Phase II Safety Study Evaluating the Novel Cardiac Myosin Activator, CK-1827452, in Patients with Ischemic Cardiomyopathy and Angina

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Introduction and Study Rationale

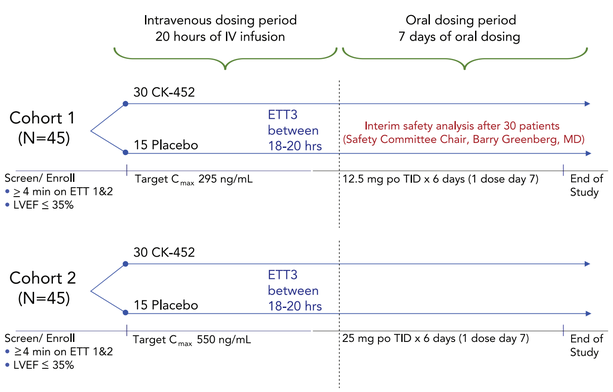
- CK-1827452 (CK-452) is a novel agent that increases systolic function by directly and selectively activating cardiac myosin
- In healthy volunteers and stable heart failure (HF) patients, CK-452 infusions resulted in concentration-dependent increases in systolic ejection time (SET), stroke volume, fractional shortening, and left ventricular ejection fraction[1,2]
- The dose limiting effect of CK-452 is believed to be related to excessive prolongation of SET, which can limit diastolic coronary flow and ventricular filling
- The present study (CY 1221) investigated whether symptom-limited exercise tolerance in heart failure patients with ischemic cardiomyopathy and angina (who would theoretically be most vulnerable to the adverse effects of SET prolongation) was diminished by CK-452 at concentrations previously shown to improve cardiac function

Methods

Study Design

- Double-blind, randomized (2:1; CK-452:placebo), placebo-controlled study of 2 sequential cohorts to evaluate effect of IV CK-452 on symptom-limited exercise tolerance in heart failure patients with ischemic cardiomyopathy and angina
- Key eligibility criteria
  - Documented ischemic cardiomyopathy
  - Current history of exercise-induced angina
  - LVEF ≤ 35% and [LVEDD ≥ 55 mm or LVEDD index ≥ 32 mm/m^2]
  - NYHA Class II-III
  - Able to complete at least 2 stages (4 minutes) of a modified Naughton exercise treadmill protocol on each of 2 separate screening ETTs
  - Receiving ACE inhibitor (and/or ARB) and beta blocker therapy
- Sample size was empirically determined to gain clinical safety experience, and not to formally test statistical hypotheses
- No clinical efficacy or pharmacodynamic assessments were intended in the design or objectives

Study Design Schematic



Study Endpoints

- Primary Safety Endpoint
  - Proportion who stop ETT3 due to angina at a stage earlier than baseline (defined as shorter of the 2 screening ETTs)
- Secondary Safety Endpoints
  - Proportion who stop ETT3 for any reason at a stage earlier than baseline
  - Exercise duration during ETT3
  - Proportion who stop ETT3 for angina
  - Time to angina during ETT3
  - Proportion with 1 mm ST depression during ETT3
  - Time to 1 mm ST depression during ETT3
- Other Safety Assessments
  - Vital signs, ECGs
  - Cardiac enzymes
  - AEs and SAEs

Results

Baseline Characteristics

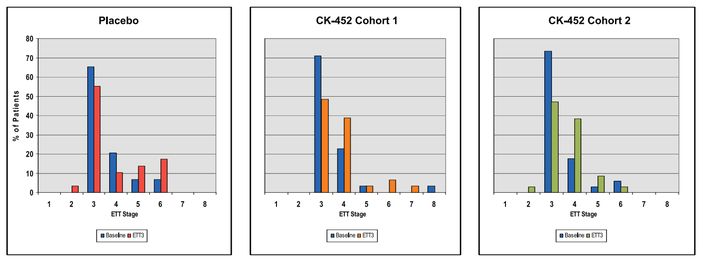
Baseline Characteristic	Placebo (N=29)	CK-452 Cohort 1 (N=31)	CK-452 Cohort 2 (N=34)	Total (N=94)
Age, mean (SD), years	62 (10)	65 (10)	63 (8)	63 (9)
Sex (male), n (%)	23 (79)	23 (74)	29 (85)	75 (80)
LVEDD, mean (SD), cm	7.2 (0.7)	7.1 (1.1)	7.2 (0.9)	7.1 (0.9)
LVEF, mean (SD), %	23 (6)	22 (7)	21 (7)	22 (7)
ETT duration (shorter of ETT1 or ETT2), mean (SD), seconds	351 (127)	348 (127)	334 (117)	344 (122)
Stopped ETT 1 or 2 for angina, n (%)	4 (14)	0 (0)	7 (21)	11 (12)

Safety Endpoints Summary

Primary Endpoint	Placebo (N=29)	CK-452 Cohort 1 (N=31)	CK-452 Cohort 2 (N=34)	Comments
Proportion Stopping ETT3 for Angina at Stage Earlier than Baseline, n (%)	1 (3.4%)	0 (0.0%)	0 (0.0%)	
Secondary Endpoint	**Placebo (N=29)**	**CK-452 Cohort 1 (N=31)**	**CK-452 Cohort 2 (N=34)**	**Comments**
Proportion Stopping ETT3 for Any Reason at Stage Earlier than Baseline, n (%)	1 (3.4%)	4 (12.9%)	2 (5.9%)	No dose dependent deleterious signal observed for higher (Cohort 2) vs. lower dose (Cohort 1) of CK-452
Change in Exercise Duration During ETT3 vs. Baseline, mean (SD) (seconds)	60.1 (71.2)	41.5 (113.1)	40.5 (70.6)	Cohort 1 placebo group mean (SD) increase from baseline: 72.6 (93.0) seconds Cohort 2 placebo group mean (SD) increase from baseline: 46.8 (35.0) seconds
Proportion Stopping ETT3 for Angina, n (%)	2 (6.9%)	0 (0.0%)	7 (20.6%)	All nine patients also stopped at least one of their baseline ETTs for angina
Time to Angina During ETT3, mean (SD) (seconds)	325.5 (123.7)	N/A	345.9 (69.4)	Time to angina during ETT3 for each of the nine patients was not clinically different than time to angina during their baseline ETT
Secondary Endpoint	**Placebo (N=7)**	**CK-452 Cohort 1 (N=10)**	**CK-452 Cohort 2 (N=12)**	**Comments**
Proportion with 1 mm ST Depression During ETT3, n (%)*	2 (28.6%)	0 (0.0%)	1 (8.3%)	Majority of patients did not have ECGs assessable (per protocol) for 1 mm ST depression*
Time to 1 mm ST Depression During ETT3 (seconds)*	300, 620	N/A	235	The time to ST depression during ETT3 for the Cohort 2 CK-452 patient was similar to his baseline ETTs

*Per protocol, patients with baseline ST depression ≥ 1 mm, LBBB or RBBB, ventricular pacing, or receiving digoxin were not considered to have ECGs interpretable for ST segment analysis

Exercise Duration by Stage at Baseline vs. ETT3



Other Safety Assessments

- No clinically important changes in summary vitals signs (SBP/DBP, HR, RR, O_2 saturation) for any of the treatment groups were observed
- No clinically important changes in summary ECG parameters (QT & QTc intervals, RR interval, QRS interval, PR interval) for any of the treatment groups were observed
- No clinically important changes in cardiac enzymes (troponin I, CK-MB, total CK) for any of the treatment groups were observed
  - Two patients (one each from CK-452 Cohorts 1 and 2) had central lab troponin I results that were just above the ULN after ETT3; clinical significance is unclear as neither patient experienced clinical signs or symptoms of ischemia during the study and troponin elevations of uncertain clinical significance can occur spontaneously in this patient population

Adverse Events

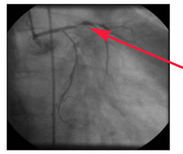
- 19 patients experienced at least one treatment-emergent AE
- 29 distinct AEs, including 2 distinct SAEs
  - 23 out of 29 AEs were reported as mild in severity, 4 out of 29 as moderate in severity, and 2 out of 29 as serious/severe in severity
  - 14 out of 29 AEs were reported as not related to treatment, 8 out of 29 as possibly related to treatment, and 7 out of 29 as probably related to treatment

Incidence of Treatment-Emergent Adverse Events Occurring in 2 or More Patients

Treatment-Emergent Adverse Event	Placebo (N=29)	CK-452 Cohort 1 (N=31)	CK-452 Cohort 2 (N=34)	Total (N=34)
Dyspnea	1 (3.4%)	0 (0.0%)	3 (8.8%)	4 (4.3%)
Hypotension	0 (0.0%)	1 (3.2%)	1 (2.9%)	2 (2.1%)
Infusion site pain	1 (3.4%)	1 (3.2%)	0 (0.0%)	2 (2.1%)
Photopsia	1 (3.4%)	0 (0.0%)	1 (2.9%)	2 (2.1%)
Ventricular extrasystoles	0 (0.0%)	0 (0.0%)	2 (5.9%)	2 (2.1%)

Serious Adverse Events

- Both SAEs were from the same patient who experienced angina and ST depression during ETT3 which also occurred during baseline ETTs
  - First SAE reported as Acute Coronary Syndrome during ETT3
  - Angiogram procedure revealed critical proximal LAD stenosis, and patient successfully received stent
    - Local lab troponins were elevated after PTCA procedure prompting the second SAE of Post-procedural Myocardial Infarction
    - Central lab troponin 19-hours after PTCA procedure was normal
- Both SAEs were reported as unrelated to treatment by Investigator

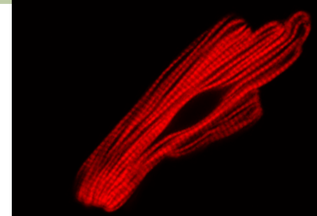


Proximal LAD Lesion
- History MI x 3
- Most recent MI in April 2008
- No angiogram prior to this event

Study Investigators

CY 1221 Investigator	Location
Dr. Barry Greenberg, Chair, Safety Review Committee*	San Diego, United States
Prof. Bondo Kobulia	Tbilisi, Georgia
Prof. Vakhtang Chumburidze	Tbilisi, Georgia
Prof. Tamaz Shaburishvili	Tbilisi, Georgia
Dr. Kakhi Paposhvili	Tbilisi, Georgia
Prof. Nodar Emukhvari	Tbilisi, Georgia
Prof. Irakli Megreladze	Tbilisi, Georgia
Dr. Alexander Timofeev	Barnaul, Russia
Prof. Alexey Panov	St. Petersburg, Russia
Dr. Tatyana Treshkur	St. Petersburg, Russia
Prof. Maria Glezer	Moscow, Russia
Prof. Yury Lopatin	Volgograd, Russia
Prof. Valentin Moiseev	Moscow, Russia

*Dr. Greenberg was not a CY 1221 Investigator but served as Chair of the Safety Review Committee.



Conclusions

1. In heart failure patients with ischemic cardiomyopathy and angina who theoretically would be most vulnerable to SET prolongation, treatment with CK-452 at concentrations that increase cardiac function did not deleteriously affect a broad range of safety assessments in the setting of exercise
2. Results of this study, together with previous studies evaluating the pharmacodynamic effects of CK-452 in healthy volunteers and stable heart failure patients, support further clinical assessment of CK-452 in patients with acute and chronic heart failure

References

1. Malik FI, Saikali KG, Clarke CP, Teerlink JR, Wolff AA. *Systolic Ejection Time is a Sensitive Indicator of Left Ventricular Systolic Function During Treatment with the Selective Cardiac Myosin Activator, CK-1827452.* 2007 Annual Heart Failure Society of America Meeting, Washington, DC. September, 2007.
2. Senior R, Malik FI, Saikali KG, Lee JH, Chen MM, Brand G, Wolff AA, and the CY 1121 Investigators. *The Selective Cardiac Myosin Activator, CK-1827452, Increases Systolic Function in a Concentration-Dependent Manner in Patients with Stable Heart Failure.* 2009 Annual American College of Cardiology (ACC), Orlando, FL. March, 2009.

CYTOKINETICS