Danicamtiv (MYK-491) A Novel Small-Molecule Cardiac Activator: in vitro/in vivo Evidence for Overall Myocardial Inotropy

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Danicamtiv (formerly MYK-491) is an investigational drug
**Background:** What is Danicamtiv (MYK-491)?

**Danicamtiv** is a novel, selective small-molecule direct activator of cardiac acto-myosin, that enhances the **force-producing** chemo-mechanical cycle.

- **Increases the rate of phosphate (Pi) release** of cardiac myosin (acto-myosin)
- **Increases availability of myosin-heads** that can form cross-bridges (closer to actin)
- **Preserves both ADP release** (increased) and **power-stroke rates** (+2% @ ~AC90)

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**Ca2+ off-rate** (relaxation)

- **-7%**
- No effects on Ca2+ homeostasis/transients

**ATPase Rate (fold)**

- **hrS1**: human (recombinant) cardiac sub-fragment 1 myosin
- **rskS1**: rabbit (fast) skeletal sub-fragment 1 myosin
- **cgS1**: chicken gizzard (smooth muscle) sub-fragment 1 myosin
**Background:** What is Danicamtiv (MYK-491)?

Danicamtiv is a novel, selective small-molecule direct activator of cardiac acto-myosin, that enhances the force-producing chemo-mechanical cycle.

Danicamtiv can increase overall (LV and LA) cardiac performance in vivo, improving mechanical efficiency while preserving resting (diastolic) tension and filling.

- No effects on Ca2+ homeostasis/transients
- Increases the rate of phosphate (Pi) release of cardiac myosin (acto-myosin)
- Increases availability of myosin-heads that can form cross-bridges (closer to actin)

**hrS1:** human (recombinant) cardiac sub-fragment 1 myosin
**rskS1:** rabbit (fast) skeletal sub-fragment 1 myosin
**cgS1:** chicken gizzard (smooth muscle) sub-fragment 1 myosin
**RESULTS:** Direct LV and LA systolic activation (ex vivo)

- Increases myofibrilar (ATPase) activity…
- ...and tension generation in both LA and LV

**SYSTEM:** myofibrils and fibers from healthy Yucatan mini-pigs
**RESULTS:** Efficient Improvement in Myocardial Function (1)

- Increases contractility and stroke-volume (SV)

![Graphs showing changes in Ees, PRSW, SV, SW, PVA, SW/PVA](image)

...as well as stroke-work, enhancing mechanical efficiency (SW/PVA)

SYSTEM: conscious healthy beagle dogs (chronically instrumented for left-ventricular pressure-volume relationships). Danicamtiv (3 mg/kg PO); data at baseline (PRE) and +5hr post-dose.
**RESULTS:** Efficient Improvement in Myocardial Function (2)

- Increases contractility and stroke-volume (SV)
  …as well as stroke-work, enhancing mechanical efficiency (SW/PVA)

- Prolongs systole (SET), but preserves compliance

- **Improves LV and LA performance**, decreasing LA size (chronic HF)

![Graphs showing changes in SET, LVFS, LVSV, LA EF, LA Volmin, and LA FI with Danicamtiv](image)

**SYSTEM:** conscious beagle dogs with induced cardiac dysfunction/heart failure (serial coronary microembolizations) Danicamtiv (2-3 mg/kg PO); data at baseline (PRE) and +5hr post-dose
Direct acto-myosin activation with danicamtilv has a unique cardiovascular profile characterized by direct atrial and ventricular systolic activation, as well as by both preserved efficiency and diastolic properties.

Data provides mechanistic support for the (preliminary) observations in healthy volunteers and DCM patients.