Oral Pharmacokinetics of CK-2017357 in Healthy Subjects

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Abstract

Purpose: CK-2017357 is a novel small molecule activator of the fast skeletal muscle troponin complex that has been developed to improve skeletal muscle function in disease states associated with muscular weakness or fatigue. This presentation summarizes the pharmacokinetics of CK-2017357 in healthy subjects following single and multiple oral doses from two Phase I clinical trials.

Methods: The single ascending dose study explored a dose range from 20 to 2500 mg under fasting conditions using two oral formulations (API-in-Capsule and a liquid suspension). The multiple dose study was conducted at two dose levels, 250 and 375 mg q.d. for 7 days using API-in-Capsule. An intensive PK sampling scheme was utilized for both studies, and plasma samples were collected up to 96 hrs post-dose. PK data analysis was conducted using WinNonlin by noncompartmental methods.

Results: Following a single oral dose of 20 – 2500 mg to fasted healthy subjects, the systemic exposure of CK-2017357 was high with relatively low inter-subject variability. The elimination kinetics were monophasic with a median terminal $t_{1/2}$ of 11.3 hr. At higher doses, a prolonged absorption phase was observed, likely due to dissolution- or solubility-limited absorption. Apparent clearance and volume of distribution were relatively dose independent, but showed an increasing trend at higher doses. Following multiple oral daily doses, steady-state was achieved by day 7, and drug accumulation at steady-state was less than 2-fold.

Conclusion: CK-2017357 demonstrated desirable pharmacokinetics in healthy subjects following single and multiple oral doses. These pharmacokinetic results support the continued clinical development of this novel agent as a once-daily oral therapy for the potential treatment of chronic neuromuscular diseases such as ALS.

Introduction

- CK-2017357 is a novel, selective small molecule activator of fast skeletal muscle
- CK-2017357 slows the rate of calcium release from the regulatory troponin complex of fast skeletal muscle and sensitizes the sarcomere to calcium
- Preclinically, CK-2017357 increases skeletal muscle force during sub-maximal neural stimulation and increases the time to fatigue
- In multiple animal species (mouse, rat, and dog), CK-2017357 showed desirable pharmacokinetics (PK) with excellent oral bioavailability, and was predicted to exhibit good oral PK in humans

Objective

To characterize the pharmacokinetics of CK-2017357 in healthy male subjects following single and multiple oral doses using two formulations (solid and liquid) in two Phase I trials, CY 4011A and CY 4012.

Methods

Study Design

- CY 4011A was a Phase I, double-blind, randomized, placebo-controlled study of single ascending doses of CK-2017357 ranging from 20 to 2500 mg, administered orally to healthy male subjects under fasting conditions
  - 57 healthy volunteers in 7 cohorts
  - Each dose group contained 8 subjects randomized 4:1 active vs. placebo
- CY 4012 was a Phase I, double-blind, randomized, placebo-controlled, multiple dose study of CK-2017357 at two dose levels, 250 and 375 mg, administered orally to healthy male subjects under fasting conditions
  - 24 healthy volunteers in 2 cohorts
  - Each dose group contained 12 subjects randomized 2:1 active vs. placebo

Sample collection and PK data analysis

- Plasma samples were collected at various time points after single and multiple oral doses. CK-2017357 plasma concentration was measured using a validated LC/MS/MS method with a method range of 10 – 10,000 ng/mL
- Non-compartmental (NCA) methods were used to calculate descriptive PK parameters after single and multiple oral doses
- Statistical analysis was conducted to evaluate dose proportionality (power model), and attainment of steady-state following multiple doses

Methods

Table 1. CK-2017357 Phase I Trial Design

Study #	Single or Multiple	Cohort	PK Population (n)	Dosage Regimen	Dosing Period (days)	Formulation	PK Sampling
CY 4011A	Single dose	1	6	20 mg QD	1	API-in-Cap	Pre-dose, 0.25, 0.5, 0.75, 1, 2, 3, 4, 5, 6, 8, 10, 12, 16, 20, 24, 30, 36, and 48 hrs
		2	6	40 mg QD	1	API-in-Cap	
		1	6	80 mg QD	1	API-in-Cap	
		2	6	160 mg QD	1	API-in-Cap	
		3	6	320 mg QD	1	API-in-Cap	Pre-dose, 0.25, 0.5, 0.75, 1, 2, 3, 4, 5, 6, 8, 10, 12, 16, 20, 24, 30, 36, 48, 72, and 96 hrs
		4	6	640 mg QD	1	API-in-Cap	
		3	6	1000 mg QD	1	API-in-Cap	
		4	6	1250 mg QD	1	API-in-Cap	
		5	6	640 mg QD	1	Liquid	
		6	6	1000 mg QD	1	Liquid	
		5	6	1500 mg QD	1	Liquid	
		6	5	2000 mg QD	1	Liquid	
		7	6	2500 mg QD	1	Liquid	
CY 4012	Multiple dose	1	8	250 mg QD	7	API-in-Cap	Day 1: Pre-dose, 0.25, 0.5, 1, 2, 4, 6, 8, and 12 hrs Day 2 to 5: Pre-dose Day 6 and 7: Pre-dose, 0.25, 0.5, 1, 2, 4, 6, 8, and 12 hrs Day 8 to 11: 24, 48, 72, and 96 hrs post-last dose
		2	8	375 mg QD	7	API-in-Cap	

Results

Figure 1. CK-2017357 mean plasma concentration – time profiles following a single oral dose (CY 4011A)

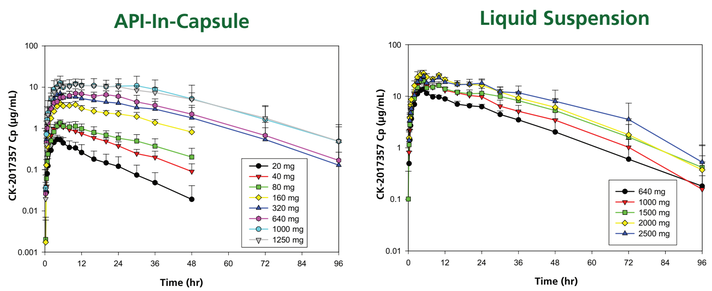
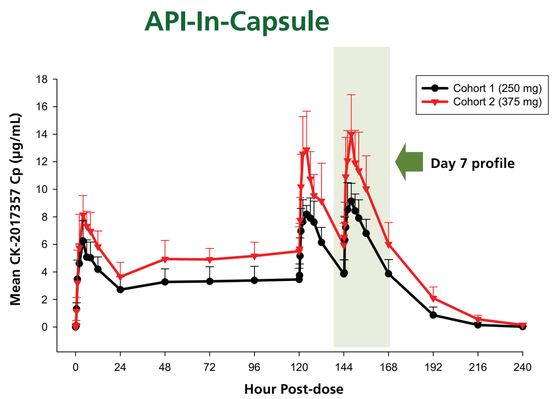


Figure 2. CK-2017357 mean plasma concentration – time profiles following multiple oral doses, dailyx7 (CY 4012)



Results (contd.)

Figure 3. Dose proportionality assessment, single dose (CY 4011A)

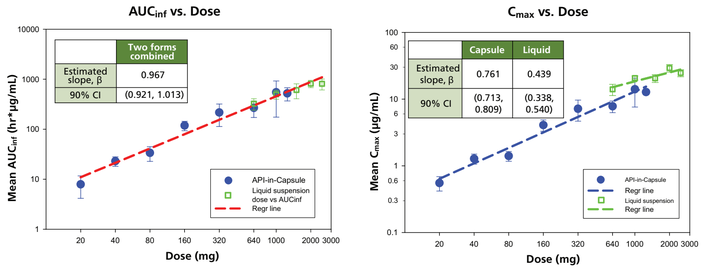


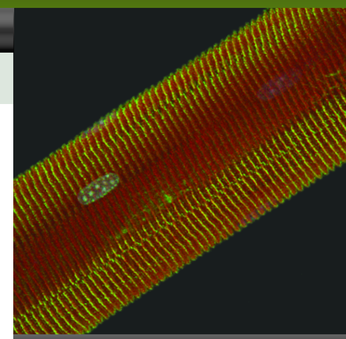
Table 2. Pharmacokinetic parameters of CK-2017357 following a single oral dose (CY 4011A)

Form	Dose		C_{max} (µg/ml)	T_{max}* (hr)	AUC_{inf} (hr*µg/ml)	$t_{1/2}$ (hr)	Cl/F (l/hr)	Vz/F (l)
API-in-Cap	20	Mean	0.55	4.5	7.99	9.94	2.95	40.29
		SD	0.13	4.0, 5.0	3.79	3.27	1.16	15.39
API-in-Cap	40	Mean	1.28	5.0	23.22	11.22	1.79	28.22
		SD	0.22	4.0, 5.0	4.98	2.48	0.41	5.17
API-in-Cap	80	Mean	1.40	5.0	32.00	13.33	2.72	52.12
		SD	0.24	4.0, 10.0	11.06	3.42	0.85	20.87
API-in-Cap	160	Mean	4.08	5.0	119.35	14.82	1.40	28.82
		SD	0.80	5.0, 10.0	25.01	3.27	0.35	4.16
API-in-Cap	320	Mean	7.17	4.5	221.95	11.99	1.65	27.59
		SD	2.51	4.0, 5.0	106.01	2.26	0.54	7.83
API-in-Cap	640	Mean	7.81	10.0	275.00	11.10	2.57	38.48
		SD	1.54	5.0, 24.0	97.77	3.84	0.83	9.27
API-in-Cap	1000	Mean	14.06	10.0	562.54	11.49	2.45	35.89
		SD	6.46	5.0, 30.0	385.05	3.82	1.30	14.09
API-in-Cap	1250	Mean	12.77	7.5	536.28	13.54	2.48	43.05
		SD	1.11	5.0, 24.0	152.72	8.88	0.66	15.20
Liquid	640	Mean	14.00	5.0	331.15	10.70	2.02	29.24
		SD	2.68	4.0, 6.0	84.03	4.32	0.42	3.97
Liquid	1000	Mean	20.70	4.5	510.77	12.09	2.03	33.91
		SD	1.50	4.0, 5.0	102.99	3.39	0.45	4.32
Liquid	1500	Mean	20.52	4.5	625.00	10.49	2.57	36.14
		SD	2.77	4.0, 10.0	204.27	3.99	0.64	4.85
Liquid	2000	Mean	29.24	5.0	832.74	11.92	2.47	42.37
		SD	3.79	4.0, 10.0	139.44	1.92	0.52	10.04
Liquid	2500	Mean	24.63	5.0	830.12	12.58	3.15	55.50
		SD	2.97	5.0, 10.0	204.46	4.97	0.72	21.08

*T_{max} presented as median (min, max)

Table 3. Steady-state pharmacokinetic parameters of CK-2017357 following multiple oral doses (CY 4012)

Cohort	Dose		λ_z (1/hr)	$t_{1/2}$ (hr)	t_{max} (hr)	C_{max} (µg/ml)	C_{min} (µg/ml)	C_{avg} (µg/ml)	PTF (%)	CL/F_{ss} (ml/hr)	MRT (hr)	Vz/F_{ss} (ml)	AUC_{SSlast} (hr*µg/ml)
1	250	N	8	8	8	8	8	8	8	8	8	8	8
		Mean	0.08	8.99	4.50	9.64	3.68	6.52	92.65	1625.85	19.34	20683.38	156.55
		SD	0.02	1.91	2.33	1.21	0.89	0.92	17.55	235.85	3.75	2971.77	22.08
		Min	0.06	6.11	2.00	7.84	2.59	5.18	68.35	1338.42	14.23	15737.47	124.30
		Median	0.08	8.64	5.00	9.70	3.72	6.62	94.75	1574.51	19.05	20318.12	158.81
		Max	0.11	12.14	8.00	11.10	5.14	7.78	123.19	2011.26	25.07	24493.26	186.79
		Range	0.06	6.02	6.00	3.26	2.55	2.60	54.84	672.84	10.84	8755.79	62.49
		CV%	21.9	21.3	51.8	12.6	24.3	14.1	18.9	14.5	19.4	14.4	14.1
2	375	N	8	8	8	8	8	8	8	8	8	8	8
		Mean	0.06	12.28	3.75	14.14	5.81	9.64	87.83	1678.61	23.82	30534.61	231.42
		SD	0.02	3.74	0.71	2.69	1.61	1.95	20.48	334.00	3.43	12840.97	46.71
		Min	0.04	8.51	2.00	11.30	3.98	7.08	47.74	1224.95	16.64	15036.20	169.84
		Median	0.06	11.00	4.00	13.90	5.48	9.31	89.35	1693.13	25.00	29149.09	223.48
		Max	0.08	18.90	4.00	18.50	9.01	12.76	111.30	2207.95	27.20	50527.18	306.14
		Range	0.04	10.39	2.00	7.20	5.03	5.68	63.56	983.00	10.56	35490.98	136.29
		CV%	27.4	30.4	18.9	19	27.7	20.2	23.3	19.9	14.4	42.1	20.2



Conclusions

1. CK-2017357 exhibited high systemic exposure following oral administration in healthy male subjects with relatively low inter-subject variability.
2. At higher doses (>640 mg), a prolonged absorption phase was observed, likely due to dissolution- or solubility-limited absorption.
3. The elimination kinetics of CK-2017357 were monophasic with a median terminal $t_{1/2}$ of 11.3 hr.
4. The apparent clearance and volume of distribution were relatively dose independent, but showed an increasing trend at higher doses (≥ 1000 mg).
5. AUC_{inf} was dose proportional over the dose range of 20 – 2500 mg and was independent of the formulation, while C_{max} was less than dose proportional. The liquid formulation produced a higher C_{max}, but did not influence AUC_{inf}.
6. Following multiple oral daily doses, steady-state was achieved by day 7, and drug accumulation (AUC) at steady-state was less than 2-fold (1.63 and 1.76-fold for the 250 and 375 mg dose, respectively)
7. These pharmacokinetic results support the continued clinical development of this novel agent as a once-daily oral therapy for the potential treatment of chronic neuromuscular diseases such as ALS.

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