A 14-Day Intravenous Infusion Toxicity and Toxicokinetic Study of DUR-928, a Novel, First in Class, Investigational Therapeutic in Sprague-Dawley Rats

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INTRODUCTION

DUR-928 is an endogenous sulfated oxysterol that has been demonstrated to play a key regulatory role in mammalian lipid metabolism, inflammatory responses, and cell survival.

MATERIALS & METHODS

DUR-928 was administered as a daily IV infusion at doses of 15, 50, and 150 mg/kg/day to 12 rats/sex/dose group. Control animals received the aqueous vehicle containing hydroxypropyl-beta-cyclodextrin and sodium phosphate buffer. At the onset of dosing, the animals were 8 to 9 weeks old.

Study Design

Treatment Group	Dose Level (mg/kg/day)	No. of Animals	
		M	F
1.Control*	0	12	12
2.DUR-928 Low Dose	15	12	12
3.DUR-928 Mid Dose	50	12	12
4.DUR-928 High Dose	150	12	12

**Group 1 animals received the vehicle: 250 mg/mL hydroxypropyl betadex, NF (hydroxypropyl-beta-cyclodextrin) with 10 mM sodium phosphate buffer in sterile water for injection, USP*
M: male; F: female

RESULTS

- DUR-928 was well-tolerated, and there were no drug-related deaths during the course of the study
- There was a slight drug-related reduction in body weight gain in males at the high dose

RESULTS

Table 1: Body Weight Summary[a] - Males

Group No.		Day -8	Day -1	Day 7	Day 14
1	MEAN	234.3	273.7	331.1	381.1
	SD	10.9	15.2	19.5	27.8
	N	12	12	12	12
2	MEAN	236.5	275.7	332.3	380.4
	SD	12.6	19.3	23.8	31.2
	N	12	12	12	12
3	MEAN	231.8	274.7	330.3	379.6
	SD	16.2	14.2	20	24.7
	N	12	12	11	11
4	MEAN	236.9	273.2	320.8	360.6
	SD	16.9	21.9	22.5	25.1
	N	12	12	12	12

[a] mean body weights were not significantly different (p> 0.05) across dose groups but mean weight gain was significantly different (p< 0.05) for the high-dose group versus the control group on Day 7 and Day 14

Table 2: Body Weight Summary - Females

Group No.		Day -8	Day -1	Day 7	Day 14
1	MEAN	188.2	203.3	228.3	249.5
	SD	12.2	9.8	10.8	10.6
	N	12	12	12	12
2	MEAN	191.5	209.9	237.2	256.8
	SD	13.8	15.2	28.5	28.4
	N	12	12	12	12
3	MEAN	189.8	213.4	241.8	261.3
	SD	14.7	16.1	21.5	23.2
	N	12	12	12	12
4	MEAN	183.3	204.4	227.3	247.3
	SD	9.7	10.9	13.0	12.5
	N	12	12	12	12

Table 3: Mean Plasma DUR-928 Toxicokinetic Parameters in Male and Female Sprague-Dawley Rats Following Intravenous Infusion at Selected Dose Levels on Day 1 and Day 13

Day	1						13					
Group No.	2		3		4		2		3		4	
Dose Level (mg/kg/day)	15		50		150		15		50		150	
Sex	M	F	M	F	M	F	M	F	M	F	M	F
C_{max} (ng/mL)	160	237	1,600	1,240	26,400	19,700	479	233	1,090	1,420	17,200	29,300
C_{last} (ng/mL)	3.03	24.4	3.94	4.79	20.9	53.2	4.04	14.4	9.84	13.8	8.5	142
$AUC_{(last)}$ (h*ng/mL)	417	535	3,210	2,330	61,800	54,600	878	500	2,260	3,490	40,400	76,100

Table 4: Group Incidence and Severity of DUR-928 Vehicle-related Microscopic Changes to the Kidney and Lungs

	Males				Females			
Group	1	2	3	4	1	2	3	4
Dose (mg/kg/day)	0	15	50	150	0	15	50	15
Number of Animals	12	12	11	12	12	12	12	12
Kidney#								
Vacuolation, tubular	**12**	**12**	**11**	**12**	**12**	**12**	**12**	**12**
Minimal	0	0	0	0	0	2	0	0
Mild	4	12	1	4	7	9	9	3
Moderate	8	0	10	8	5	1	3	9
Lungs#								
Histiocytosis	**12**	**12**	**11**	**11**	**12**	**10**	**11**	**10**
Minimal	7	12	11	11	11	10	11	9
Mild	5	0	0	0	1	0	0	1
Inflammation	**0**	**1**	**4**	**1**	**3**	**0**	**2**	**2**
Minimal	0	1	4	1	1	0	1	1
Mild	0	0	0	0	2	0	1	1

RESULTS

- Vehicle-related, non-adverse, microscopic changes consisted of renal tubular vacuolation and pulmonary histiocytosis
- DUR-928 was quickly eliminated from the plasma with half-lives ranging from 0.5 to 1.6 hours
- On Days 1 and 13, the systemic exposure to DUR-928 generally followed non-linear kinetics (not dose-proportional) over the entire dose range, suggesting possible saturable drug elimination processes
- Pre-dose (24-hour) plasma samples were free of DUR-928, consistent with a short half-life
- $AUC_{(last)}$ and C_{max} were generally similar on Day 13 when compared to Day 1, indicating the absence of plasma accumulation

CONCLUSIONS

- In summary, DUR-928 was well-tolerated in this study
- Based on the results of this study, the NOAEL was the high dose of 150 mg/kg/day
- At the NOAEL, the mean C_{max} was 23,150 ng/mL and the mean $AUC_{(last)}$ was 58,225 h*ng/ml, averaged over both sexes and time intervals (Day 1 and Day 13)

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