

Supplementary Materials

Table S1. Standard experimental protocol in the range finding dog toxicity studies.

Test system		
Animal species	Beagle dog, pure bred	
Source	Marschall Farms, New York, NY, USA	
Age at start	approx 5–6 months	
Husbandry		
Conditions	room temp, RH 40–80%, 12 h night-day cycle	
Accommodation	individual in stainless steel cages	
Diet	standard dog maintenance pelleted food (Altromin diet 4029)	
Water	tap water <i>ad libitum</i>	
Study design	Intravenous studies (T4 and T6)	Subcutaneous study (T5)
Number of animals	2 males, 2 females	2 males, 2 females
Treatment days	day 1 (0.01 mg/kg); day 8 (0.1 mg/kg); day 15 (0.5 mg/kg)	day 1 (0.1 mg/kg); day 15 (0.2 mg/kg); day 29 (0.4 mg/kg)
Clinical signs	daily	daily
Body weights	days 1, 8, 15, 22	days 1, 8, 15, 22, 29, 36
Food/water consumption	daily	daily
Haematology & biochemistry	days 1, 8, 15, 22	days 2, 8, 15, 22, 29, 36
Urinalysis	days 1, 8, 15	days 1, 15, 29
Toxicokinetics	days 1, 8, 15	days 1, 15, 29
Necropsy	only in 2 animals that were killed in study T4	not done

Table S2. Evolution of body weight (kg) after intravenous dosing (studies T4, T6).

Dog	Study T4					Study T6				
	pre-test	1	8	15	22	pre-test	1	8	15	22
M1	8.60	9.0	9.2	8.8	7.3 [#]	8.07	8.08	7.80	7.98	7.63
M2	7.85	7.9	9.7	7.8	7.6	8.45	8.75	8.62	8.84	8.21
<i>average</i>	8.23	8.45	9.47	8.33	7.42	8.26	8.42	8.21	8.41	7.92
<i>sd</i>	0.53	0.74	0.35	0.71	0.19	0.27	0.47	0.58	0.61	0.41
F1	6.6	6.5	6.5	6.5	5.2 [#]	7.52	7.92	7.99	8.21	8.22
F2	8.0	8.2	8.4	8.0	7.6	7.03	7.34	7.20	7.29	7.07
<i>average</i>	7.28	7.37	7.46	7.27	6.38	7.28	7.63	7.60	7.75	7.65
<i>sd</i>	1.02	1.23	1.36	1.09	1.69	0.35	0.41	0.56	0.65	0.81

[#] M1 and F1 needed to be killed in extremis due to serious side effects.

Table S3. Major clinical and pathological findings (study T4).Clinical signs and mortality

One male (M1) and one female (F1) were killed in extremis 7 days after treatment with 0.5 mg/kg due to severe toxic side effects. Clinical signs included calm behavior, decreased locomotor activity, a dull fur, vomiting of mucus, diarrhoea, salivation, purulent discharge from the eyes and an emaciated appearance at 4–7 days after drug administration. This was also reflected in both the absolute and relative food consumption (*i.e.*, after correction for body weight). No effect was noted on water consumption.

Pathology

Yellow to pale discoloration was observed for the liver, kidney, salivary glands and body fat. Both the liver and the kidneys exhibited clear morphological alterations indicative of maesabalide toxicity. The liver alterations were characterized by multifocal hepatocellular necrosis (moderate severity), vacuolization (slight to moderate) and inflammatory cell foci (moderate), cholestasis (moderate) and intra-hepatocellular basophilic aggregates (slight). The kidney findings included tubular basophilia (moderate to severe), tubular necrosis (slight) and mineralized granular casts.