Additional Clinical Assessments and Observation

All participants in whom investigational product(s) or protocol-required therapies is/are withheld (either permanently or conditionally) due to potential DILI or who experience AST/ALT elevations > 3 times ULN are to undergo a period of close observation until abnormalities return to normal or to the participant's Baseline levels. Assessments that are to be performed during this period include the following:

- Repeat liver chemistries within 24 to 48 hours (ALT, AST, alkaline phosphatase, TBL); in cases of TBL ≥ 2 times ULN or AST/ALT much greater than 3 times ULN, retesting is to be performed within 24 hours.
  - Participants are to be monitored at least twice weekly; testing frequency may decrease to once per week or less if laboratory abnormalities stabilize or the investigational product(s) or protocol-required therapies have been discontinued AND the participant is asymptomatic.
- Obtain prothrombin time/international normalized ratio, fractionated bilirubin, and any other potentially relevant laboratory evaluations of liver function or disease.
- Obtain complete blood count with differential to assess for eosinophilia.
- Obtain appropriate blood sampling for determination of plasma concentration, if this has not already been collected.
- Obtain a more detailed history of the following:
  - Prior and/or concurrent diseases or illness
  - Exposure to environmental and/or industrial chemical agents
  - Symptoms (if applicable) including right upper quadrant pain, hypersensitivity type- reactions, fatigue, nausea, vomiting, and fever
  - Prior and/or concurrent use of alcohol, recreational drugs, and special diets
  - Concomitant medications (including nonprescription medicines and herbal and dietary supplements)

- Initiate full viral and autoimmune hepatitis evaluation (serologies for hepatitis A, B, C, D, E, Epstein-Barr virus, herpes simplex virus, etc.); evaluate for other potential causes of DILI, including but not limited to: nonalcoholic steatohepatitis, hypoxic/ischemic hepatopathy, and biliary tract disease.
- Obtain gastroenterology or hepatology consult.
- Perform appropriate liver imaging or biopsy if clinically indicated; strongly consider these tests in cases of concurrent transaminase and TBL elevation, as specified in Section 6.2.2.
- Follow the participant until all laboratory abnormalities return to Baseline or normal. The close observation period is to continue for a minimum of 4 weeks after investigational product(s) or protocol-required therapies discontinuation.

The potential DILI event and additional information, such as medical history, concomitant medications, and laboratory results, must be captured in corresponding eCRFs.

APPENDIX 4 INVESTIGATOR'S SIGNATURE

MYK-491-006, Amendment 5 release date: 28 Aug 2023

I have read and understand the contents of the clinical protocol, MYK-491-006, "An Open-Label, Exploratory Study of the Safety and Preliminary Efficacy of Danicamtiv in Stable Ambulatory Participants with Primary Dilated Cardiomyopathy due to either MYH7 or TTN Variants or Other Causalities," and I agree to the following:

- To assume responsibility for the proper conduct of this clinical study at this clinical site and to conduct the study in compliance with this protocol, any future amendments, and any other study conduct procedures provided by the Sponsor/designee
- That I am aware of and will comply with the internationally recognized code of Good Clinical Practices (GCP) and all other applicable regulatory requirements to obtain written and dated approval for the Ethics Committee (EC) (eg, Institutional or Central Review Board [IRB] or Independent Ethics Committee [IEC]) for the study protocol, written informed consents, consent form updates, study participant recruitment procedures, and any other written information to be provided to the study participants before initiating this clinical study
- Not to implement any changes to, or deviations from the protocol without prior agreement from the Sponsor and reviewed and documented approval from the EC, except to eliminate an immediate hazard to the study participants, or when change(s) involves only logistical or administrative aspects of the clinical study
- To permit direct monitoring and auditing by the Sponsor or the Sponsor's representatives and inspection by the appropriate regulatory authority(ies)
- That I am thoroughly familiar with the appropriate use of the Investigational Medicinal Product (IMP) and other study medication(s) (if applicable), as described in this protocol, and any other information provided by the Sponsor or designee, including, but not limited to the current Investigator's Brochure (IB) or equivalent document and marketed prescription information (if applicable)
- To provide sufficient time and adequate numbers of qualified staff and facilities for the foreseen duration of the clinical study to conduct the study properly, ethically, and safely
- To ensure that all persons assisting in this study are adequately informed about the protocol, study drug, and their clinical study-related duties and functions

Signed: _____ Date: _____
(sign name with credentials)

Printed Name: _____
(print name with credentials)

APPENDIX 5 ALLOWANCES FOR STUDY OPERATIONS AFFECTED BY PANDEMIC PRECAUTIONS (INCLUDING COVID-19)

Recent developments worldwide have seen unprecedented alterations in the operations of clinical research. Additionally, it is recognized that the dilated cardiomyopathy (DCM) patient population is at increased risk of adverse outcomes because of their underlying disease state. Individual clinical sites have since evaluated benefits and risks to participants of reopening to clinical research and made decisions to restart such activities accordingly. In these cases, discussions shall begin as soon as a site is contemplating reopening to clinical studies and should include the Sponsor as well as the Contract Research Organization (CRO). The site will determine a workflow for participants to be assessed and move through the conduct of the study in as safe a manner and environment as possible, limiting the exposure of these participants as well as members of the site's staff and study monitors. This workflow will be documented in the investigator site file and should include provisions for adequate remote source document verification (for example by access to the investigator site file).

Participants may be tested for COVID-19 in accordance with site standard practices and local guidelines.

APPENDIX 6 WOMEN OF CHILDBEARING POTENTIAL DEFINITIONS AND METHODS OF CONTRACEPTION

Appendix 5 provides general information and definitions related to Women of Childbearing Potential (WOCBP) and methods of contraception that can be applied to most clinical trials. For information specific to this study regarding acceptable contraception requirements for female and male participants, refer to Section 10.2.3 of the protocol. Only the contraception methods as described in Section 10.2.3 are acceptable for this study.

DEFINITIONS

Women of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, bilateral oophorectomy, and/or bilateral tubal occlusion or ligation.

Women in the following categories are not considered WOCBP:

Premenarchal

Premenopausal female with 1 of the following:

-Documented hysterectomy

-Documented bilateral salpingectomy

-Documented bilateral oophorectomy

-Documented bilateral tubal occlusion or ligation

Note: Documentation can come from the site personnel's review of the participant's

medical records, medical examination, or medical history interview.

Postmenopausal female

-A postmenopausal state is defined as 12 months of amenorrhea in a woman over the age of 45 years in the absence of other biological or physiological causes. In addition, females under the age of 55 years must have a serum follicle-stimulating hormone (FSH) level >40mIU/mL to confirm menopause.

Note: Females treated with hormone replacement therapy (HRT) are likely to have artificially suppressed FSH levels and my require a washout period in order to obtain a physiologic FSH level. The duration of the washout period is a function of the type of HRT used. Suggested guidelines for the duration of the washout periods for HRT types are presented below. Investigators should use their judgment in checking serum FSH levels.

1-week minimum for vaginal hormonal products (ring, creams, gels)

4- week minimum for transdermal products

8-week minimum for oral products

Other parenteral products may require washout periods as long as 6 months. If the serum FSH level is >40 mIU/mL at any time during the washout period, the woman can be considered postmenopausal.

APPENDIX 7 PROTOCOL AMENDMENT SUMMARY OF CHANGE HISTORY

Overall Rationale for the Protocol Amendment 4, 20-Dec-2022

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment

The primary purpose of this amendment is to reflect the change in the study design.

(1) Addition of a cohort of primary DCM not related to MYH7 or TTN variants to assess safety and PD responses with danicamtiv. Data assessment between the DCM cohort, the MYH7 and TTN cohorts will be explored.

(2) To evaluate if MYH7 or TTN disease-causing variants are involved in DCM causality, genetic testing reports will be reviewed and approved for study eligibility by the central reviewers at Screening. Genetic testing can be performed at a local or central genetic testing lab when available in the region to determine participant eligibility. For participants who are enrolled using genetic testing reports from other than a central genetic laboratory, their genetic status will be confirmed via testing at a central genetic laboratory retrospectively.

A summary of additional changes that were made to the protocol are included in the table below to add clarity, consistency in terminology, and accuracy throughout the document.

Section Number & Title	Description of Changes	Brief Rationale
Title page; Synopsis	Added CV028005 for the protocol number; Changed the title to "An Open-Label, Exploratory Study of the Safety and Preliminary Efficacy of Danicamtiv in Stable Ambulatory Participants with Primary Dilated Cardiomyopathy due to either MYH7 or TTN Variants or Other Causalities."	Added CV028005, which is study ID at BMS. To reflect the new cohort added.
Synopsis - Study Title; Primary Objective; Secondary Objective; Exploratory Objectives; Study Design; Section 5.1 Primary Objective; Section 5.2 Secondary Objectives; Section 5.3 Exploratory Objectives; Section 6.1 Study Design	Added a new cohort of primary DCM. For this cohort, other causalities than MHY7 or TTN variants as eligibility to participate. Primary and secondary objectives updated to reflect this new cohort. Added an exploratory objective to explore the PD comparisons between the DCM and the two genetic variants	The addition of this new cohort allows safety and PD assessments with danicamtiv in DCM participants due to other causalities than MYH7 or TTN variants. Data assessment between those three cohorts, DCM and the two genetic variants, will be explored.
Synopsis – Study Design; Section 6.1.1 Part A	Added that the Pre-Screening using a historical genetic report may be conducted prior to Screening visit where allowed by local regulations	Pre-Screening has been described in the Part A Schedule of Assessment in the previous version of the study protocols. Specified it in the main protocol for clarity.

Section Number & Title	Description of Changes	Brief Rationale
Synopsis – Study Design; Section 6.1.2 Part B And Synopsis – Study Treatment; Section 4.2 Rationale for Dose and Dosing Schedule; Section 9.2.2 Part B	Added participation criteria for Part B for those participants who did not complete Part A	Allows treatment to continue except for participants who experience drug related TEAEs, met stopping criteria or withdrew consent. This may allow cases, such as COVID-19 infection to continue. Participation is assessed by the sponsor and PI
	Deleted the word "always" from Part B doses will always be based on the [redacted] in Part A	To accommodate the case in which the [redacted] is not available in Part A. Part B participation for such case is described above
Synopsis – Study Design; Section 6.1.2 Part B	Deleted "If Visits 5A and 1B are performed on the same day, Part B study drug dosing should not start for at least 14 days after the last dose of the study drug in Part A."	To reflect the changes in study design made in PA3. This information was removed since it's no longer applicable
Synopsis – Study Design; Section 6.1.2 Part B; Section 11.4.6 Troponin Levels	Clarified that hsTnT, hsTnI, and TnI will be evaluated throughout Parts A and B.	To specify types of troponin assessed in the study
Section 4.1 Rationale for the Study	Added rationale for the DCM cohort	Reflects the change in study design by adding a new cohort
Synopsis –Number of Participants; Sample Size and Statistical Considerations; Section 13.1 Determination of Sample Size	Updated participants to approximately 40 including 16 participants with DCM not related to MYH7 or TTN variant	Added DCM cohort
Synopsis –Number of Participants; Part A Inclusion Criteria I8; Section 6.1 Study Design; Section 7.1 Inclusion Criteria – Only for Part A	Added that the ratio of participants with DCM causing variants (other than MYH7 or TTN) and non-genetic cause will be approximately 1:1	To clarify planned enrollment ratio

Section Number & Title	Description of Changes	Brief Rationale
Synopsis - Study Treatment; Section 4.2 Rationale for Dose and Dosing Schedule; Section 9.2.2 Part B Figure 3: Part B Study Schema	Added the following: • If both doses in Part A resulted in a [redacted] of [redacted] **with 10 and 25 mg BID,** then the Part B dose is 5 mg BID • **If both doses in Part A resulted in a [redacted] of [redacted] with 25 and 50 mg BID, then the Part B dose for that participant was previously5 mg and has been changed to 10 mg BID with this amendment**	To be able to select the one dose lower than the doses administered in Part A. To date, all participants have received 25mg BID and 50mg BID in Part A. Safety and tolerability of danicamtiv with those doses have been acceptable in this population. Based on previously conducted PK assessment in healthy volunteer, [redacted] Furthermore, there will be [redacted] assessments at 2weeks and 6 weeks after starting 10mg in Part B. Dose optimization at 6 weeks in Part B will be performed depending on [redacted]
Synopsis – Study Treatment; Section 4.2 Rationale for Dose and Dosing Schedule; Section 9.2.2 Part B	Added the following: • If [redacted] of both doses were unavailable or performed significantly outside of the assessment window (see Appendix 1. Part A SoA footnote g), then the Part B dose will be 50 mg BID. • If a [redacted] was only available with 25 mg BID (Treatment Period 1) and a [redacted] was [redacted] and [redacted], then 25mg BID is the dose for Part B. If a [redacted] was [redacted], then the Part B dose is 50 mg BID. If 25 mg BID dose resulted in a [redacted], then the Part B dose for that participant is 10 mg BID	Part B starting dose for such case was indicated based on available [redacted] in Part A or 50mg BID, which all Part A participant have received in Part A treatment period 2 to date with acceptable safety and tolerability
Synopsis – Study Design Part B, Study Duration; Section 6.1.2 Part B; Section 6.3 Study Duration	Updated the expected Part B duration to 102 weeks if Rescreening is needed.	To align with the updated Schedule of Activities
Synopsis – Part A Inclusion Criteria I3; Section 7.1 Inclusion Criteria –Part A	Clarified that for MYH7 and TTN cohorts, I3 criteria (a) through (f), specific for these variant type, must be met. Clarified that for all participants must meet I3 criteria of LVEF (g) and HF GDMT (h)	To reflect the inclusion criteria for the primary DCM cohort of other causalities

Section Number & Title	Description of Changes	Brief Rationale
Synopsis – Part A Inclusion Criteria I3; Section 7.1Inclusion Criteria –Part A	Deleted inclusion for variants involving certain myosin residues	To streamline genetic eligibility criteria. Based on reported data, it is unlikely to affect the listed myosin amino acid residues by disease causing variants in MYH7 gene.
Synopsis – Part A Inclusion Criteria I6; Section 7.1 Inclusion Criteria –Part A; Section 10.2.1 Avoidance of Pregnancy; Section 10.2.3 Acceptable Forms of Contraception	Changed to "documented" hysterectomy, bilateral oophorectomy, bilateral salpingectomy, and/or bilateral tubal occlusion "or ligation" prior to Screening	To align with the standard contraception requirement. Also, clarified how to confirm those previous procedures
Synopsis – Part A Inclusion Criteria I8; Section 7.1 Inclusion Criteria –Part A	Added I8 criteria for cohort of DCM due to causalities other than MYH7 and TTN	To clarify the eligibility criteria
Synopsis – Inclusion Criteria Part B I; Section 7.1 Inclusion Criteria –Part B	Added inclusion criteria for Part B	To clarify inclusion criteria for participants continuing to Part B to ensure their condition still meet for study participation
Synopsis – Part A Exclusion Criteria E3; Section 7.2 Exclusion Criteria – Part A	Clarified that MYH7 and TTN cohorts and DCM due to other causalities are mutually exclusive in E3	To clarify the eligibility criteria
Synopsis – Part A Exclusion Criteria E15; Section 7.2 Exclusion Criteria – Part A Section 11.4.8 Safety Laboratory Tests (Other than Troponin); Appendix 2 Laboratory Assessments; Appendix 1. Schedule of Assessments, Part A; Appendix 1. Schedule of Assessments, Part B (Active Cohort)	Clarified that the exclusion is for out-of-range laboratory parameters (safety and nonsafety) at Screening Added TSH, Fe/TIBC/ferritin for Screening	To clarify the eligibility criteria. TSH and Fe/TIBC/ferritin will be assessed at Screen to evaluate cause of DCM is probably not due to abnormal thyroid function or Fe overload.
Synopsis – Part A Exclusion Criteria E22, E23; Part B E11, E12; Section 7.2 Exclusion Criteria – Part A, Part B	Added EC of requirement for an ICD in participants who meets class I recommendation in the HF guidelines (E22 Part A and E11 Part B) and severe ventricular arrythmia (E23 Part A and E12 Part B). Individuals with unstable or untreated severe ventricular arrythmia is not eligible for study participation.	To assure safety of study participants those who are with elevated risk of sudden cardiac death due to ventricular arrythmia.

Section Number & Title	Description of Changes	Brief Rationale
Synopsis – Part A Exclusion Criteria E11; Section 7.2 Exclusion Criteria – Part A Synopsis – Part B Exclusion Criteria E4; Section 7.2 Exclusion Criteria – Part B	EC of COVID-19 infection within 30 days from Screening (Part A) or Rescreening (Part B) was replaced by below EC. In the case of SARS-CoV-2 (COVID-19) infection within 4 weeks prior to and during Screening for Part A or within 4 weeks prior to Part B Baseline Visit or Rescreening , symptoms must have completely resolved and based on Investigator assessment in consultation with the Clinical Trial Physician, there are no sequelae that would place the participant at a higher risk of receiving investigational treatment.	To update the COVID 19 related exclusion criteria for Parts A and B given notable changes associated with COVID-19 since previous EC was made in 2020. There have been available vaccines and treatments for COVID-19 and symptoms also varies per individual. Individual cases can be assessed by the PI and Sponsor Medical Monitor.
Synopsis – Part A Exclusion Criteria E11, Part B Exclusion Criteria E4; Section 7.2 Exclusion Criteria – Part B	PCR test to confirm positive COVID-19 infection was replaced by the tests including PCR, antigen test and serology tests	To allow other types of COVID-19 test to diagnose positive infection. Each study sites should follow requirement per local institution or regulatory guidance
Synopsis – Part B Exclusion Criteria E5; Section 7.2 Exclusion Criteria – Part B	Clarified that Part B E5 of renal insufficiency and E6 of clinically significant out-of-range safety lab apply to participants that need Rescreening only	To clarify applicable criteria which require safety lab test results only performed for Rescreening
Synopsis – Part B Exclusion Criteria; Section 7.2 Exclusion Criteria – Part B	Added Part B Exclusion Criteria E8, E9, and E10. These are also Part A Exclusion criteria	To clarify that these ECs required for Part A are also required for Part B
Synopsis – Study Endpoints; Section 13.2.1 Primary Endpoints	Clarified that the primary endpoints are for Part A only	Part B is an optional extension to the study. Part A is required for all participants, hence primary endpoints will be collected in Part A only.
Synopsis – Study Endpoints; Section 13.2.2 Secondary Endpoints; Section 11.1.1 Transthoracic Echocardiography	Clarified that the parameters of left ventricular diastolic function will include, but not be limited to, TDI of mitral valve annulus peak velocity in diastole (e', lateral, septal), ratio of peak inflow velocities in early and late diastole (E/A), ratio of early mitral peak inflow velocity to early mitral peak annulus velocity (TDI) (E/e') lateral, septal, and average	To specify the Echo parameters to be assessed for diastolic dysfunction.

Section Number & Title	Description of Changes	Brief Rationale
Synopsis – Study Endpoints; Section 13.2.3 Exploratory Endpoints	Updated Exploratory Endpoints as follows:	To clarify the planned exploratory endpoints
	• [redacted] will be summarized by the cohort (MYH7, TTN, and other DCM) using descriptive statistics	To accommodate the new cohort of DCM
	• Clinical safety and tolerability in Part B	To define safety and tolerability for Part B
	• Additional exploratory endpoints, including concentration-PD effect and soluble biomarkers of cardiac physiopathology may be included	To assess the added exploratory objectives for biomarker for cardiac physiopathology
	• Frequency of left ventricular reverse remodeling (LVRR) during Part B, defined by the following criteria by TTE and CMR (if any)	To define assessment endpoint for the exploratory objective of effect of danicamtiv on cardiac structure and function in Part A and Part B
	• Frequency of improvements in LVEF during Part A	To define assessment endpoint for the exploratory objective of effect of danicamtiv on cardiac structure and function in Part A and Part B
Synopsis – Sample Size and Statistical Considerations; Section 13.3.2 General Considerations	Added that clinical data will be summarized by MYH7, TTN, and other DCM. For MYH7 and TTN cohorts, data may be summarized by variant type and the location. For DCM cohort, data will be further evaluated by genetic mutation-positive and genetic mutation-negative variable. If positive genetics are identified, additional analysis may be performed by variant type.	To reflect statistical consideration for the added DCM cohort which will include genetic and non-genetic causes.
	Added that Depending on reports from central genetic testing laboratory, participant reallocation to adequate cohort and additional analysis may be performed.	To clarify participant reallocation and additional data analysis may be performed if there was significant discrepancy between the information used for genetic eligibility at Screening and reports from a central genetic laboratory

Section Number & Title	Description of Changes	Brief Rationale
Section 1 Introduction	Added definition of DCM as a disease of the myocardium defined by left ventricular enlargement and myocardial systolic and diastolic dysfunction in the absence of known abnormal loading condition or significant coronary artery disease. Added that recently, hypokinetic non-dilated cardiomyopathy (HNDC) which is defined as LV or biventricular global systolic dysfunction without dilatation in the absence of the same conditions for previously described DCM has been considered as a part of DCM.	To add disease state background
Figure 2: Part A Study Schema	Updated to include the new cohort	To reflect the new cohort
Synopsis – Study Design; Section 6.1.2 Part B; Synopsis – Study Treatment; Appendix I Schedule of Assessments, Part B (Observational Cohort)	Added as an option for those who did not opt to participate in Part B, an observational study without the study drug administration will be available (Part B observational study). The limited study assessments at the reduced study visits will be performed after participants consent to this observational study	Allows patients who did not opt to Part B to participate in a new observational study which aims to observe natural course of cardiac status.
Section 6.2.3 Data Reviews; Section 13.3 Statistical Analysis	Added that additional reviews may be conducted	To clarify potential review which may be considered
Section 6.2.3 Data Reviews	Changed the section title to Data Reviews from Safety Review	To generalize data type to be reviewed during study
Section 9.1.1 Supply of Investigational Medical Product	Added that [redacted] tablets will be supplied in high-density polyethylene bottles with induction seals and child-resistant caps of 3 strengths: 5 mg (to support the 5 mg BID and 10 mg BID doses), 25 mg, and 50 mg for Part A	To clarify the additional type of IMP will be provided for Part A
Section 9.3 Treatment Compliance	Added that during Part B, an investigational product diary will be used to ensure compliance	A diary to record IMP administration will be used in Part B to ensure compliance
Section 11.3.2 Genetic/Genotype/Pharmacogenetic/Biomarker Assessment	Added “circulating biomarkers” as potential future analysis Added “Beside genetic testing for variants associated with cardiomyopathies that is mandatory.”	To clarify, genetic testing to assess variants associated with cardiomyopathy will be performed for all participants. Testing will be conducted prospectively at Screening or retrospectively after being enrolled.
Section 11.6 Participant Restrictions During the Study	Added that the restrictions will not apply to the participants of the Part B observational study	Restriction to ensure adequate dosing and safety related to danicamtiv will not be required for Part B observational study since there will be no danicamtiv treatment

Section Number & Title	Description of Changes	Brief Rationale
Section 12.1.2 Serious Adverse Events	Removed treatment-emergent period from this section. Updated that the SAE collection period is from ICF signing to 30 days after the last study drug administration	To update the SAE collection period
Section 12.1.2 Serious Adverse Events; Section 12.3 Reporting Period and Follow Up	Clarified that SAEs will be collected whether or not the events are considered related to the study medication or study procedure	To clarify that SAEs will be collected regardless of relatedness to the study medication or procedure
Section 12.3 Reporting Period and Follow Up	Deleted the statement that the AEs occurring after providing informed consent but before the study dose administration will be reported as AEs only if considered related to protocol or study procedures.	To clarify that AEs occurring after signing ICF to be reported regardless of study drug or procedure relatedness
Section 13.3.7.1 Adverse Events	Moved the definition of TEAEs to this section. Added that TEAEs are defined as AEs with onset on or after the first dose of the study drug to 14 days after the last study drug administration	The same information was described in SAE section (12.1.2) in previous protocol. TEAE definition is moved to this section.
6.2.1. Temporary Treatment Discontinuation (or Treatment Interruption)	Change in protocol text: hsTnI (high sensitive Troponin I) was changed to TnI (standard Troponin I)	To reflect protocol clarification letter (PCL) dated 30 June 2022. To correct a typographical error and to be consistent with Section 11.4.6.
Appendix 1. Schedule of Assessments, Part B (Active Cohort)	If Visits 5A and 1B are not performed on the same day, Part B Medical History assessment to be done on study participants who require Rescreening Visit for Part B (V0B) or sign the Part B ICF at V1B and are less than or equal to 56 days from completion of Part A.	To reflect PCL dated 30 June 2022. To clarify that Part B Medical History will also be assessed on study participants who sign the Part B ICF at V1B and are less than or equal to 56 days from completion of Part A
Protocol Synopsis-Study Duration	Change in protocol text: The expected study duration of Part A for each participant ranges from approximately 4 to 11 weeks, including 2 to 8 weeks for Screening, 9 to 16 days for treatment, and approximately **2 weeks** for follow-up.	To reflect protocol clarification letter date 03 May 2022. To correct a typographical error and to be consistent with Section 6.1.1. and Appendix 1. Schedule of Assessments regarding Visit 5A.
Protocol Synopsis-Part A Exclusion Criteria	Removed the comma following “pacing” in E2. A participant has a QTcF interval > 480 milliseconds, not attributable to ventricular pacing or has prolonged QRS duration ≥ 120 milliseconds, average of triplicate ECGs.	To reflect protocol clarification letter date 03 May 2022. To correct a typographical error and to be consistent with Section 7.2. regarding exclusion criterion #2.
Appendix 1. Schedule of Assessments, Part A	Changed the TH3A visit to 1-3 days after V4A.	To reflect protocol clarification letter date 03 May 2022. To correct a typographical error and to be consistent with Section 6.1.1 regarding Part A telehealth visit (TH) 3A.

Section Number & Title	Description of Changes	Brief Rationale
Appendix 1. Schedule of Assessments, Part A	FSH level assessment done at Screening (V1.1A) is only for women of non-childbearing potential (WONCBP).	To reflect protocol clarification letter date 03 May 2022. To clarify that FSH level assessment is only for WONCBP to determine if FSH levels meet postmenopausal level defined in Appendix 6.
Appendix 1. Schedule of Assessments, Part A	Added to footnote “o” for Blood sample for pharmacogenetic testing:	Additional samples for pharmacogenetic testing will be collected if needed (eg., samples determined as not adequate for DNA extraction) anytime during the study after participants provided consent for additional sample collection.
Appendix 1. Schedule of Assessments, Part A (Active Cohort)	Added footnote “x” for KCCQ-23	To indicate that this should be done before any other assessments
Appendix 1. Schedule of Assessments, Part B (Active Cohort)	Added 12-lead ECG to Rescreening Visit	To evaluate any changes in ECG prior to participating in Part B
Appendix 1. Schedule of Assessments, Part B (Active Cohort)	Changed the Follow up visit to Week 98	To align with the Follow up visit schedule in Part A
Appendix 1. Schedule of Assessments, Part B (Active Cohort)	Added ± 2 days visit window to V2B	To allow for flexibility
Appendix 1. Schedule of Assessments, Part B (Active Cohort)	Added Medical history to V1B if needed	To allow for medical history assessment if needed at Part B baseline
Appendix 1. Schedule of Assessments, Part B (Active Cohort)	Added footnote “o” to denote that screening laboratory tests will include TSH and Fe/TIBC/ferritin to V0B visit	To exclude uncontrolled thyroid function and Fe overload
Appendix 1 Schedule of Assessments, Part B (Observational Cohort)	Added to list schedule of assessments for the observational study	To clarify assessments during the study
Appendix 6. Women of Childbearing Potential Definitions and Methods of Contraception	Added “and/or bilateral tubal occlusion or ligation” and “documented bilateral tubal occlusion or ligation.”	To update the contraception methodology by including an additional acceptable method