Selective Cardiac Myosin Activators in Heart Failure

John McMurray
Eugene Braunwald Scholar in Cardiovascular Diseases, Brigham and Women’s Hospital, Boston & Visiting Professor, Harvard Medical School
Cardiac Myosin Activation: A Potential Therapeutic Approach for Systolic Heart Failure


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Omecamtiv mecarbil (CK-1827452/AMG 423): A selective cardiac myosin activator

To the rescue of the failing heart

Heart failure is characterized by weakened contractions of heart muscle. A drug that directly activates the key force-generating molecule in this muscle may be a valuable tool to strengthen the failing heart.

DONALD M. BERS & SAMANTHA P. HARRIS

Heart failure affects tens of millions of people worldwide, with patients’ prognosis often being a bleak five-year survival from the time of diagnosis. Patients...
How does omecamtiv mecarbil work?

The actin-myosin cycle

OM increases the transition rate from weak to strong binding states

Omecamtiv mecarbil increases the number of independent force generators (myosin heads) interacting with the actin filament

“More hands pulling on the rope”

Malik FI, et al. Science 2011
Omecamtiv mecarbil (CK-1827452/AMG 423): Experimental actions

Malik FI, et al. Science 2011
Omecamtiv mecarbil: summary of preclinical findings

- Selective activator of cardiac myosin
- Increases duration of systole by
  - Increasing entry rate of myosin into force-producing state
  - Therefore increasing overall number of active cross-bridges
- No increase in intracellular Ca$^{2+}$
- No change in dP/dt$_{max}$
- No increase in MVO$_2$
Human studies in heart failure

- Proof of concept study in CHF (CY1121)
- Ischaemic cardiomyopathy safety study (CY1221)
- Newly initiated study in AHF (AMG 20100754)
Study CY 1121: Objectives

- **Primary**
  - Evaluate the safety and tolerability of CK-1827452 administered as an intravenous infusion to patients with stable heart failure

- **Secondary**
  - Pharmacokinetics in stable heart failure
  - Pharmacodynamics as function of dose & plasma concentration: LV function by echocardiography
Study CY 1121: Patients

- **Inclusion**
  - Clinical diagnosis of heart failure
  - EF < 40% (Cohort 4; EF < 30%)
  - Sinus rhythm
  - Stable drug regimen including
    - ACE inhibitor or ARB
    - Beta-blocker
    - Diuretics (if needed)

- **Exclusion**
  - CV hospitalization within 6 weeks of entry
  - CCS Class III or IV angina
Study CY 1121: Study Design

**Stable Heart Failure Patients**
Double-Blind/Placebo Controlled

- **Cohort 1**
  - N = 8
  - 2-hr Infusion
  - 4 Treatments
  - 3 Active Doses
  - 1 Placebo
  - Median Cmax: 93-333 ng/ml

- **Cohort 2**
  - N = 9
  - 2-hr Infusion
  - 4 Treatments
  - 3 Active Doses
  - 1 Placebo
  - Median Cmax: 333-662 ng/ml

- **Cohort 3**
  - N = 10
  - 24-hr Infusion
  - 4 Treatments
  - 3 Active Doses
  - 1 Placebo
  - Median Cmax: 150-625 ng/ml

- **Cohort 4**
  - N = 8
  - 24-hr Infusion
  - 4 Treatments
  - 3 Active Doses
  - 1 Placebo
  - Median Cmax: 152-626 ng/ml

- **Cohort 5**
  - N = 10
  - 72-hr Infusion
  - 2 Treatments
  - 1 Active Dose
  - 1 Placebo
  - Median Cmax: 750 ng/ml

- 45 Patients
- 564 Echos
- 151 Treatment Periods
# Study CY 1121: Demographics and baseline characteristics

Cohorts 1-5  
(n = 45 patients)

<table>
<thead>
<tr>
<th></th>
<th>Mean</th>
<th>(Min.- Max.)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex</strong> (male/female)</td>
<td>39/6</td>
<td></td>
</tr>
<tr>
<td><strong>Aetiology</strong> (ischemic/non-ischemic)</td>
<td>29/16</td>
<td></td>
</tr>
<tr>
<td><strong>Age (yrs)</strong></td>
<td>58</td>
<td>30 – 77</td>
</tr>
<tr>
<td><strong>Systolic BP (mmHg)</strong></td>
<td>124</td>
<td>96 – 183</td>
</tr>
<tr>
<td><strong>Diastolic BP (mmHg)</strong></td>
<td>75</td>
<td>57 – 117</td>
</tr>
<tr>
<td><strong>Heart rate (bpm)</strong></td>
<td>69</td>
<td>48 – 96</td>
</tr>
<tr>
<td><strong>Ejection fraction (%)</strong></td>
<td>33</td>
<td>20 – 55</td>
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</tbody>
</table>
Study CY 1121: Systolic ejection time
Placebo Corrected Change from Baseline

Δ SET (msec)

<100  >100-200  >200-300  >300-400  >400-500  >500

[CK-452] (ng/mL)

p value for correlation < 0.0001

* p < 0.05
** p < 0.01
*** p < 0.001
Study CY 1121: Stroke volume and heart rate
Placebo Corrected Change from Baseline

**Δ Stroke Volume (mL)**
(Baseline 69 mL)

**Δ Heart Rate (bpm)**
(Baseline 66 bpm)

p value for correlation < 0.0001

p value for correlation = 0.0003

* p < 0.05  ** p < 0.01  *** p < 0.001
Study CY 1121: LV end systolic volume and end diastolic volume

Placebo Corrected Change from Baseline

Δ LV ESV (mL) (Baseline 168 mL)

Δ LV EDV (mL) (Baseline 243 mL)

p value for correlation < 0.0001

p value for correlation = 0.0005

* p < 0.05  ** p < 0.01  *** p < 0.001
Study CY 1121: LV ejection fraction†
Placebo Corrected Change from Baseline (=32%)

\[ \Delta \text{LVEF}_{\text{Hybrid}} \] (LSM ± SEM)

- <100
- >100-200
- >200-300
- >300-400
- >400-500
- >500

\[ [\text{CK-452}] \] (ng/mL)

\( p \) value for correlation < 0.0001

\( ^{\dagger} \text{LVEF}_{\text{Hybrid}} = \text{LVOT SV/LVEDV}_{\text{MOD}} \)
Study CY 1121: Safety

- **Three SAEs (one deemed related to CK-452)**
  - Non ST elevation MI in patient with a drug overdose
  - Septicemia in setting of diabetic foot ulcer
  - Pneumonia

- **Five patients were discontinued on study drug**
  - Two syndromes of clinical intolerance due to excessive [CK-452]
  - Asymptomatic troponin I increase in severely hypertensive patient
  - Local contractile dysfunction noted on echocardiogram; peer review of echocardiograms did not confirm finding
  - QTc > 500 msec during infusion; core lab determined QTcF 493 msec at baseline, 499 msec at termination

- **For patients tolerant of all study drug infusions, no consistent pattern of adverse events with either dose or duration of infusion emerged**
CY 1221: Ischaemic cardiomyopathy trial

Phase IIa
Patients with ischaemic cardiomyopathy and angina
(Ejection fraction ≤ 35%)

Assess effect of i.v. infusion of omecamtiv mecarbil
on symptom-limited treadmill exercise
tolerability and plasma concentrations of oral formulation

Cohort 1
45 patients
Randomized 2:1
*Omeamtiv mecarbil* at lower dose
i.v. (295 ng/ml) 20 hours
oral (184 ng/ml) 7 days or placebo

Cohort 2
45 patients
Randomized 2:1
*Omeamtiv mecarbil* at higher dose
i.v. (550 ng/ml) 20 hours
Oral (368 ng/ml) 7 days or placebo
Omecamtiv mecarbil did not have a negative impact on exercise performance/exercise induced ischaemia* at either dose
No clinically important changes in vital signs, ECG parameters or cardiac enzymes
Majority of adverse events classified as mild in severity
2 SAE’s (both in same patient); determined by investigator unrelated to treatment

<table>
<thead>
<tr>
<th>Adverse Event Classification</th>
<th># Events</th>
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<tr>
<td>Mild</td>
<td>23</td>
</tr>
<tr>
<td>Moderate</td>
<td>4</td>
</tr>
<tr>
<td>Severe</td>
<td>2</td>
</tr>
<tr>
<td>Total</td>
<td>29</td>
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Final data demonstrated drug dosing regimen was reasonably well-tolerated. Data support progression into additional clinical trials

* Proportion of patients who stopped exercise during i.v. infusion at a stage earlier than baseline and due to unacceptable angina (placebo: 1, omecamtiv mecarbil: 0)
Acute heart failure

Ultrafiltration: Aqual natriuresis

Bilevel or continuous positive airway pressure: Preload reduction

Nitrates, nitroprusside, dobutamine: Arterial vasodilation

Dobutamine, dopamine, milrinone: Increased inotropy

Nitrates, morphine: Venodilation

Furosemide: Natriuresis
Minimal in-hospital follow-up until 24 hrs after ending IP
Minimal telemetry until 12 hrs after ending IP
Earliest Discharge on Day 4
Study assessments: Daily until discharge or day 8, whichever is earlier
On day of discharge

Sequence cohort enrollment of low, medium and high dose target AMG 423 plasma concentrations: 115, 230, 310 ng/mL

**Study 20100754: Design**

Presentation for AHF → Screening → Randomization 1:1

Omecamtiv mecarbil IV → Placebo IV

Randomization within 16 hours of presentation

Loading Dose | Maintenance Dose

Time

0 hr | 4 hrs | 48 hrs | 72 hrs “Day 4” | Day 30 EOS | Month 6

Vital Status (phone call)

MANDATORY IN - HOSPITAL STAY
Study 20100754: Sequential dosing design

Randomized, double-blind, placebo-controlled, sequential cohort trial in subjects with LVSD and hospitalization for AHF

Enrollment and Treatment of Low Dose Cohort

Placebo IV

1:1 randomization

Omecamtiv IV: target conc ~115 ng/mL

DMC data review and recommendation for next dose level

Enrollment and Treatment of Medium Dose Cohort

Placebo IV

1:1 randomization

Omecamtiv IV: target conc ~230 ng/mL

DMC data review and recommendation for next dose level

Enrollment and Treatment of High Dose Cohort

Placebo IV

1:1 randomization

Omecamtiv IV: target conc ~310 ng/mL
**Study 20100754: Efficacy endpoints**

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<tr>
<th>Primary Endpoint</th>
<th>Secondary Endpoints</th>
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| • Dyspnea symptom response: Minimally, moderately or markedly better by 7-point Likert scale at 6 hours after investigational product initiation, AND moderately or markedly better at 24 and 48 hours after investigational product initiation without worsening heart failure or death from any cause by 48 hours | • Death from any cause or worsening HF within 7 days of IP  
• Worsening heart failure within 7 days of IP  
• Dyspnea at each scheduled assessment  
• Patient Global Assessment  
• NT-proBNP  
• Length of initial hospital stay and days alive out of hospital until day 30 |
## Study 20100754: Safety and PK endpoints

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<thead>
<tr>
<th>Safety Endpoint</th>
<th>PK (All Subjects)</th>
</tr>
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</table>
| • Adverse events and serious adverse events  
• Significant changes in laboratory values and vital signs  
• Significant changes from baseline ECGs | • Plasma concentration of omecamtiv mecarbil at selected time points  
• Plasma concentration of circulating metabolites, including omecamtiv mecarbil M1 and M3 metabolites at selected time points |
Omecamtiv mecarbil (CK-1827452/AMG 423) is a novel agent which increases the duration of systole by selectively activating cardiac myosin.

Does not seem to have effects that characterise previously studied inotropes i.e. does not increase intracellular calcium concentrations and myocardial oxygen consumption.

Evolving clinical programme includes:
- Intravenous formulation being tested in acute HF
- Oral formulation is being developed for possible use in outpatient setting