Pharmacokinetics, pharmacodynamics, and their relationship of KZR-616 in healthy volunteers

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Biography and Contact Information

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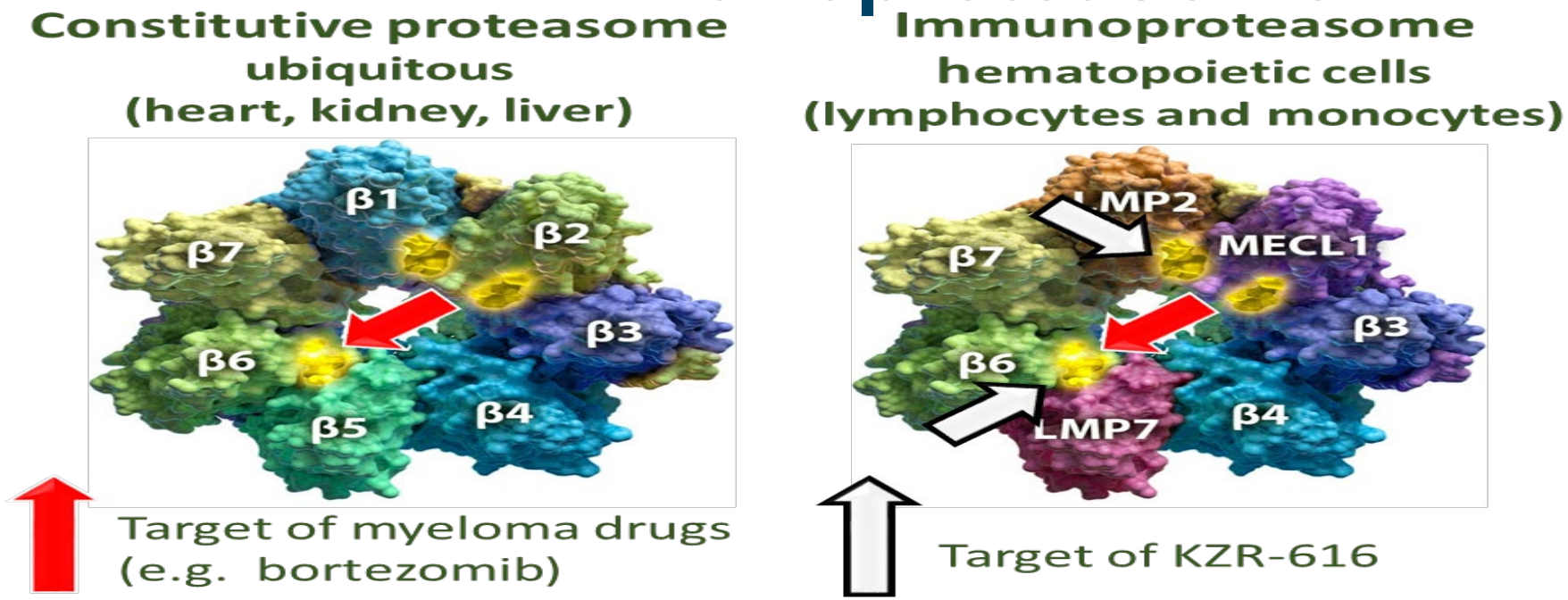
KZR-616, a selective inhibitor of the immunoproteasome



- Proteasome inhibitors (e.g. bortezomib and carfilzomib) are approved to treat multiple myeloma[1-2]
- They target both forms of proteasome found in cells; Bortezomib has been used successfully to treat patients with SLE and LN[3-5]
- KZR-616 (analog of carfilzomib) is a selective inhibitor of multiple subunits of the immunoproteasome and is active in mouse models of SLE and LN

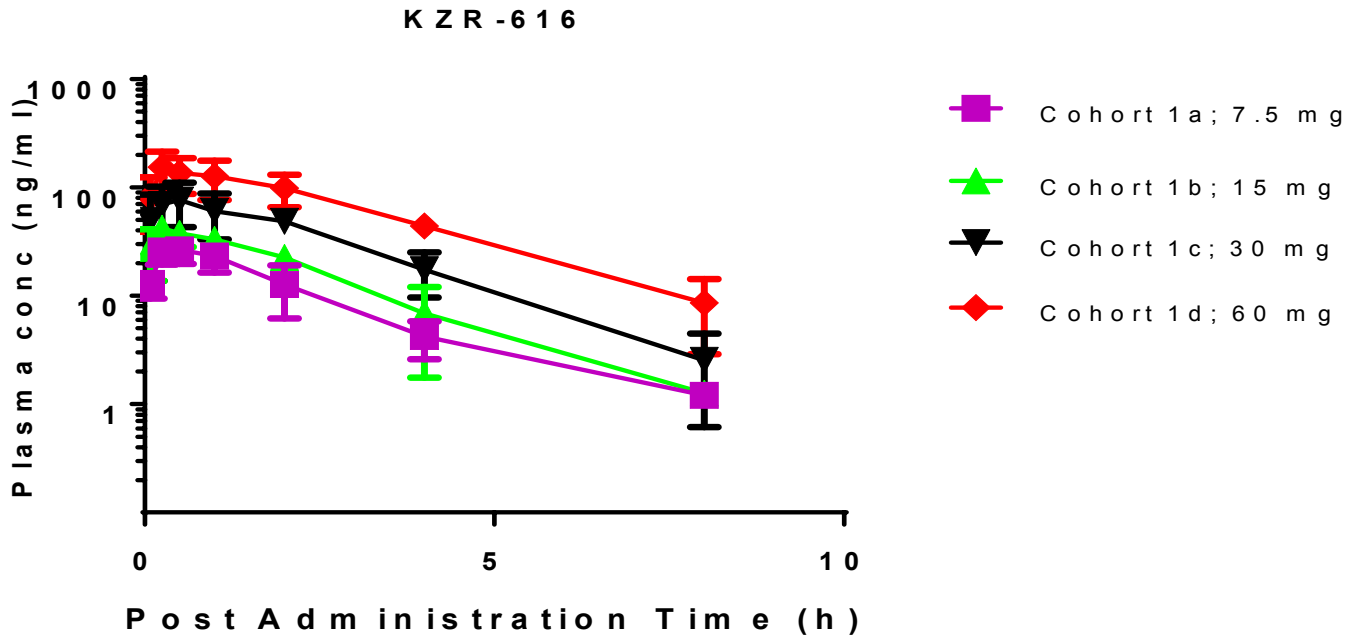
KZR-616-001 in healthy volunteers

- 82 subjects, single center study (Australia)
- 7 cohorts in single dose portion (6:2 drug:placebo)
  - 7.5, 15, 30 and 60 mg (2 cohorts) via subcutaneous(SC) administration
  - 7.5 mg via 30-minute intravenous (IV) infusion
- 4 cohorts in multi-dose portion (6:2 drug:placebo)
  - Weekly administration for 4 weeks
- 30 mg, 45 mg, and 30 → 45 mg (2 cohorts) via SC administration

Part	Cohort	Dose (mg)	Subjects
1 SAD SC	1a	7.5	6
	1b	15	6
	1c	30	6
	1d	60	6
	Placebo	NA	8
2 MAD SC	2a	60[a]	6
	2b	30[b]	6
	2c	30/45	6
	2d	45	6
	2e	30/45[c]	6
	Placebo	NA	10
3 SAD IV	3a[d]	15	1
	3b	7.5	6
	Placebo	NA	3

- [a] 8 subjects withdrawn after 1 dose (2 due to AE, 6 due to PI decision); [b] 1 subject withdrawn after 3 injections due to AE; [c] 2 subjects received ¾ injections due to PI decision; [d] stopped due to AEs in sentinel subject ; oral hydration/pre-medication for MAD 2b – 2e (prednisone 25 mg. loratadine 10 mg, ranitidine 150 mg)

KZR-616 PK Following Single SC Dose



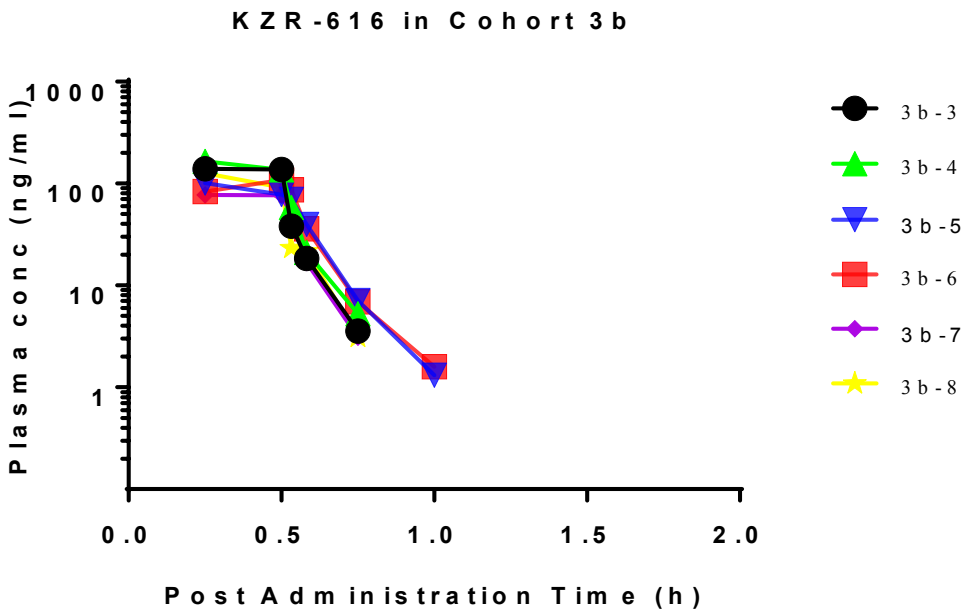
- SAD: 4 Cohorts, six healthy subjects with KZR-616 and two with placebo for each cohort
- No KZR-616 detected in plasmas with placebo controlled subjects
- KZR-616 absorbed rapidly with T_{max} about 0.5 hrs, and cleared fast with $T_{1/2}$ ranged from 1.0 to 1.8 hrs
- Systematic exposures increase proportional to the dose

KZR-616 SAD (SC) PK Parameters

Cohort	Dose of (mg)	$T_{½}$ (hr)	C_{max} (ng/mL)	Λ_z (1/hr)	AUC_{last} (ng.hr/mL)	C_{max}/D (ng/mL/mg)	T_{max} (hr)	$AUC_{0-\infty}/D$ (ng•hr/mL/mg)	CL_z/F (L/h)
1a	7.5	1.37	28.3	0.57	52.3	3.77	0.42	8.32	126
1b	15.0	0.99	42.4	0.63	90.0	2.83	0.33	6.42	158
1c	30.0	1.24	77.2	0.54	195	2.57	0.46	7.18	150
1d	60.0	1.82	165	0.44	444	2.75	0.42	7.65	135

- Dose proportional increase in AUC
- Other PK parameters similar across cohorts
- clearance > hepatic blood flow (~95 L/h)

KZR-616 PK Following a Single IV Infusion



Cohort	Dose (mg)	T_{max} (hr)	$t_{1/2}$ (hr)	C_{max} (ng/mL)	AUC_{last} (hr*ng/mL)	V_z (L)	CL (L/h)
3b	7.5	0.29	0.07	120	47.8	16.7	163

- KZR-616 was absorbed rapidly with T_{max} of 17 minutes and cleared quickly of $T_{1/2}$ of 4 minutes
- Drug levels were below limits of quantitation by 1 hour post end of infusion

KZR-616 is 100% Bioavailable Following a SC Dose

PK parameters (units)	Cohort 1a KZR-616 SC SAD (7.5 mg)		Cohort 3b KZR-616 IV SAD (7.5 mg)		Ratio of LS Means (SC/IV)	One sided 90% CI for ratio of LS means	
	N	LS mean	N	LS mean		Lower	Upper
AUC (0-inf) (h*ng/mL)	4	60.89	6	47.10	1.293	0.853	1.959
AUC (0-t) (h*ng/mL)	6	50.81	6	46.82	1.085	0.702	1.677

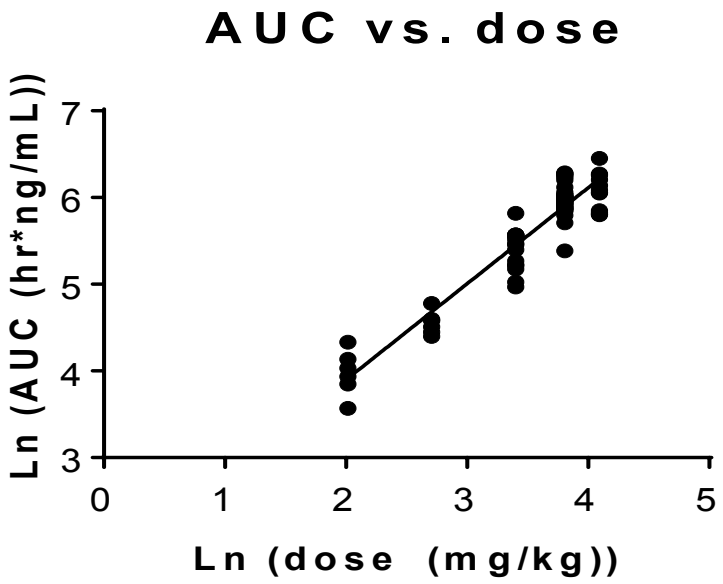
KZR-616 PK Following Repeat SC Doses

Cohort	Dose (mg)	Dose Day	N	T_{max} (hr)	$T_{1/2}$ (hr)	C_{max} (ng/mL)	AUC_{last} (hr*ng/mL)	AUC_{Inf} or AUC (0-tau) (hr*ng/mL)	CL/F or CL/Fss (L/h)	C_{ssave} (ng/mL)	AI
2b	30.0	1	6	0.50	1.63	73.1	207	220	141		
	30.0	22	5	0.27	1.64	111	253	267	116	1.59	1..00
2c	45.0	8	6	0.33	1.80	160	404	434	105		
	45.0	22	6	0.29	1.78	164	383	416	116	2.48	1.00
2d	45.0	1	6	0.67	1.92	102	354	392	115		
	45.0	22	6	0.38	2.09	109	363	393	115	2.34	1.00
2e	45.0	8	6	0.53	1.81	151	391	444	104		
	45.0	22	6	0.38	1.40	149	382	409	113	2.43	1.00

- Exposures on Day 1 or 8 were similar to those on Day 22
- No effects of premedication or step up dosing on exposure
- No accumulations were observed
- Other PK parameters were consistent across cohorts

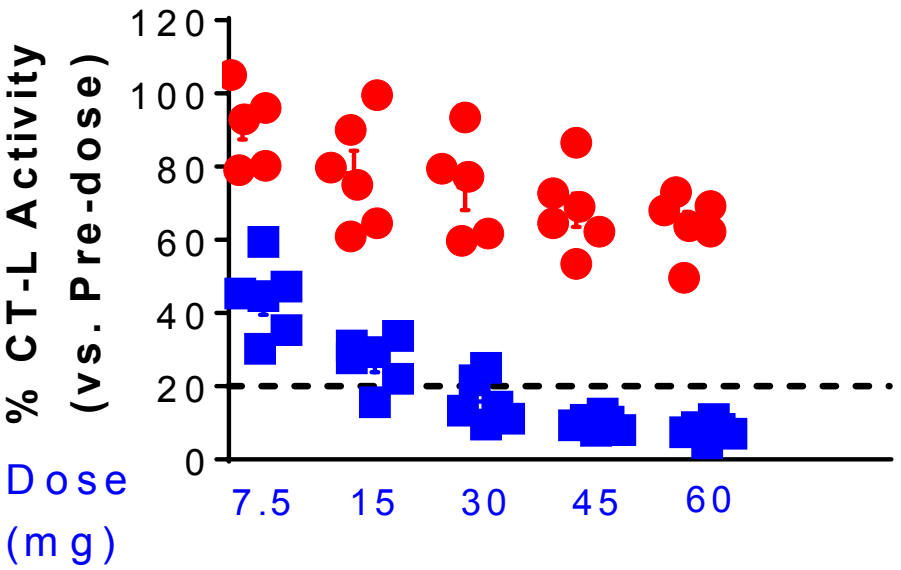
C_{max} and AUC Show Dose Proportionality with SC Dosing

	PK Parameter	R^2	Model Coefficient	Coefficient Value (95% CI)
ALL SC cohorts	AUC_{0-t} (h*ng/mL)	0.89	β0 (Intercept) β1 (Linear)	1.66 (1.35, 1.97) 1.10 (1.01, 0.96)
	C_{max} (ng/mL)	0.65	β0 (Intercept) β1 (Linear)	1.44 (0.90, 1.19) 0.89 (0.74, 1.04)



- **Ln (PK parameter) = β_0 + βLn (Dose) + ε; PK Parameter = α Dose$^{\beta}$**
- P <0.0001; the linear effect P<0.0001
- KZR-616 exposure increased in a dose proportional manner from 7.5 mg to 60 mg range

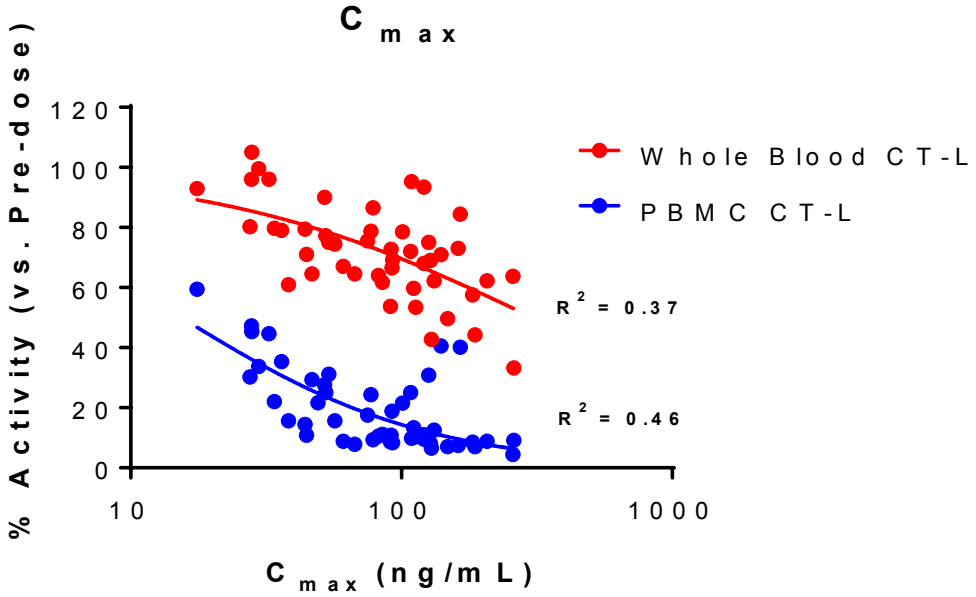
Dose Dependent Target (Immunoproteasome) inhibition

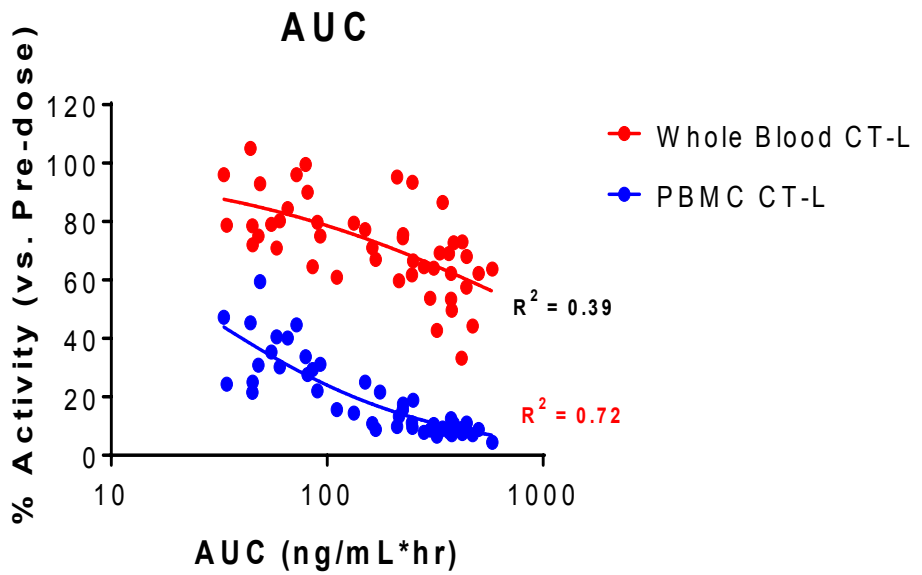


- Whole Blood (constitutive proteasome) and PBMC (immunoproteasome taken pre-dose & 4 hours post-dose
- Samples (N=6/cohort) analyzed for proteasome chymotrypsin-like (CT-L)
  - β5 and LMP7 mediate CT-L activity

- Immunoproteasome inhibition correlated with the dose
- LMP7 inhibition > 90% at ≥ 45 mg
- β5 inhibition < 35% for all dose levels

Relationship between the immunoproteasome inhibition and the PK exposures





- Immunoproteasome inhibition was related to AUC but not to C_{max}
- Constitutive proteasome inhibition showed little correlation to AUC and C_{max}

Summary

- KZR-616 shows rapid absorption and clearance following SC administration to healthy volunteers
- Exposure was dose proportional and did not change with repeat (weekly) dosing
- Immunoproteasome inhibition was dose dependent and correlated to AUC but not C_{max}
- KZR-616 currently is in a phase 1b/2 clinical trial in patients with SLE and Lupus nephritis (NCT03393013)

References

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Acknowledgments

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- Nucleus Network, Melbourne, Victoria, Australia: Jason Lickliter

Questions

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