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The Pharmacokinetic Differences between Humans and Animals of KZR-616, a First-in-Class, Selective Immunoproteasome Inhibitor, in Two Clinical Formulations

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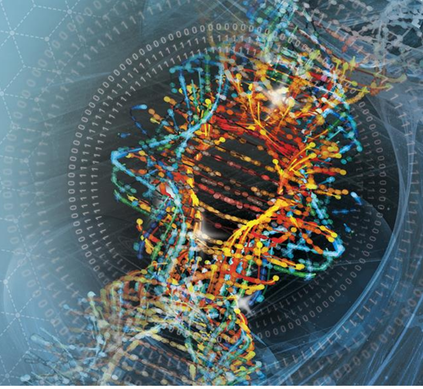
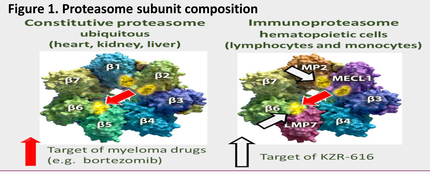


PURPOSE

- Proteasome inhibitors (e.g., bortezomib and carfilzomib) are used to treat multiple myeloma[1,2]
- These agents target both forms of the proteasome found in cells (Figure 1)
- Bortezomib has been used to treat several refractory autoimmune diseases, but side effects preclude it from being used chronically in this setting[3,4,5]
- KZR-616 (analog of carfilzomib) is a selective inhibitor of multiple subunits of the immunoproteasome and is being evaluated in three Phase 2 clinical trials across 5 separate autoimmune diseases

Figure 1. Proteasome subunit composition



OBJECTIVE(S)

- To evaluate the PK of KZR-616 in rats, monkeys, and healthy volunteers (HV) following single and repeated subcutaneous (SC) administration with 2 formulations
- To evaluate the clinical formulation for use in the phase 2 program

METHOD(S)

- Frozen and lyophilized KZR-616 were formulated in aqueous 10% (w/w) Polysorbate 80 (PS-80) and 2% α-trehalose, respectively
- Sprague Dawley rats and cynomolgus monkeys received weekly SC doses for 13 and 26 (39 for monkey) weeks, in 10% PS-80 and 2% α-trehalose, respectively
- Toxicokinetics (TK) were determined on Days 1, 22, and 85 in 10% PS-80 for rats, and monkeys, and Days 1 and 183 for rats and Days 1, 183, and 267 for monkeys in 2% α-trehalose, respectively
- Doses included 1.5 and 3 mg/kg for rats and 1, 2, and 4 mg/kg for monkeys
- Human volunteers across 2 separate studies received 1, 2, or 4 weekly SC doses, and PK was measured following the first and last doses at 30, 45, and 60 mg
- TK and PK samples were analyzed by LC-MS/MS for KZR-616 and KZR-595987 (metabolite)

RESULT(S)

- KZR-616 was rapidly absorbed and cleared with a t_{max} of less than 60 min, and $t_{1/2}$ of about 50 min in both formulations following SC administration to rats (Table 1)
- The C_{max} for the trehalose formulation was about 1.5-fold higher than that for the PS-80 formulation, and the total exposure (AUC) was slightly lower in trehalose formulation on Day 1
- The C_{max} and AUC were comparable for both formulations at the last measurement

Table 1. Rat TK comparison (Mean ± SEM)

	Frozen KZR-616					Lyophilized KZR-616				
Dose (mg/kg)	Day	T_{max} (hr)	$T_{1/2}$ (hr)	C_{max} (ng/mL)	AUC (ng*hr/mL)	Day	T_{max} (hr)	$T_{1/2}$ (hr)	C_{max} (ng/mL)	AUC (ng*hr/mL)
1.5	1	0.50	0.53	365	453 ± 20.3	1	0.25	0.20	563	401 ± 17.2
3.0	1	0.25	0.46	637	1050 ± 42.1	1	0.25	0.32	856	740 ±34.2
1.5	85	0.50	0.63	281	510 ± 33.4	176	1.0	NR	325	500 ± 33.8
3.0	85	0.50	0.55	575	1250 ± 55.7	176	1.0	0.45	615	1000 ± 71.3

- In monkeys, similar to rats, KZR-616 was rapidly absorbed and eliminated. However, the absorption and elimination were 2- and 3-fold faster, respectively, in the trehalose vs PS-80 formulation following SC administration to monkeys (Table 2)
- Unlike in rats, the C_{max} for the trehalose formulation was more than 2-fold higher than that for the PS-80 formulation *in monkeys*, while the total exposure (AUC) was comparable for both formulations across dose groups and dosing days

Table 2. Monkey TK comparison (Mean ± SD)

	Frozen KZR-616					Lyophilized KZR-616				
Dose (mg/kg)	Day	T_{max} (hr)	$T_{1/2}$ (hr)	C_{max} (ng/mL)	AUC (ng*hr/mL)	Day	T_{max} (hr)	$T_{1/2}$ (hr)	C_{max} (ng/mL)	AUC (ng*hr/mL)
1.0	1	0.33 ± 0.18	0.50 ± 0.10	200 ± 45.5	212 ± 38.6	1	0.10 ± 0.054	0.14 ± 0.028	523 ± 118	198 ± 50.5
2.0	1	0.32 ± 0.26	0.55 ± 0.13	373 ± 108	413 ± 81.4	1	0.11 ± 0.064	0.17 ± 0.025	1010 ± 377	384 ± 104
4.0	1	0.26 ± 0.19	0.53 ± 0.14	792 ± 232	785 ± 97.9	1	0.11 ± 0.064	0.18 ± 0.061	2270 ± 892	786 ± 172
1.0	85	0.24 ± 0.045	0.55 ± 0.064	291 ± 76.6	326 ± 56.0	267	0.14 ± 0.081	0.18 ± 0.030	529 ± 137	214 ± 32.6
2.0	85	0.26 ± 0.083	0.64 ± 0.10	518 ± 133	642 ± 85.9	267	0.16 ± 0.085	0.19 ± 0.038	1310 ± 403	494 ± 102

- In HV, KZR-616 was also rapidly absorbed and eliminated. However, while the absorption was similar for both formulations, elimination was about 2-fold slower in trehalose formulation following SC administration to HV (Table 3)
- Unlike in rats and monkeys, in HV the C_{max} and the total exposure (AUC) were comparable for both formulations across dose groups and dosing days

Table 3. Human PK comparison (Mean ± SD)

	Frozen KZR-616					Lyophilized KZR-616				
Dose (mg)	Day	T_{max} (hr)	$T_{1/2}$ (hr)	C_{max} (ng/mL)	AUC (ng*hr/mL)	Day	T_{max} (hr)	$T_{1/2}$ (hr)	C_{max} (ng/mL)	AUC (ng*hr/mL)
30	1, 22	0.42 ± 0.21	1.51 ± 0.54	85.6 ± 35.0	216 ± 48.5	1	0.29 ± 0.12	2.70 ± 0.80	71.6 ± 16.1	195 ± 34.7
45	1, 8, 22	0.43 ± 0.34	1.80 ± 0.60	139 ± 56.6	379 ± 62.2	8	0.26 ± 0.020	3.09 ± 1.17	90.1 ± 32.3	303 ± 57.0
60	1	0.47 ± 0.34	1.57 ± 0.52	160 ± 61.1	411 ± 85.8	8, 15	0.32 ± 0.19	4.19 ± 1.94	140 ± 52.2	425 ± 112

Table 4. SC Bioavailability of Frozen KZR-616 in HV

PK parameters (units)	Cohort 1a SC SAD (7.5 mg)		Cohort 3b 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
$AUC_{0\text{-}inf}$ (hr•ng/mL)	4	60.89	6	47.10	1.293	0.853	1.959
$AUC_{0\text{-}t}$ (hr•ng/mL)	6	50.81	6	46.82	1.085	0.702	1.677

Table 5. SC Bioavailability of Lyophilized KZR-616 in HV

PK parameters (units)	Cohort 1a SC SAD (30 mg)		Cohort 2b IV SAD (30 mg)		Ratio of LS means (SC/IV)	One sided 90% CI for ratio of LS means	
	N	LS mean	N	LS mean		Lower	Upper
$AUC_{0\text{-}inf}$ (hr•ng/mL)	19	219	6	212	1.03	0.892	1.199
$AUC_{0\text{-}t}$ (hr•ng/mL)	19	192	6	211	0.91	0.789	1.052

- SC bioavailability was calculated based on IV infusion (data not shown), and the F% were 100% and 70-100% for the frozen and lyophilized formulations, respectively. KZR-616 was highly bioavailable in both formulations (Tables 4 and 5)
- KZR-59587, the sole metabolite, was also analyzed. In rats, the AUC of KZR-59587 relative to KZR-616 was less than 40%, however, the AUC ratios in monkeys, and humans were more than 150%, regardless of the formulations used (Table 6)

Table 6. PK comparison between rats, monkeys, and humans (Mean ± SD)

Species	Formulation	Dose Day	Pharmacokinetics		
			Parameter	KZR-616	KZR-59587 (% of KZR-616)
Rat	Frozen KZR-616	3 mg/kg Day 85	C_{max} (ng/mL)	575±62.4*	66.1±4.26* (12%)
			$AUC_{0\text{-}6}$ (ng*h/mL)	1250±55.7*	193±9.01* (15%)
	Lyophilized KZR-616	1.5 mg/kg Day 176	C_{max} (ng/mL)	325	96.4 (30%)
			$AUC_{0\text{-}6}$ (ng*h/mL)	500±33.8*	165±12.8* (33%)
Monkey	Frozen KZR-616	4 mg/kg Day 85	C_{max} (ng/mL)	1270±369	950±301 (75%)
			$AUC_{0\text{-}6}$ (ng*h/mL)	1350±172	2140±481 (158%)
	Lyophilized KZR-616	3 mg/kg Day 176	C_{max} (ng/mL)	1820±594	1050±269 (58%)
			$AUC_{0\text{-}6}$ (ng*h/mL)	776±148	2180±624 (281%)
Human	Frozen KZR-616	30 mg Days 1 and 22	C_{max} (ng/mL)	85.6±35.0	103±28.1 (120%)
			AUC_{last} (ng*h/mL)	216±48.5	490±121(227%)
	Lyophilized KZR-616	30 mg Day 1	C_{max} (ng/mL)	71.6±16.1	74.8±22.9 (105%)
			AUC_{last} (ng*h/mL)	195±34.7	455±132 (233%)

* SEM

CONCLUSION(S)

- There are no apparent differences in maximum and total exposures between both formulations in humans
- In rats and monkeys, a higher C_{max} was observed with the trehalose formulation than with the PS-80 formulation, whereas AUCs were comparable for both formulations
- Based on these data, the lyophilized formulation has been determined to be bioequivalent to the frozen formulation and suitable for clinical studies. The lyophilized formulation will be used in the KZR-616 Phase 2 program evaluating the safety and efficacy of KZR-616 in patients with lupus nephritis (NCT03393013 [MISSION]) as well as patients with autoimmune hemolytic anemia and immune thrombocytopenia (NCT04039477 [MARINA])) and patients with dermatomyositis and polymyositis (NCT04033926 [PRESDIO])

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