HFSA 2007 (452: Chronic Oral Inotropic Therapy for Heart Failure?)

Oral Bioavailability of the Selective Cardiac Myosin Activator CK-1827452: Chronic Oral Inotropic Therapy for Heart Failure?

Markus Jerling, MD, PhD[1], Terrence Chew, MD[1], Rafael Escandon, PhD[1], Jacqueline Lee[1], Khalil Saikali, PhD, MBA[1], Esther Venables[2], Cyril Clarke, MBBS[2], Fady Malik, MD, PhD[1], and Andrew Wolff, MD[1]

[1]Cytokinetics, Inc., South San Francisco, CA; [2]ICON Development Solutions, Manchester, UK

Introduction

CK-1827452 is a novel small molecule activator of cardiac myosin, a sarcomere-directed therapy intended to improve cardiac contractility in heart failure. The results of a Phase 1 first in human dose escalation trial using an intravenous formulation have recently been reported. In this study, CK-1827452 produced dose-dependent and statistically significant increases in ejection fraction (EF) and fractional shortening (FS), confirming its pharmacological activity in humans. The intravenous formulation is now under study in heart failure. This study, CY 1011, is intended to determine the pharmacokinetics of various oral formulations in anticipation of its application in chronic heart failure.

Objective

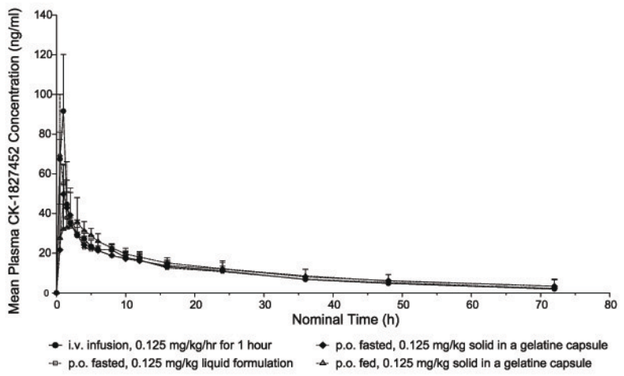
To determine the bioavailability of an oral liquid and a capsule formulation of CK-1827452 versus a reference intravenous infusion and to determine the bioavailability of the capsule dose in fed and fasted states relative to the liquid dose.

Methods

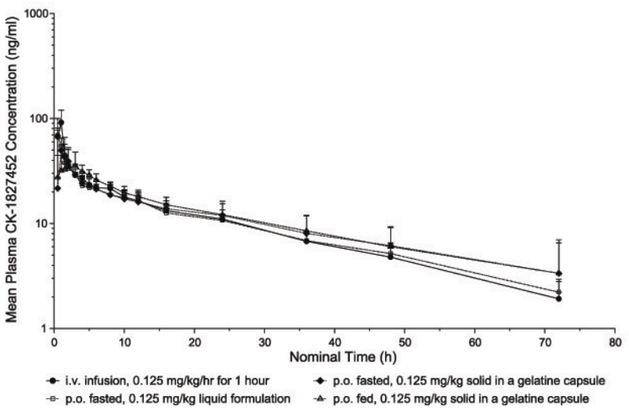
- Single center, open-label, randomized, crossover, bioavailability study.
- Eight healthy male volunteers.
- Ages 18 - 50 inclusive.
- BMI between 18 and 30 kg/m^2.
- Normal cardiac parameters and laboratory parameters.
- Each subject received four doses of CK-1827452:
  - one i.v. infusion (0.125 mg/kg/hr for 1 hour)
  - one oral dose liquid formulation (0.125 mg/kg) fasted
  - one oral capsule dose (0.125 mg/kg) fasted
  - one oral capsule dose (0.125 mg/kg) fed
- Subjects were randomized to one of four treatment sequences, two subjects per treatment sequence.
- Blood samples were taken at pre-dose and 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 16, 24, 36, 48 and 72 hours post-dose.
- The following parameters were determined by model independent analysis: C_{max}, t_{max}, t ½, AUC_{last}, AUC_{inf}, CL (i.v. only), CL/F, Vz (i.v. only), Vz/F, MRT (i.v. only) and MRT p.o.

Results

Pharmacokinetic Profiles (linear-linear scale)



Pharmacokinetic Profiles (log-linear scale)



Safety

- Twenty-five adverse events were reported, 96% of which were mild in severity.
- Three subjects were withdrawn due to adverse events that were unrelated to the study drug.
- No serious adverse events or significant safety issues were found with regards to vital signs, ECGs or laboratory tests.

Summary of Pharmacokinetic Parameters

PK Parameter	Formulation Administered: Intravenous infusion (n = 6)[2]	p.o. liquid (fasted) (n = 7)	p.o. capsule (fasted) (n = 7)	p.o. capsule (fed) (n = 7)
C_{max} (ng/mL)	92.7 ± 27.3	72.8 ± 27.9	56.9 ± 19.3	64.5 ± 34.8
t_{max} (h)[1]	1.0 (0.5-1.0)	0.5 (0.50-1.00)	1.0 (1.0-2.0)	3.0 (0.5-4.9)
AUC_{last} (ng·h/mL)	747.4 ± 108.5	719.5 ± 99	764.8 ± 258.6	807.3 ± 240.8
AUC_{inf} (ng·h/mL)	800.4 ± 140.2	787.7 ± 122.8	936.4 ± 514.5	981.1 ± 546.9
AUC_{0-48} (ng·h/mL)	667.1 ± 80.5	630.8 ± 78.5	650.8 ±187.7	695.0 ± 159.2
$t_{½}$ (h)	18.2 ± 2.7	20.7 ± 2.7	25.7 ± 12.2	23.8 ± 13.1
MRT or $MRT_{p.o.}$ (h)	23.8 ± 4.1	27.6 ± 4.0	35.3 ± 17.2	33.5 ± 18.9
CL (i.v.) or CL/F (p.o.) (L/h/kg)	0.160 ± 0.023	0.162 ± 0.026	0.160 ± 0.057	0.150 ± 0.044
V_z (i.v.) or V_z /F (p.o.) (L/kg)	4.12 ± 0.40	4.79 ± 0.67	5.13 ± 0.83	4.38 ± 0.06

Mean ± S.D.
[1] Median (range) for tmax
[2] One subject was excluded due to an uncharacteristic plasma profile

Analysis of Bioavailability and Food Effect

Comparison of Absolute and Relative Bioavailability

Parameter	Treatment[1]	Least Square Mean (LSMean) Test	Least Square Mean (LSMean) Reference	Treatment LSmean Ratio (Test /Reference) Point Estimate [Lower - Upper 95% CI]
AUC_{inf}	B versus A[2]	807.31	810.79	0.9957 [0.8998 – 1.1019]
	C versus A[2]	733.41	810.79	0.9046 [0.8162 – 1.0024]
	C versus B	804.09	752.76	1.0682 [0.8194 – 1.3926]

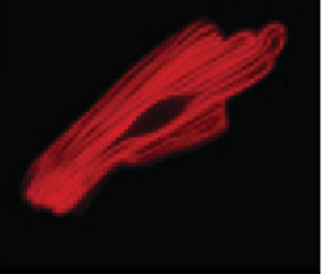
[1] A = 0.125 mg/kg i.v. infusion, B = 0.125 mg/kg p.o. liquid (fasted), C = 0.125 mg/kg p.o. capsule (fasted).
[2] One subject was excluded due to an uncharacteristic plasma profile

Analysis of Food Effect on Selected PK parameters

Parameter	LSmean Capsule (Fed)	LSmean Capsule (Fasted)	Treatment LSmean Ratio (Capsule Fed / Capsule Fasted) Point Estimate [Lower - Upper 90% CI]
C_{max}	57.59	52.05	1.1065 [0.8422 – 1.4538]
AUC_{last}	771.26	702.61	1.0977 [0.9442 – 1.2761]
AUC_{inf}	879.57	804.09	1.0939 [0.8802 – 1.3594]

Analysis of Food Effect on t_{max}

Parameter	Median Capsule (Fed)	Median Capsule (Fasted)	Hodges-Lehmann Estimator for Difference in Location (Capsule Fed - Capsule Fasted) Point Estimate [Lower - Upper 90% CI]	p-value
t_{max}	3.0	1.0	1.25 [-0.50 – 2.94]	0.1719



Conclusions

In this oral bioavailability study:

1) The absolute bioavailability of CK-1827452 approached 100% for all formulations administered in the study.
2) The near complete absolute bioavailability suggests there is essentially no first-pass metabolism.
3) Food did not have a substantial effect on bioavailability but appeared to delay drug absorption in 4/7 subjects.
4) CK-1827452 in both intravenous and oral formulations was well tolerated with no significant safety issues.

CYTOKINETICS