Spleen congestion	50 (f)	-	
Liver necrosis	100 (f)	50 (m) 100 (f)	(Wk 52)
Liver, hepatocellular vacuolation	-	50 (m), 100 (f)	(Wk 26-52)
Liver, increased eosinophilia	-	50(f), 100 (m)	(Wk 26)
Thymus involution	100 (m)	50	(Wk 26-52)
Vagina, infiltrate	-	5	(Wk 26-52)
Lymph node, pigmented macrophages	-	5 (m), 50 (f)	(Wk 26-52)
Bone marrow, lymphoid germinal center	-	5 (f) , 50 (m)	(Wk 26-52)
Testis, juvenile	50	-	

dd dose-dependent
nd not determined

Reversibility of findings at 100 mkd HD after 2 wks (3-mo study), or 4 wks (1-year study):

Reversible were: body weight changes, RBC/Hb/Hct changes (partial in 1-yr study), serum Ca, serum P (partial), ALT, AST, cholesterol, triglyceride, CK changes, urine changes in f (1-year study), thymus involution, liver necrosis

Not reversible were: RBC/Hb/Hct changes in 3-mo study

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EXPOSURE MULTIPLES (PARENT DRUG) IN RAT AND MONKEY TOXICITY STUDIES

RAT (oral toxicity studies)

Study	Study Nr.	Doses (mg/kg/day) M / F	Cmax (ng/mL) M / F	AUC parent (ngxh/mL) M / F	AUC metabolite M7 (ngxh/mL)	**AUC multiple RAT:HUMAN* (parent) M / F**	Comment
Acute	#	1000, 2000					
	#970151	10, 100, 500					
	#100326	1000, 1500					
14-day	# 970018	50		941		**1.5x**	Day 14 values (m only)
		250		6690		**10.3x**	
		500		14700		**23x**	
28-day	#970070	5		81		**0.13x**	Day 28 values, m and f avg
		50		1400		**2.2x**	
		125		6180		**9.5x**	
3-month	#100001	5		49		**0.08x**	Wk 13 values
dietary		15		402		**0.6x**	Dietary DRF study
		50		1520		**2.3x**	
		75		2690		**4.2x**	
6-month	#100082	5		85 / 61		**0.13x / 0.09x**	M / F; Wk 13+26 avg
		25		845 / 1001		**1.3x / 1.5x**	
		100		3450 / 7090 4840 (m+f)		**5.3x / 11x** **7.5x (m+f)**	
24-month	#100209	5 / 5		132 / 144	6360 / 6590	**0.2x / 0.2x**	Carcinogenicity study
		15 / 20		462 / 374	18700 / 33400	**0.7x / 0.6x**	Wk78 values; Dietary study
		50 / 50→35		1620 / 894	37600 / 45000	**2.5x / 1.4x**	
28-day	#101939	0.5		3.2 / 4.7		**0.01x**	D27 values
Juvenile		1.5		24 / 26		**0.04x**	
		5.0		94 / 108		**0.15x**	

MONKEY (oral toxicity studies)

Study	Study Nr.	Doses (mg/kg/d)	Cmax (ng/mL) M / F	AUC parent (ngxh/mL) M / F	AUC metabolite M7 (ngxh/mL)	**AUC multiple MONKEY:HUMAN (parent)***	Comment
DRF	#970142	16		562		**0.9x**	Escalating single doses
		32		869		**1.3x**	
		48		1190		**1.8x**	
1-week	#970147	24		556		**0.9x**	D8 values
DRF		48		1170		**1.8x**	
		96		1330		**2.1x**	
3-month	#100020	5		60 / 74		**0.10x**	D83+D27 avg values (D83 for 150-100gp); M,F avg
		50		900 / 463		**1.1**	
		100		1239/1100		**1.9x**	For multiples: 100 and 150-100gp data pooled
		150-100		1380/1280			
12-month	#100188	5		99	4840	**0.15x**	D180+D358 avg values; M and F avg; M7 (and M5): ca. 50x parent AUC
		50		1055	6100	**1.6x**	
		100		1180	65900 (1.1x)	**1.8x**	AUC multiple (M5+M7) monkey:human: ca. 1.1x

*Human dose 180mg/60kg= ——— AUC=648ngxh/mL; Cmax= ———

DOG (oral toxicity studies)

Study	Study Nr.	Doses (mg/kg/day) m / f	Cmax (ng/mL)	AUC parent (ngxh/mL)	**AUC multiple DOG:HUMAN* (parent)**	Comment
4-day	# 970060	16		97	**0.15x**	Escalating dose study
		32		213	**0.33x**	4-day dosing; 1-wk period
		64		329	**0.51x**	
		96		430	**0.66x**	
		128		552	**0.85x**	
		160		808	**1.2x**	
		200		769	**1.2x**	
28-day	#970078	5		21	**0.03x**	Day 28 values, m and f avg
		50		152	**0.23x**	
		100		503	**0.8x**	
28-day	#101938	0.5		3.4	**0.01x**	D27 values
Juvenile		1.5		9.9	**0.02x**	
		5.0		47.5	**0.07x**	

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HUMAN PK data

PK of parent drug was evaluated in human subjects with chronic renal failure in an ascending, multiple-dose, double-blind, randomized, placebo-controlled study (#20000187). Each subject received a dose for days (once daily), starting with 25 mg or placebo, and if no dose-limiting toxicity occurred after >= 7 doses, the dose was increased by 25 mg. Maximum dose was 300 mg. Doses were given sequentially. Blood samples were taken on study days 4, 6, 7 of each period, and at 0.5, 1, 2, 3, 4, 6, 8, 12, 24h after dosing. N=22 (4f, 18m). Total dosing time was up to 12 weeks. N=17 received AMG073, and N=5 received placebo. N=8 completed all dose levels.

Results: T max was 2-3h. Exposure (Cmax, AUC) was linear with dose up to [redacted]. This suggests doses >200 mg may not provide additional clinical benefit. Steady state concentrations (trough) were achieved by Day 4 of each period.

Pharmacokinetic Results:
Large inter-individual variations were observed in subjects' pharmacokinetic parameters, with some apparent outlying values. For this reason, median pharmacokinetic values were examined and are presented in the following table:

Dose (mg)	N	AUC(0-24) (ng·hr/mL) Median	AUC(0-24) (ng·hr/mL) Range	C_{max} (ng/mL) Median	C_{max} (ng/mL) Range	T_{max} (hr) Median	T_{max} (hr) Range
25	16	76.8	[redacted]	7.22	[redacted]	3.00	[redacted]
50	16	179		17.2		2.00	
75	16	253	[redacted]	21.6	[redacted]	2.00	[redacted]
100	16	383	[redacted]	31.1		3.00	
125	15	427	[redacted]	36.5	[redacted]	2.00	[redacted]
150	15	530		55.5		2.00	[redacted]
175	13	648	[redacted]	56.6	[redacted]	2.00	[redacted]
200	11	900		78.3		3.00	
225	12	570	[redacted]	58.6	[redacted]	2.50	
250	11	911		67.0		3.00	[redacted]
275	9	930	[redacted]	72.1	[redacted]	3.00	
300	7	501		55.7		2.00	[redacted]

Values are presented as 3 significant figures.
NOTE: Pharmacokinetic parameters were not calculated for Subjects 14, 18, and 110 at the 175-, 150-, and 250-mg doses, respectively, because no day 7 profile was obtained. Parameters for Subject 18 were also not calculated at the 125-mg dose because sample tubes were broken. No parameters at doses > 175 mg were determined for Subject 4 because AMG 073 concentrations were very low or undetectable. The 200-mg dose parameters for Subject 9 were not used in the determination of summary statistics because the day 6 dose was missed.
Source: Appendix 13

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MAIN TOXICITIES: SUMMARY

Tabulation of main toxicity finding and LOAELs in chronic > 1-mo studies

Finding	Rat	Monkey	Indicative of
	LOAEL (mg/kg/day)	LOAEL (mg/kg/day)	
Clinical signs: abnormal breathing, dehydration, salivation	25		Pharmacologic drug effect (hypocalcemia)
Clinical signs: abnormal feces, poor appetite, emesis	-	5-100	
Decrease in serum Ca	5	5	Pharmacologic drug effect
Increase in serum P	5	50	
Decrease in serum PTH	5	5	
Urine Ca increase	5	-	
QTc prolongation	-	5	Hypocalcemia (partly)
BW reduced	25	50	GI/CNS toxicity
FC reduced	25	-	GI/CNS toxicity
RBC, Hb, Hct decrease	25	50	Anemia, bone marrow effects
PT increase	25	50	Coagulopathy/hypocalcemia
APTT incease	100	-	Coagulopathy/hypocalcemia
Triglyceride increase	-	50	?
Serum BUN increase	25	-	Kidney toxicity
Urine Na K decrease	25	(5)	Pharmacologic drug effect
Urine specific gravity decrease	-	50	Diuresis
ALT increase	100	100	Liver toxicity
AST increase	-	100	Liver toxicity
Albumin and/or protein decrease	100	-	Liver toxicity
Creatinine increase	100	-	Renal toxicity
Creatine kinase increase	-	100	Muscle/cardiac toxicity
Testosterone decrease	-	5	
VitD decrease, T3 decrease, T4 increase	-	50	
Hepatic P450 content increase	-	100	Liver enzyme induction
Liver weight increase	100	50	Liver toxicity/enzyme induction
Kidney weight increase	-	50	Kidney toxicity
Testis weight decrease	-	100	
Thymus weight decrease	-	50	
Cecum hyperplasia	5	-	GI toxicity
Heart necrosis	25	-	Cardiotoxicity
Kidney, mineralization	25	-	Renal toxicity
Thymus/spleen lymphoid atrophy	25	50	Other
Cataract formation	100	-	Eye toxicity (hypocalcemia)
Liver necrosis	-	100	Liver toxicity
Testis, atrophy	100	-	Testicular toxicity

AUC multiples in 6-mo rat and 12-mo monkey study (m + f averages)

	Dose (mg/kg/day)	AUC parent (ngxh/mL)	AUC multiple		
			parent	M5 + M7	M2-Glu
Rat	5	99	**0.11x**		
	25	1055	**1.4x**		
	100	1180	**7.5x**	**3.1x**	**(0.2x)**
Monkey	5	73	**0.15x**		
	50	923	**1.6x**		
	100	4840	**1.8x**	**1.1x**	**13x**

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