Phase 2a Study of Danicamtitiv (MYK-491) in Patients with Chronic Heart Failure with Reduced Ejection Fraction (HFrEF)

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Disclosures

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Danicamtiv (formerly MYK-491) is an investigational drug
Introduction

- Both LV and LA dysfunction and remodelling contribute to adverse outcomes in HFrEF.
- Danicamtilv is a novel, orally bioavailable, selective cardiac myosin activator that:
  - Increases the number of actin–myosin cross-bridges
  - Enhances force-production of the cardiac sarcomere
Introduction

- In preclinical studies, danicamtiv increased myocardial contraction with little effect on diastolic stiffness/tension.¹

- These findings were also observed in a first-in-human healthy-volunteer study.²

- Here, we report the first evaluation of the safety and preliminary efficacy of danicamtiv in a randomized, double-blind, multiple-dose, phase 2a study in patients with HFrEF.

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Phase 2a Multiple-Dose Study Design

Randomized, double-blind, parallel group, placebo-controlled trial

**Inclusion criteria**
- Stable chronic HFrEF
- LV ejection fraction ≤ 35%
- Treated with GDMT
- Troponin I ≤ 0.15 ng/mL
- eGFR ≥ 30 mL/min/1.73 m²
- No current or recent AF

**Dosing regimens**
- 50 mg BID (n = 9)
- 75 mg BID (n = 15)
- 100 mg BID (n = 6)
- Placebo (n = 10)

**Patients confined/closely monitored**
- Single-blind placebo (baseline)
- Double-blind period (placebo, n = 10; danicamtiv, n = 30)
- Washout

- D1–D2
- D3–D9
- D10–D11
- Follow-up visit D16

AF, atrial fibrillation; BID, twice daily; d, day; eGFR, estimated glomerular filtration rate; HFrEF, heart failure with reduced ejection fraction; ULN, upper limit normal.
### Demographics and Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n = 10)</th>
<th>Total danicamtiv (n = 30)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median age, years (IQR)</strong></td>
<td>58 (53; 62)</td>
<td>60 (55; 65)</td>
</tr>
<tr>
<td><strong>Women, n (%)</strong></td>
<td>1 (10)</td>
<td>9 (30)</td>
</tr>
<tr>
<td><strong>White / Black, n (%)</strong></td>
<td>7 (70) / 3 (30)</td>
<td>24 (80) / 6 (20)</td>
</tr>
<tr>
<td><strong>Ischaemic heart disease, n (%)</strong></td>
<td>4 (40)</td>
<td>15 (50)</td>
</tr>
<tr>
<td><strong>Median time from diagnosis, years (IQR)</strong></td>
<td>5.6 (3.9; 9.1)</td>
<td>6.6 (1.9; 10.6)</td>
</tr>
<tr>
<td><em><em>NYHA functional class</em>, n (%)</em>*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>2 (20)</td>
<td>4 (13.3)</td>
</tr>
<tr>
<td>II</td>
<td>8 (80)</td>
<td>19 (63.3)</td>
</tr>
<tr>
<td>III</td>
<td>0</td>
<td>4 (13.3)</td>
</tr>
<tr>
<td><strong>Median GFR, mL/min/1.73 m² (IQR)</strong></td>
<td>55 (52; 75)</td>
<td>73 (67; 83)</td>
</tr>
<tr>
<td><strong>Guideline-recommended medical therapy</strong>, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACE inhibitor, ARB or sacubitril/valsartan</td>
<td>10 (100)</td>
<td>29 (97)</td>
</tr>
<tr>
<td>β-blocker</td>
<td>9 (90)</td>
<td>30 (100)</td>
</tr>
<tr>
<td>MRA</td>
<td>6 (60)</td>
<td>16 (53.3)</td>
</tr>
<tr>
<td><strong>Median supine systolic blood pressure, mmHg (IQR)</strong></td>
<td>124 (110; 132)</td>
<td>108 (104; 126)</td>
</tr>
<tr>
<td><strong>Median NT-proBNP, pg/mL (IQR)</strong></td>
<td>442 (107; 847)</td>
<td>305 (172; 892)</td>
</tr>
</tbody>
</table>

*NYHA missing in 3 patients. **33% of all patients received sacubitril/valsartan.
ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker; GFR, glomerular filtration rate; IQR, interquartile range; MRA, mineralocorticoid receptor antagonist; NT-proBNP, B-type natriuretic peptide; NYHA, New York Heart Association.
Echocardiography Analysis and Results

- Each patient had multiple echos performed (at baseline and post-treatment)
  - 489 echos were performed during the study
  - Danicamtiv plasma concentrations were assessed concomitantly with each post-treatment echo (D3–D11)
- For each echo parameter, results shown are placebo-corrected change from baseline for each of the 3 danicamtiv concentration ranges; they were estimated using a mixed effects model
  - Low (<2000 ng/mL), medium (2000 – <3500 ng/mL) and high (≥3500 ng/mL)
  - All post-treatment echocardiographic data are included for assessing the effects at the danicamtiv concentration range reached concomitantly to the echocardiogram
# LV Contractility and Dimensions

<table>
<thead>
<tr>
<th>LV contractility</th>
<th>Placebo-corrected mean change (SE) from baseline by danicamtiv plasma concentration range</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline* (n = 40)</td>
</tr>
<tr>
<td></td>
<td>&lt;2000 ng/mL (n = 30)</td>
</tr>
<tr>
<td></td>
<td>2000 – &lt;3500 ng/mL (n = 26)</td>
</tr>
<tr>
<td></td>
<td>≥3500 ng/mL (n = 13)</td>
</tr>
<tr>
<td>LV stroke volume (mL)</td>
<td>59 (13)</td>
</tr>
<tr>
<td></td>
<td>3.1 (1.8)</td>
</tr>
<tr>
<td></td>
<td>7.8** (2.0)</td>
</tr>
<tr>
<td></td>
<td>5.7* (2.5)</td>
</tr>
<tr>
<td>LV ejection fraction (%)</td>
<td>32 (6)</td>
</tr>
<tr>
<td></td>
<td>-0.3 (0.9)</td>
</tr>
<tr>
<td></td>
<td>1.1 (0.9)</td>
</tr>
<tr>
<td></td>
<td>2.3 (1.2)</td>
</tr>
<tr>
<td>LV fractional shortening (%)</td>
<td>18 (5)</td>
</tr>
<tr>
<td></td>
<td>0.5 (0.5)</td>
</tr>
<tr>
<td></td>
<td>0.8 (0.6)</td>
</tr>
<tr>
<td></td>
<td>0.5 (0.7)</td>
</tr>
<tr>
<td>LV global longitudinal strain (%)</td>
<td>-11.2 (2)</td>
</tr>
<tr>
<td></td>
<td>-0.3 (0.3)</td>
</tr>
<tr>
<td></td>
<td>-0.9* (0.4)</td>
</tr>
<tr>
<td></td>
<td>-1.0* (0.4)</td>
</tr>
<tr>
<td>LV global circumferential strain (%)</td>
<td>-14.1 (4.3)</td>
</tr>
<tr>
<td></td>
<td>-0.4 (0.6)</td>
</tr>
<tr>
<td></td>
<td>-2.1** (0.7)</td>
</tr>
<tr>
<td></td>
<td>-3.3** (0.8)</td>
</tr>
<tr>
<td>LV end-systolic diameter (mm)</td>
<td>48 (8)</td>
</tr>
<tr>
<td></td>
<td>-0.8 (0.4)</td>
</tr>
<tr>
<td></td>
<td>-1.3** (0.5)</td>
</tr>
<tr>
<td></td>
<td>-1.8** (0.6)</td>
</tr>
<tr>
<td>LV end-diastolic diameter (mm)</td>
<td>58 (7)</td>
</tr>
<tr>
<td></td>
<td>-0.6 (0.3)</td>
</tr>
<tr>
<td></td>
<td>-0.9** (0.3)</td>
</tr>
<tr>
<td></td>
<td>-1.8** (0.4)</td>
</tr>
<tr>
<td>Systolic Ejection Time (msec)</td>
<td>286 (29)</td>
</tr>
<tr>
<td></td>
<td>15** (3.5)</td>
</tr>
<tr>
<td></td>
<td>36** (3.8)</td>
</tr>
<tr>
<td></td>
<td>48** (4.7)</td>
</tr>
</tbody>
</table>

* p < 0.05, ** p < 0.01, *Absolute arithmetic mean values (SD), LV, left ventricular; SE, standard error; SET, systolic ejection time.

- Treatment with danicamtiv increased LV stroke volume, improved LV longitudinal and circumferential strain, and reduced LV dimensions.
- Treatment with danicamtiv increased SET in a concentration-dependent manner.
## LV Diastolic Function

<table>
<thead>
<tr>
<th>LV diastolic function</th>
<th>Baseline(^a) (n = 40)</th>
<th>Placebo-corrected mean change (SE) from baseline by danicamtilv plasma concentration range</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;2000 ng/mL (n = 30)</td>
<td>2000 – &lt;3500 ng/mL (n = 26)</td>
</tr>
<tr>
<td>e’ (lateral)</td>
<td>6.3 (1.9)</td>
<td>–0.2 (0.2)</td>
</tr>
<tr>
<td>E/e’ (lateral)</td>
<td>12.4 (5.8)</td>
<td>–0.8 (0.5)</td>
</tr>
<tr>
<td>E-wave peak (cm/s)</td>
<td>69 (25)</td>
<td>–3.8 (2.1)</td>
</tr>
<tr>
<td>A-wave peak (cm/s)</td>
<td>74 (25)</td>
<td>4.1* (1.9)</td>
</tr>
<tr>
<td>E/A ratio</td>
<td>1.0 (0.4)</td>
<td>–0.1** (0.04)</td>
</tr>
<tr>
<td>IVRT (msec)</td>
<td>123 (24)</td>
<td>2.7 (5.1)</td>
</tr>
</tbody>
</table>

\(^a\) n = 40; \(^*\) p < 0.05; \(^\ast\) p < 0.01. \(^\ast\)Arbitrary arithmetic mean values (SD).

A, late peak wave velocity from mitral inflow Doppler; e’, peak atrioventricular valve annular velocity in early diastole; E, early peak wave velocity from mitral inflow Doppler; IVRT, isovolumic relaxation time; SE, standard error.

### Notes

- Treatment with danicamtilv had moderate impact on diastolic function and no impact on filling pressures.
## Left Atrium (LA) Parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline(^a) (n = 40)</th>
<th>&lt;2000 ng/mL (n = 30)</th>
<th>2000 – &lt;3500 ng/mL (n = 26)</th>
<th>≥3500 ng/mL (n = 13)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LA volume and function</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LA emptying fraction (%)</td>
<td>41 (8)</td>
<td>2.1 (1.2)</td>
<td>3.3* (1.3)</td>
<td>3.6* (1.6)</td>
</tr>
<tr>
<td>LA maximal volume index (mL/m(^2))</td>
<td>28 (9)</td>
<td>−1.2 (0.6)</td>
<td>−1.1 (0.7)</td>
<td>−1.3 (0.8)</td>
</tr>
<tr>
<td>LA minimal volume index (mL/m(^2))</td>
<td>17 (7)</td>
<td>−1.8** (0.6)</td>
<td>−2.1** (0.6)</td>
<td>−2.4** (0.7)</td>
</tr>
<tr>
<td>LA function index</td>
<td>26 (13)</td>
<td>2.6 (1.5)</td>
<td>6.1** (1.6)</td>
<td>5.8** (2.0)</td>
</tr>
</tbody>
</table>

\(^a\) Absolute arithmetic mean values (SD)

\(^*\) p < 0.05, \(^*\)* p < 0.01.

- Treatment with danicamtiv led to a reduction in LA minimal volume index, an increase in LA emptying fraction and a marked improvement in LA function index.
### Summary of TEAEs (Primary Objective)

<table>
<thead>
<tr>
<th>Number of patients (%) with AEs</th>
<th>Placebo (n = 10)</th>
<th>50 mg (BID) (n = 9)</th>
<th>75 mg BID (n = 15)</th>
<th>100 mg BID (n = 6)</th>
<th>Total danicamtiv (n = 30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any TEAE</td>
<td>4 (40.0)</td>
<td>7 (77.8)</td>
<td>6 (40.0)</td>
<td>4 (66.7)</td>
<td>17 (56.7)</td>
</tr>
<tr>
<td>Any serious TEAE</td>
<td>0</td>
<td>0</td>
<td>1 (6.7)</td>
<td>0</td>
<td>1 (3.3)</td>
</tr>
</tbody>
</table>

*AE, adverse event; BID, twice daily; TEAE, treatment emergent adverse event*

- All TEAEs observed with danicamtiv (except one) were considered to be of mild intensity and/or unrelated to study treatment.
- No TEAEs led to discontinuation or death.
- No particular pattern or organ specificity was observed.
- One serious event of hyperkalaemia in a patient receiving danicamtiv resolved.
Serum Troponin Concentrations (Median Change from Baseline)

- None of the troponin increases observed were associated with symptoms or with ECG changes suggestive of ischaemia.
- All troponin increases returned to normal or baseline levels.
### Holter Results (total ectopy and atrial fibrillation/NSVT)

<table>
<thead>
<tr>
<th>Number of patients (%) with increased total ectopya</th>
<th>Placebo (n = 10)</th>
<th>Danicamtiv (n = 27)b</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increase in total atrial ectopy</td>
<td>5 (50)</td>
<td>13 (48)</td>
</tr>
<tr>
<td>Increase in total ventricular ectopy</td>
<td>8 (80)</td>
<td>15 (56)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Number of patients (%) with atrial fibrillation/NSVT during treatment</th>
<th>Placebo (n = 10)</th>
<th>Danicamtiv (n = 29)c</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atrial fibrillation</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>NSVT (&gt;10 beats)</td>
<td>1 (10)</td>
<td>3 (10)</td>
</tr>
<tr>
<td>NSVT (&gt;15 beats)</td>
<td>1 (10)</td>
<td>2 (7)</td>
</tr>
</tbody>
</table>

- Total ectopy defined as number of singles + couplets + runs of 3 or more consecutive ectopic beats; Increased total ectopy is in comparison to baseline. ^ Excludes 3 patients (2 baseline Holter data not obtained, 1 corrupted data card). 
- Excludes 1 Holter (corrupted data card). 
- NSVT, non-sustained ventricular tachycardia.

- Holter monitoring revealed no increase in atrial or ventricular arrhythmias with danicamtiv compared with placebo.
Conclusions

- Danicamtiv, administered for 7 days in patients with chronic HFrEF, improved LV systolic function and markedly improved LA function.

- Danicamtiv was generally well tolerated.
  - There were slight increases in troponin concentrations

- These findings warrant follow-up danicamtiv studies with longer treatment duration in patients with HFrEF.

HFrEF, heart failure with reduced ejection fraction; LA, left atrial; LV, left ventricular.
I would like to thank the following people and teams:

• Patients and their families

• Co-authors, Investigators, Cardiac Imaging Core Lab, including:

• The MyoKardia and Medpace teams
Effects of danicamtiv, a novel cardiac myosin activator, in heart failure with reduced ejection fraction: experimental data and clinical results from a phase 2a trial