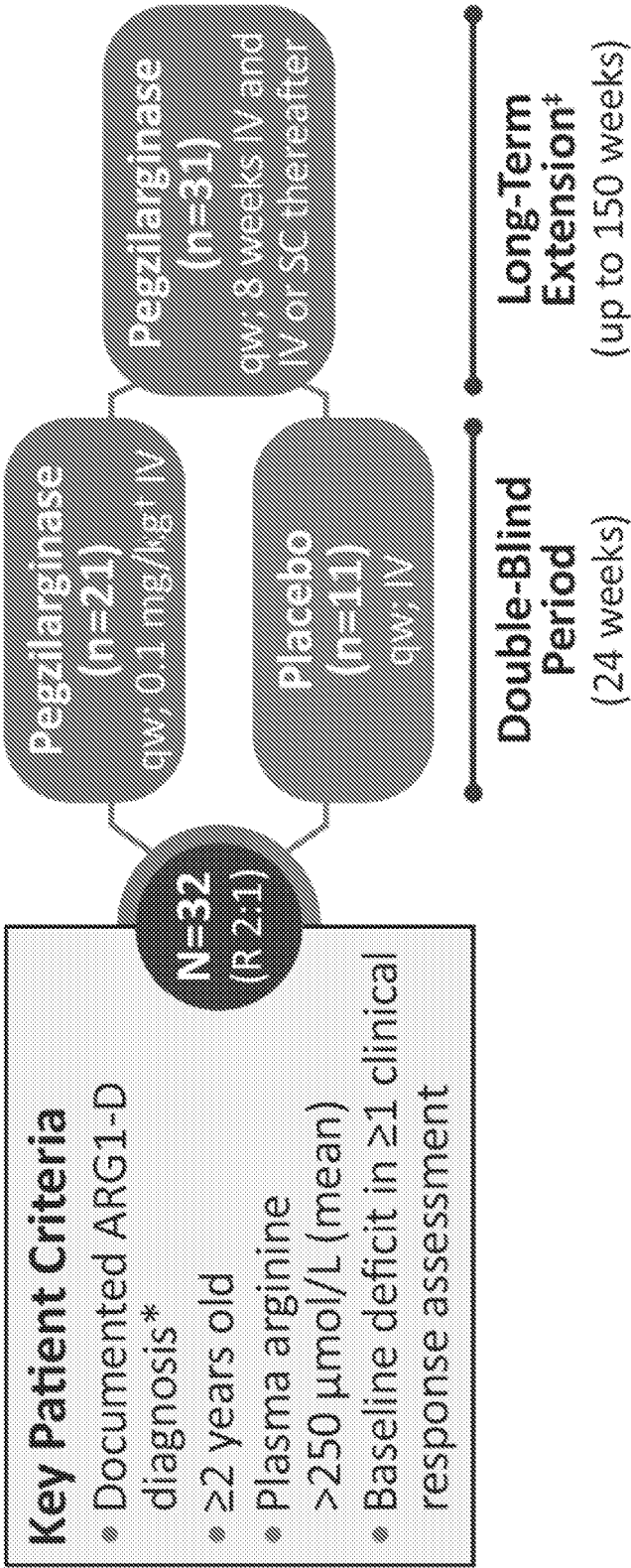


Figure 1A



ARG1-D, Arginase 1 Deficiency; IV, intravenous; qw, weekly; R, randomized; SC, subcutaneous.

*Diagnosis through elevated plasma arginine, pathogenic ARG1 variant, or diminished erythrocyte arginase activity.

†Dosing is weekly and, if needed, dose is modified based on plasma arginine levels with maintenance of blinding.

*Blinding will be maintained for the first 8 weeks of the long-term extension.

Figure 1B

Patient Information	Pegzilarginase (n=21)	Placebo (n=11)	Overall (n=32)
Age at enrollment, y			
Mean $\pm$ SD	9.6 $\pm$ 6.16	12.9 $\pm$ 6.77	10.7 $\pm$ 6.47
Range	2–28	5–29	2–29
Sex, n (%)			
Male	12 (57.1)	7 (63.6)	19 (59.4)
Female	9 (42.9)	4 (36.4)	13 (40.6)
Region, n (%)			
US	8 (38.1)	6 (54.5)	14 (43.8)
Outside US (8 countries)	13 (61.9)	5 (45.5)	18 (56.3)
Plasma arginine, μ mol/L			
Mean $\pm$ SD	365.4 $\pm$ 93.7	471.7 $\pm$ 79.9	402.0 $\pm$ 101.8
Median (range)	368.2 (202–572)	483.7 (294–573)	398.2 (202–573)
Spasticity, n (%)			
Any	13 (61.9)	8 (72.7)	21 (65.6)
Moderate to severe	6 (28.6)	6 (54.5)	12 (37.5)
GMFCS level, n (%)			
1	9 (42.9)	5 (45.5)	14 (43.8)
≥ 2	12 (57.1)	6 (54.5)	18 (56.3)
GMFM-E, points*			
Mean $\pm$ SD	48.3 $\pm$ 19.9	46.5 $\pm$ 24.6	47.7 $\pm$ 21
Median (range)	53 (5–71)	56 (0–72)	54 (0–72)
2MWT, m			
Mean $\pm$ SD	109 $\pm$ 55.7	99.9 $\pm$ 49.0	105.8 $\pm$ 52.8
Median (range)	122 (2–202)	102 (0–171)	118 (0–202)

2MWT, 2-minute walk test; GMFCS, Gross Motor Function Classification System; GMFM-E, Gross Motor Function Measure part E.
 *GMFM-E possible score range, 0–72 points; higher scores indicate better performance.

Figure 2

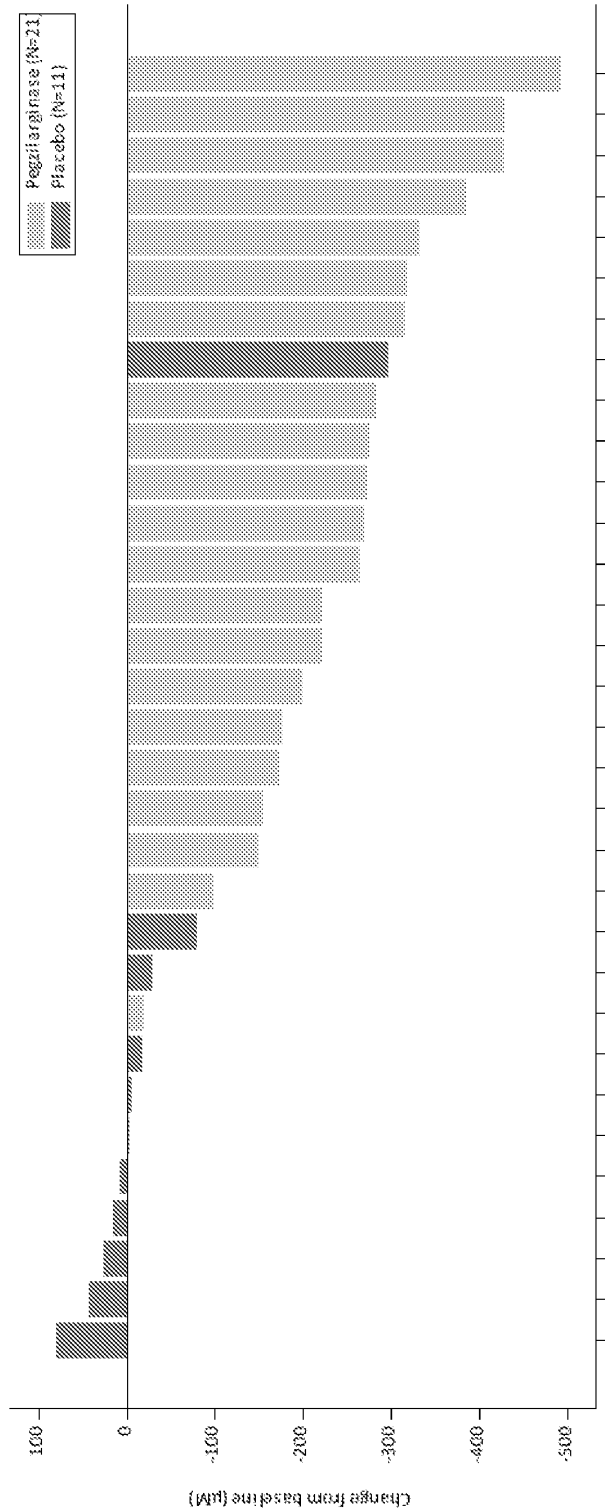
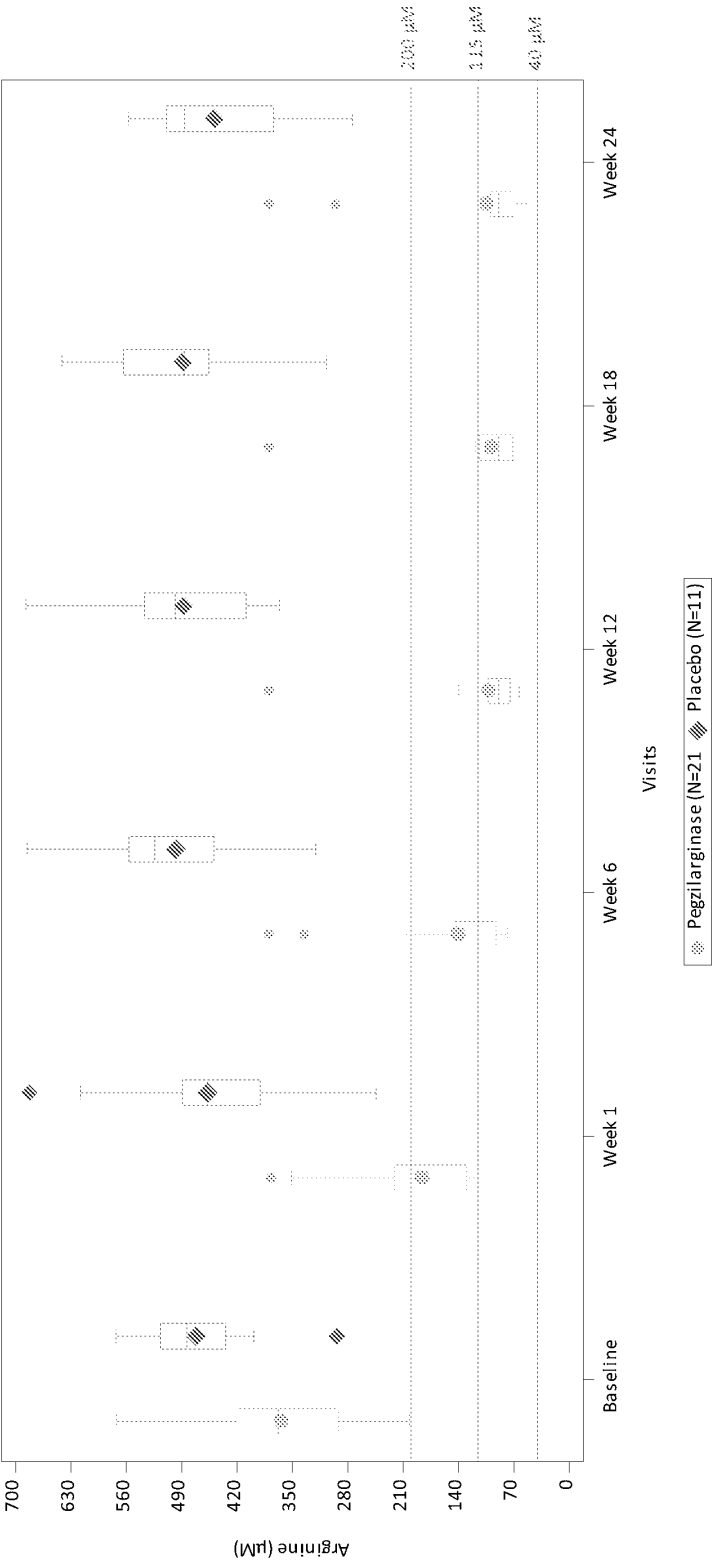
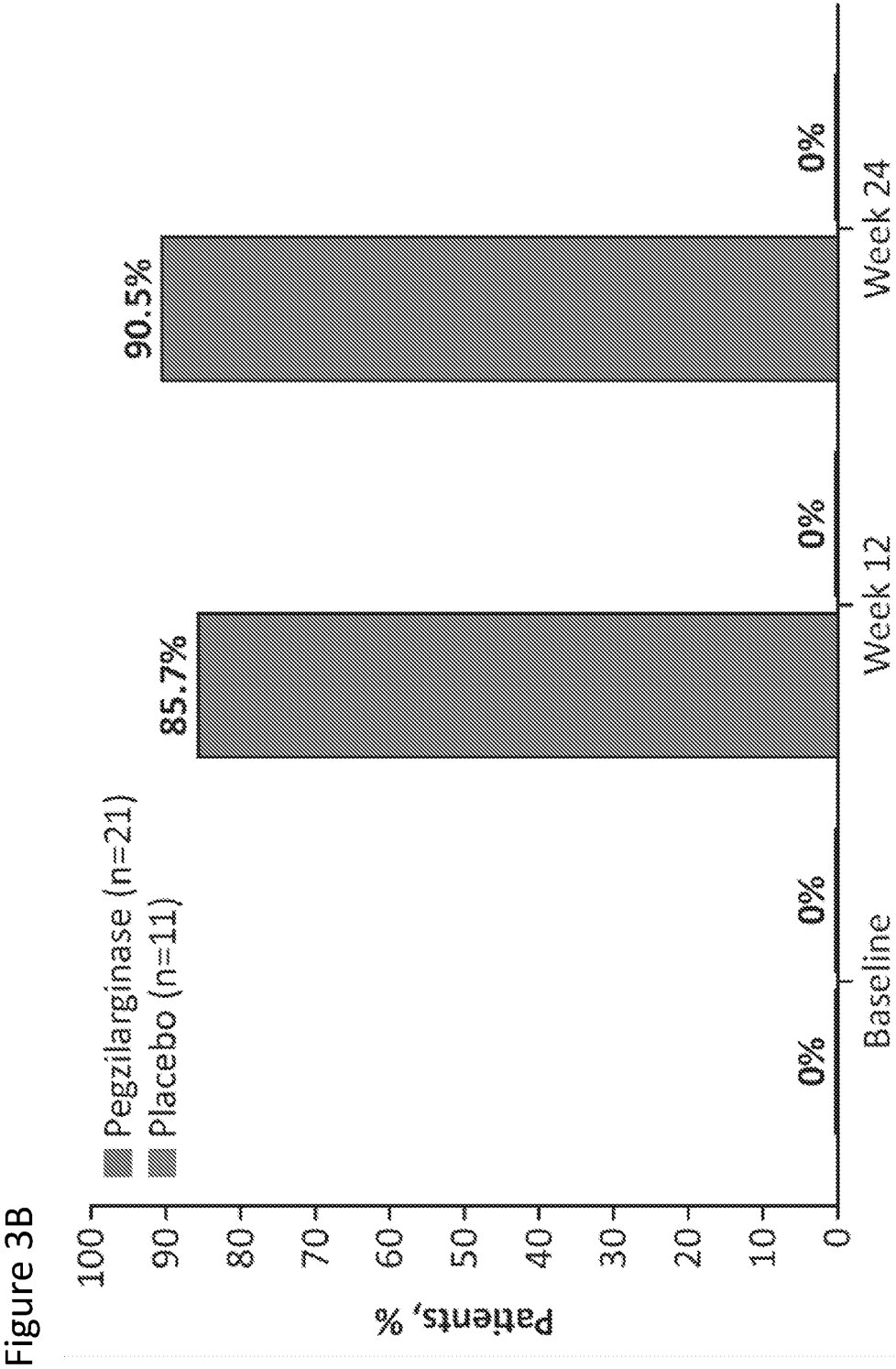


Figure 3A





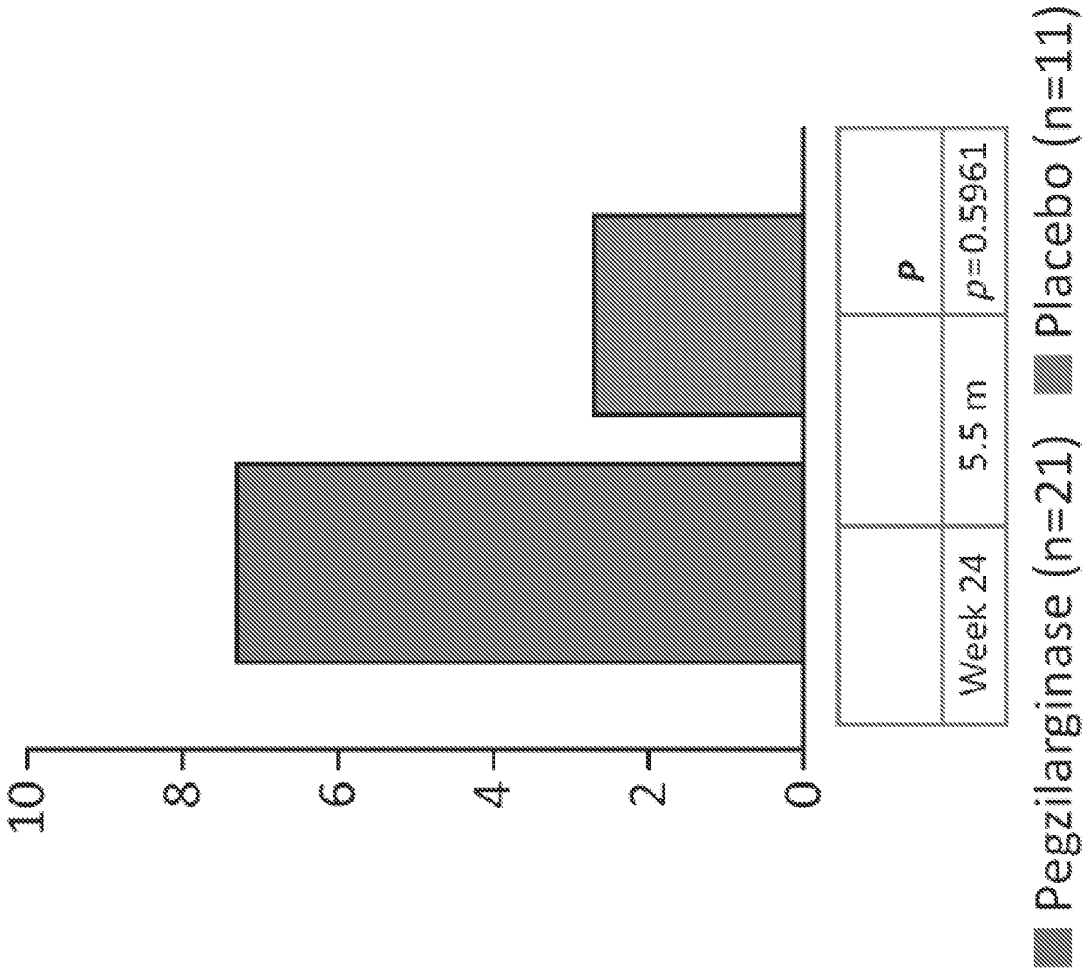
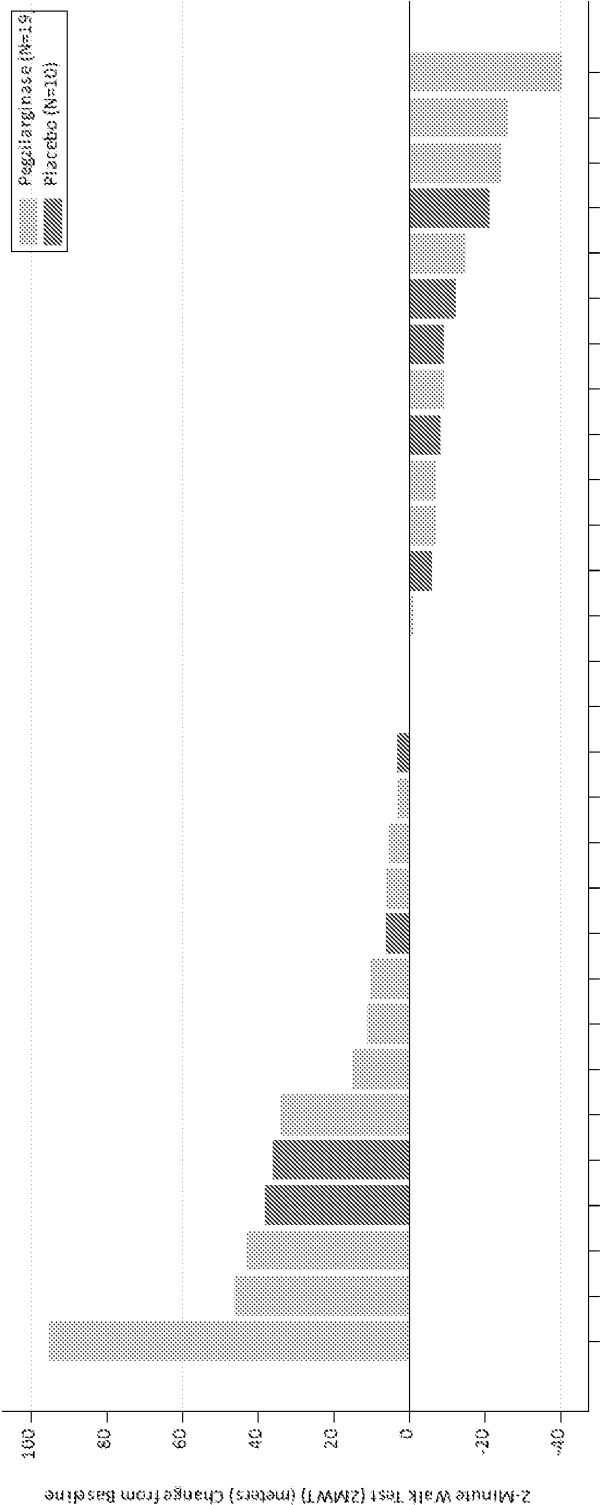


Figure 4B



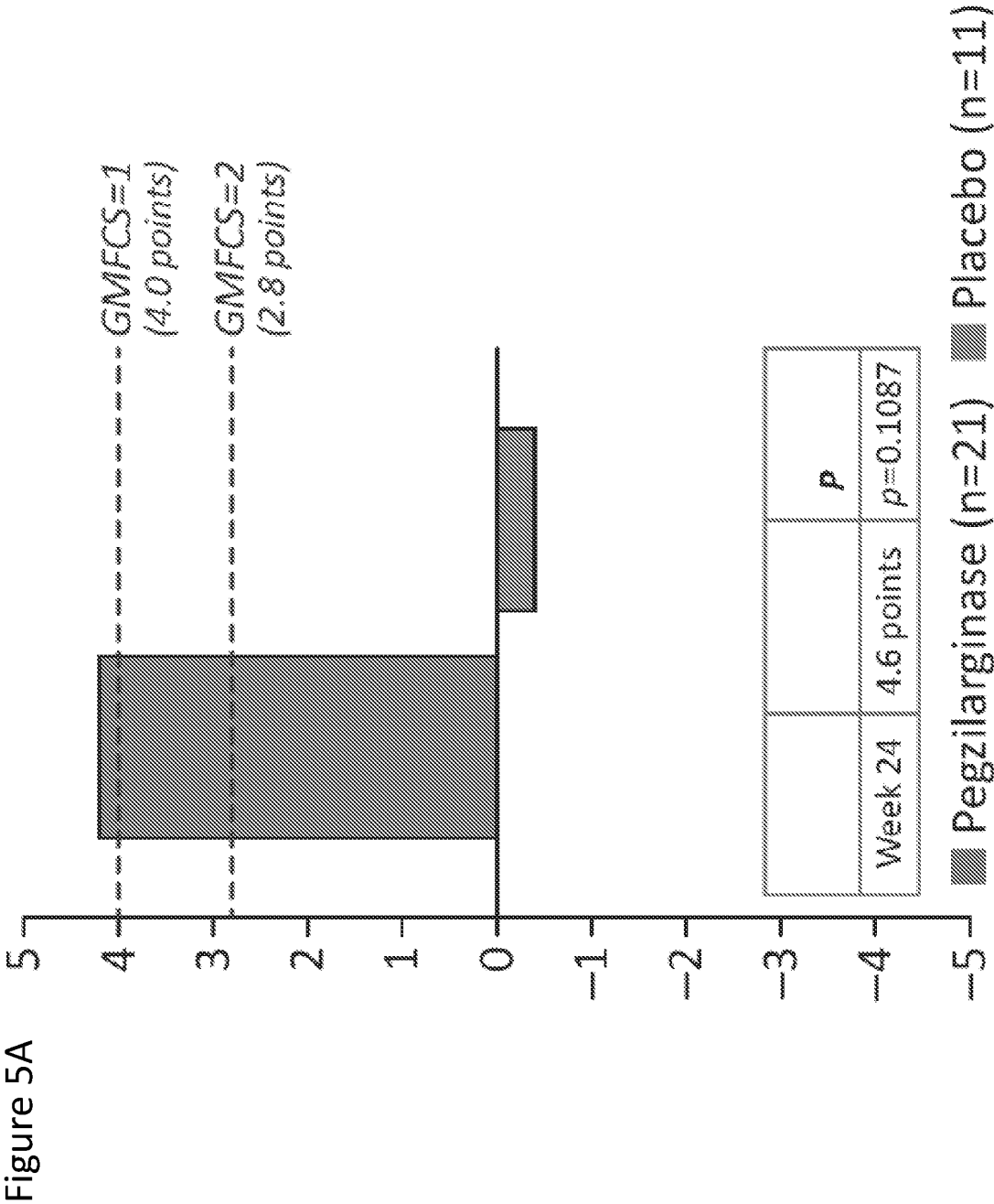


Figure 5B

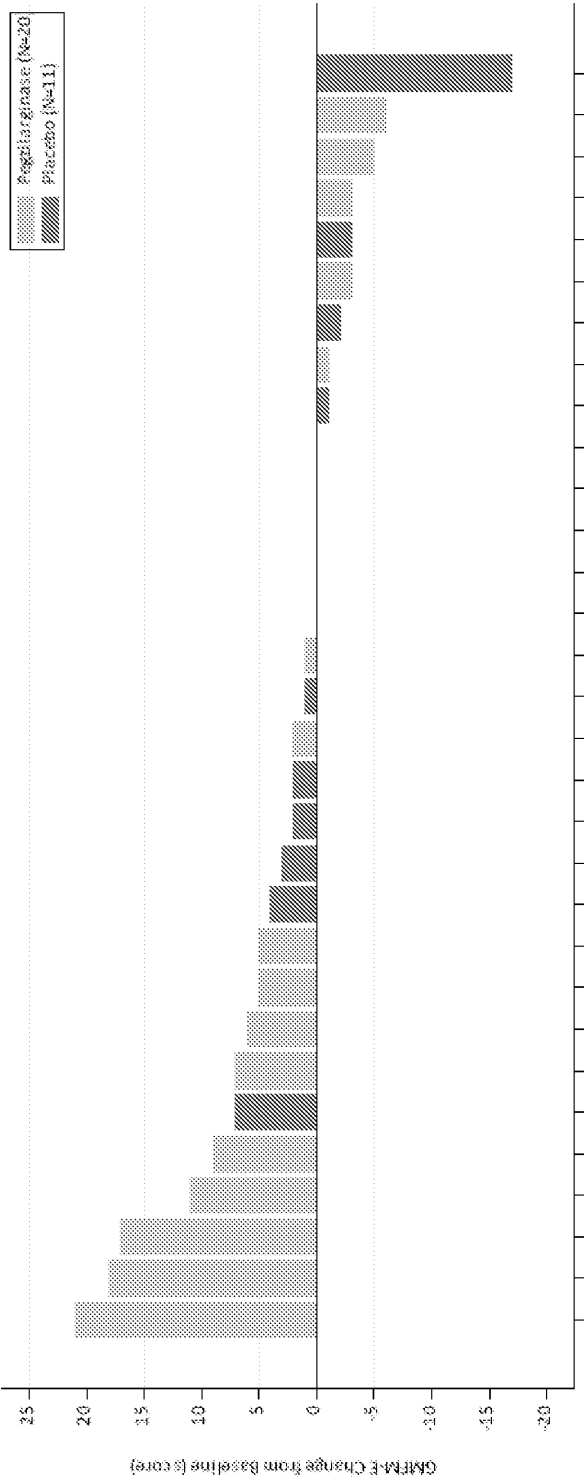


Figure 6

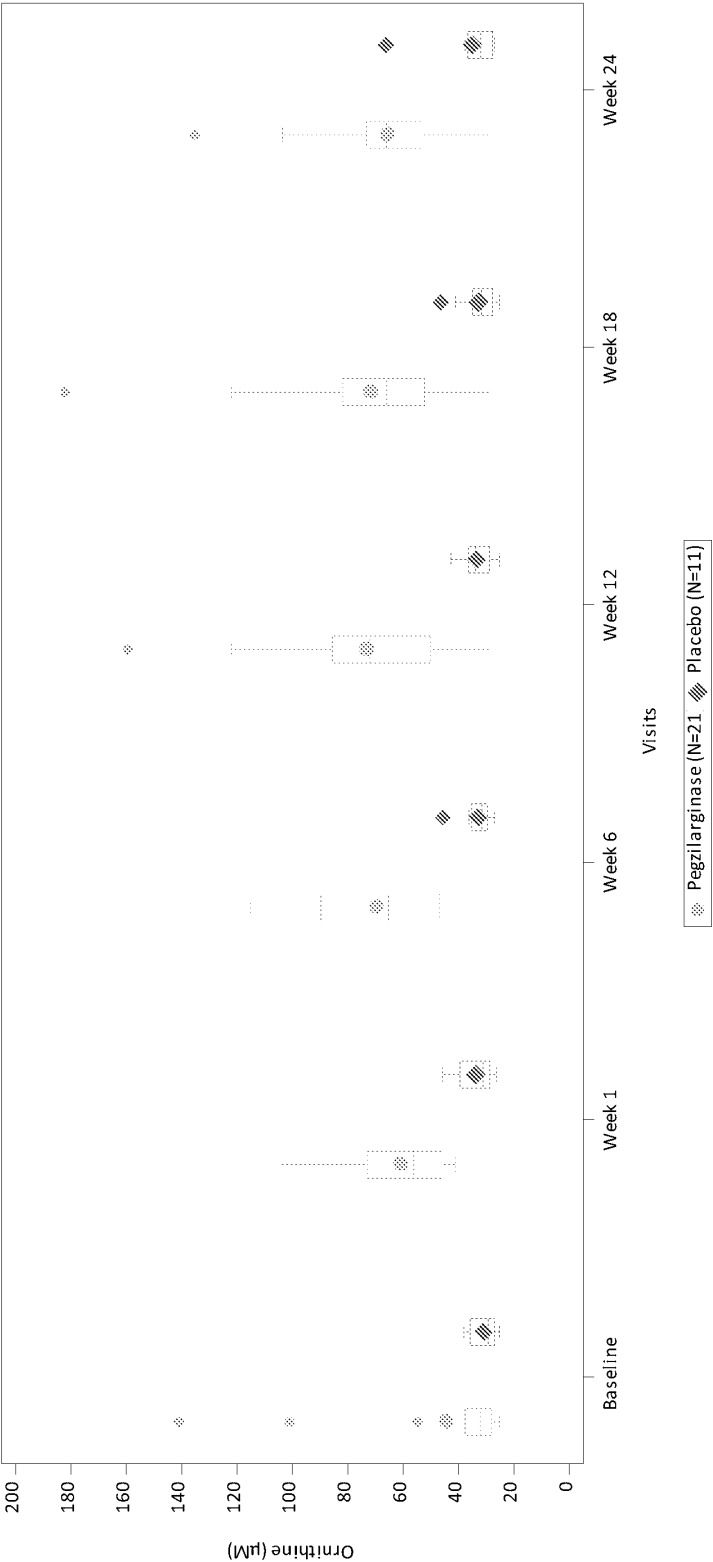


Figure 7

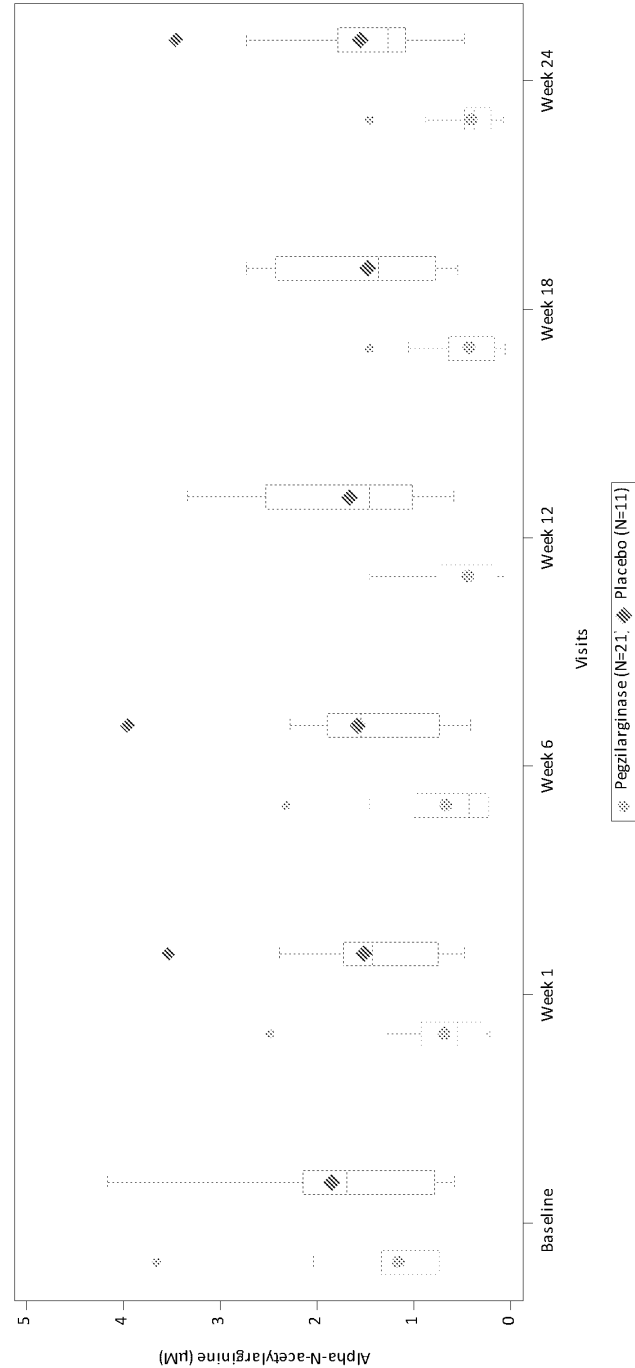


Figure 8

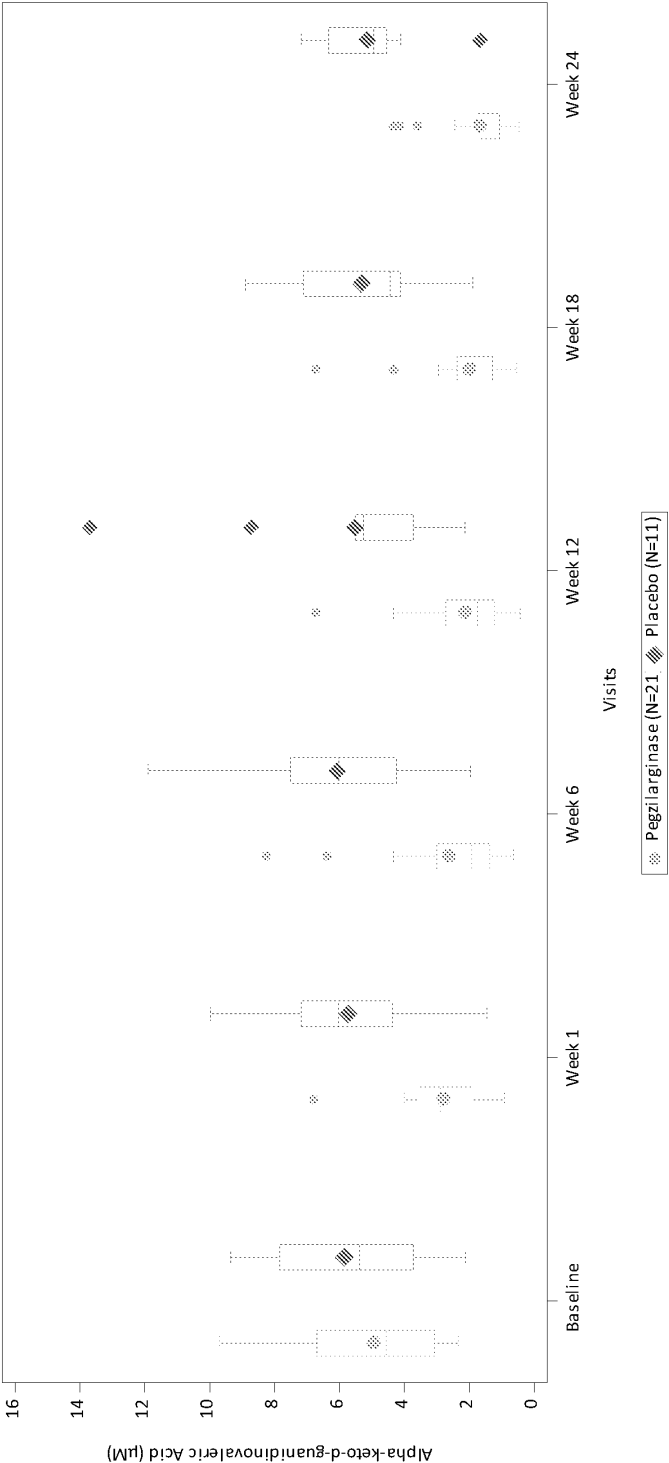


Figure 9

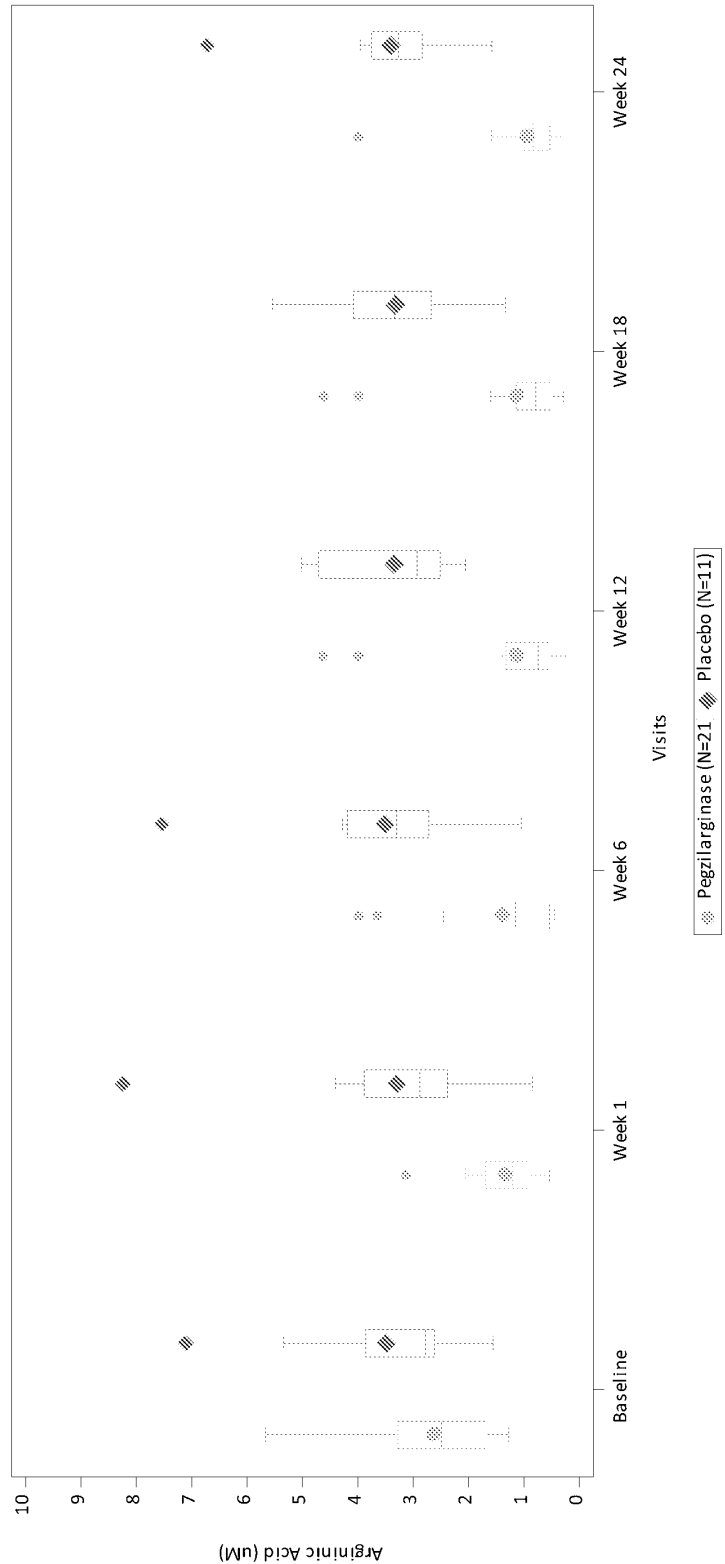


Figure 10

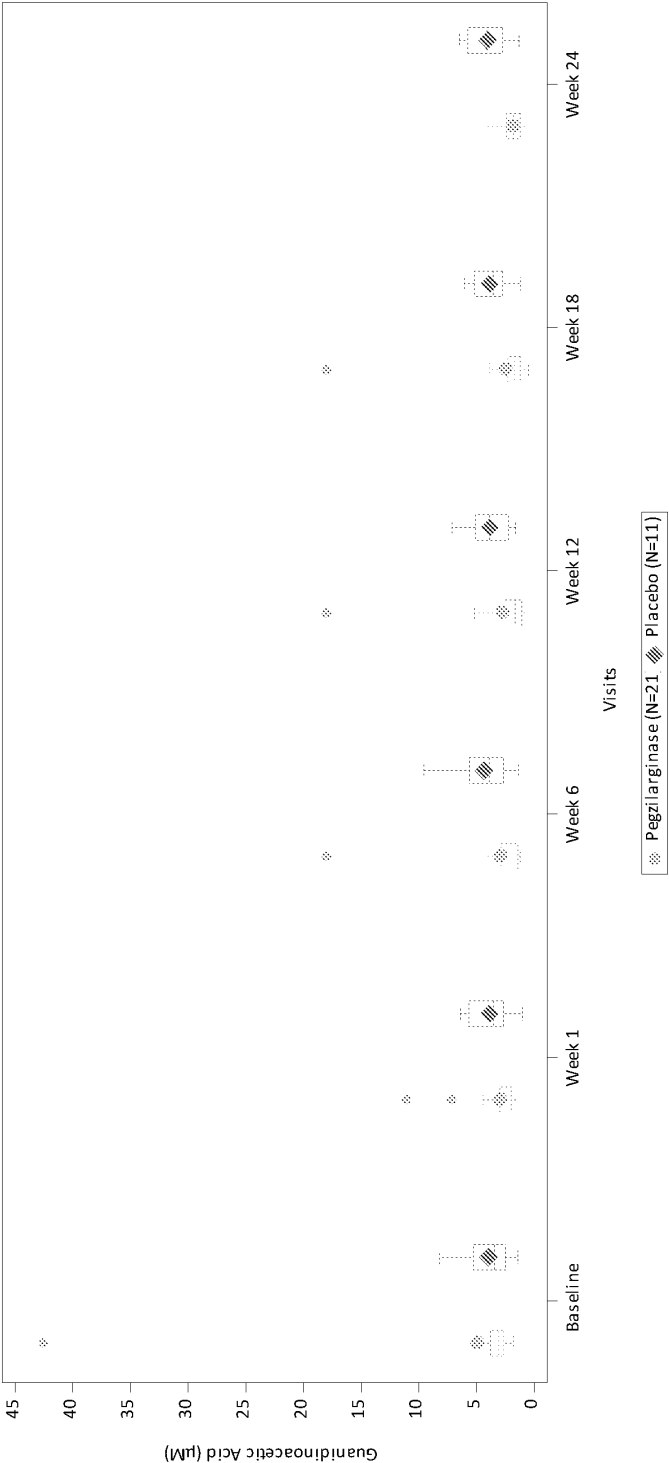


Figure 11

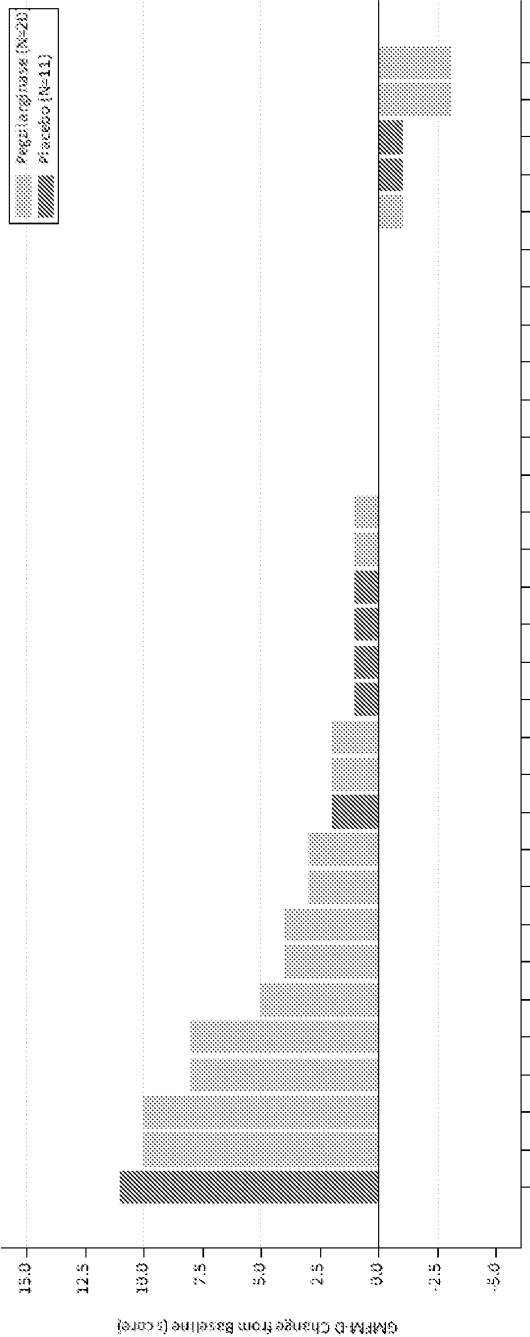


Figure 12

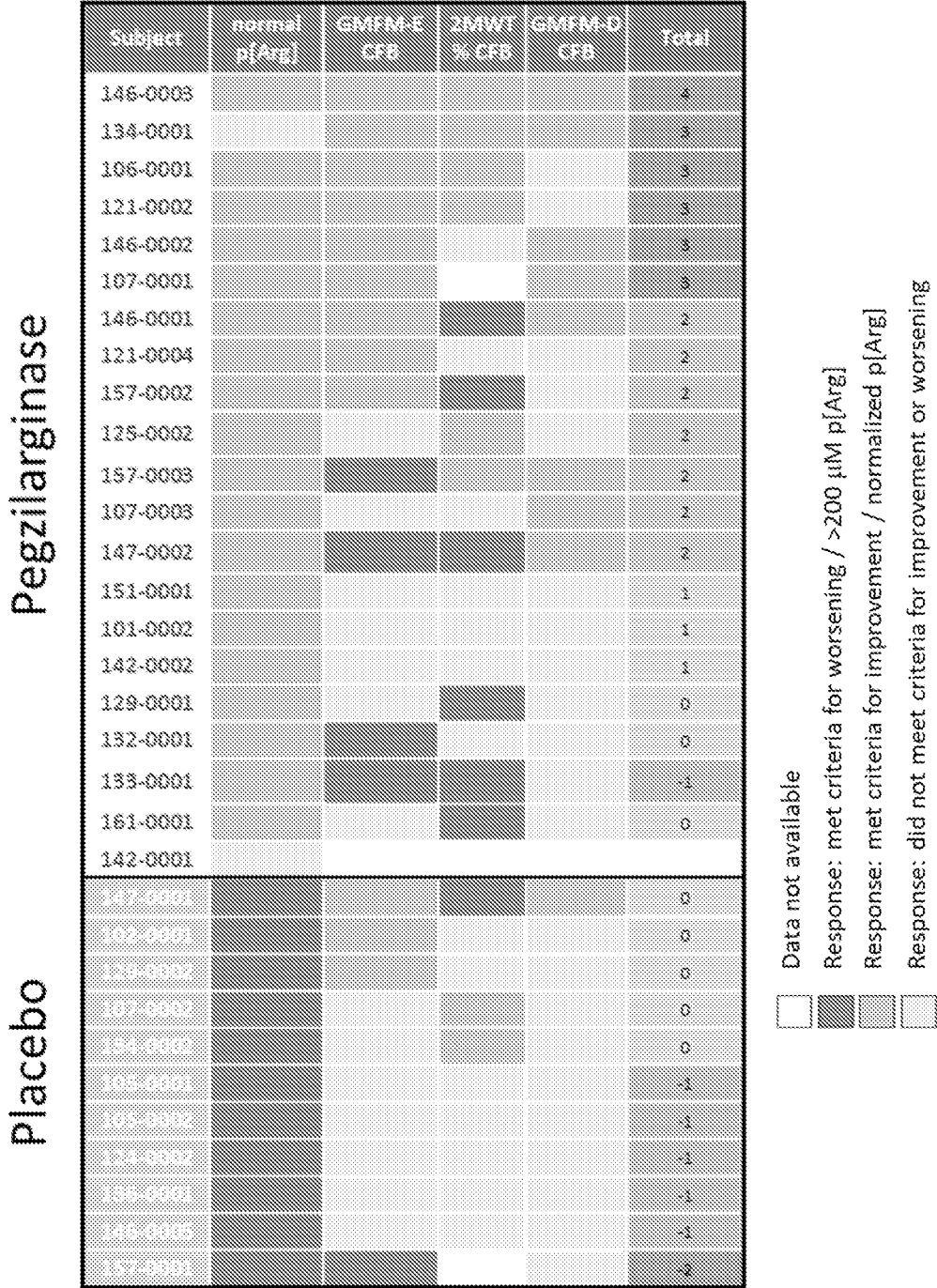


Figure 13

PROTEIN INTAKE			ENERGY REQUIREMENTS				
Age	Intake		Age	Females	Males	Females	Males
months	g/kg bw/day		years	kJ/kg bw/day		kcal/kg bw/day	
1	1.77		0.5	340	335	813	80.0
2	1.50		2.5	334	348	798	83.2
3	1.36		5.0	305	315	729	75.3
6	1.31		10	248	275	593	65.2
12	1.14		15	195	230	461	53.0
years							
1.5	1.03		Adults, moderate activity level, 70kg body weight				
2	0.97						
3	0.90		18-29	159	163	380	40.7
4-6	0.87		30-59	148	175	354	41.8
7-10	0.92						
	Females	Males	Adults, moderate activity level, 50kg body weight				
years							
11	0.90	0.91	18-29	180	212	438	50.7
12	0.89	0.90	30-59	185	212	437	50.7
13	0.88	0.90					
14	0.87	0.89					
15	0.85	0.88	trimester	kJ/day		kcal/day	
16	0.84	0.87	1st	375		90	
17	0.83	0.86	2nd	1200		287	
18	0.82	0.85	3rd	1950		466	
> 18	0.83	0.83					
			Lactation total extra energy requirements				
			months	kJ/day		kcal/day	
Pregnancy:							
Total extra protein intake							
trimester	g/day		1-6	2000		569	
1st	3		>6	1925		460	
2nd	10						
3rd	31						
Lactation:							
Total extra protein intake							
months	g/day						
1-6	19						
> 6	13						

bw: body weight.

bw: body weight.

Figure 14

Endpoint*	Pegzilarginase (n=21)		Placebo (n=11)		Change From Baseline Relative to Placebo (95% CI)†
	Baseline	24 Weeks	Baseline	24 Weeks	
Ornithine, $\mu\text{mol/L}^*$	38.6 $\pm$ 1.64	67.7 $\pm$ 1.43	30.6 $\pm$ 1.16	32.8 $\pm$ 1.23	+106.9% (56.7%, 173.1%); $p<0.0001$
Argininic acid, $\mu\text{mol/L}^*$	2.4 $\pm$ 1.54	0.7 $\pm$ 1.82	3.2 $\pm$ 1.50	3.2 $\pm$ 1.47	-69.5% (-57.2%, -78.3%); $p<0.0001$
Guanidinoacetic acid, $\mu\text{mol/L}^*$	3.4 $\pm$ 1.87	1.7 $\pm$ 1.60	3.6 $\pm$ 1.63	3.7 $\pm$ 1.62	-53.3% (-32.2%, -67.8%); $p=0.0003$
α -keto- δ -guanidinovaleic acid, $\mu\text{mol/L}^*$	4.5 $\pm$ 1.59	1.3 $\pm$ 1.84	5.4 $\pm$ 1.57	4.8 $\pm$ 1.50	-68.3% (-54.6%, -77.9%); $p<0.0001$
α -N-acetylarginine, $\mu\text{mol/L}^*$	1.0 $\pm$ 1.94	0.3 $\pm$ 2.12	1.5 $\pm$ 1.90	1.3 $\pm$ 1.73	-69.8% (-51.8%, -81.1%); $p<0.0001$
GMFM-D, points‡	28.0 $\pm$ 9.61	30.5 $\pm$ 10.09	29.5 $\pm$ 12.42	28.2 $\pm$ 13.28	+2.25 (-0.37, 4.87); $p=0.0896$

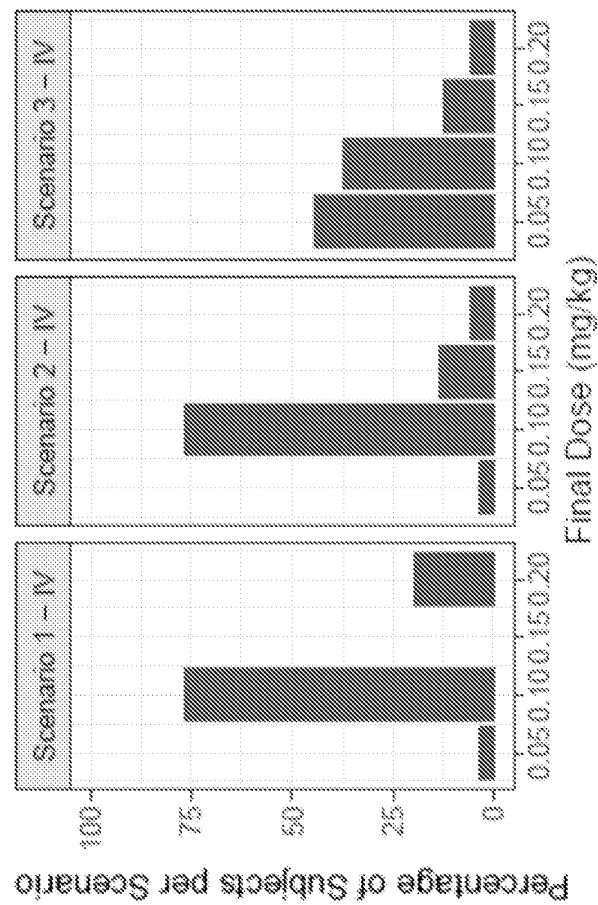
GMFM-D, Gross Motor Function Measure part D.

*Ornithine and guanidino compounds presented as geometric mean $\pm$ SD; GMFM-D presented as mean $\pm$ SD. †Ornithine and guanidino compounds presented as estimated percentage change from baseline relative to placebo; GMFM-D presented as least squares mean difference vs placebo. ‡Significance based on mixed model for repeated measures. †Reflects ad hoc analysis addressing data entry error in placebo arm; 1 patient had a missing baseline assessment that was originally scored as zero rather than a nonnumeric entry of "not assessed."

Figure 15

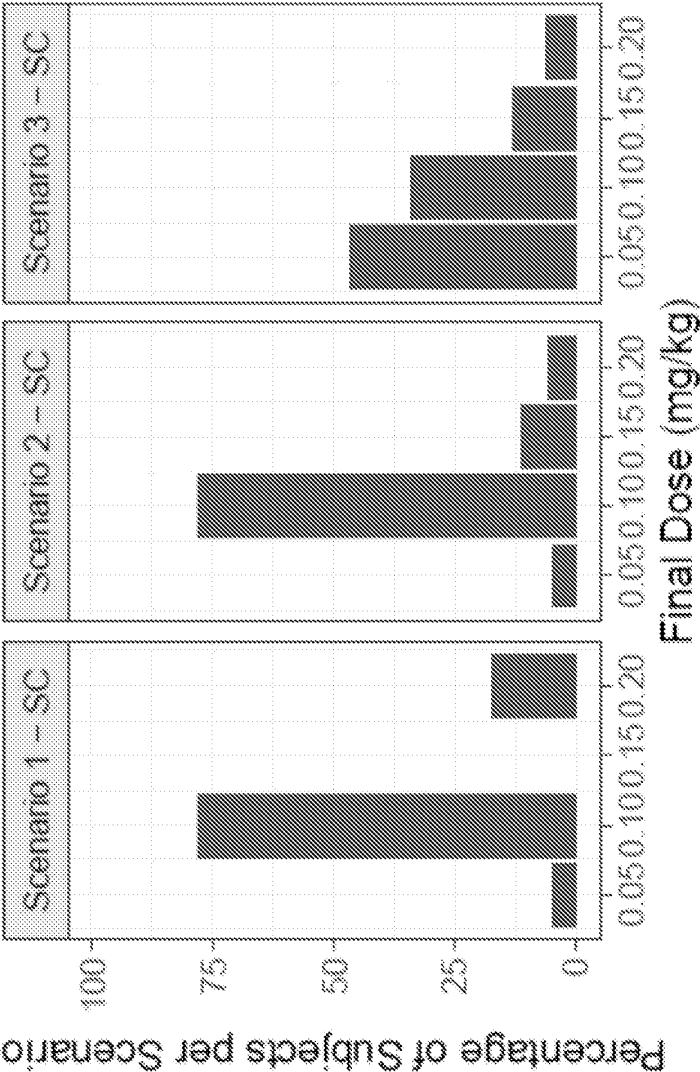
Scenario	Starting Dose (mg/kg)	Dose Increase (mg/kg)	Dose Decrease (mg/kg)	Reference Name
1	0.1	0.1	0.05	0.1/0.1 mg/kg
2	0.1	0.05	0.05	0.1/0.05 mg/kg
3	0.05	0.05	0.05	0.05/0.05 mg/kg

Figure 16



Scenario 1 = 0.1/0.1 mg/kg, Scenario 2 = 0.1/0.05 mg/kg, Scenario 3 = 0.05/0.05 mg/kg

Figure 17



Scenario 1 = 0.1/0.1 mg/kg, Scenario 2 = 0.1/0.05 mg/kg, Scenario 3 = 0.05/0.05 mg/kg

Figure 18

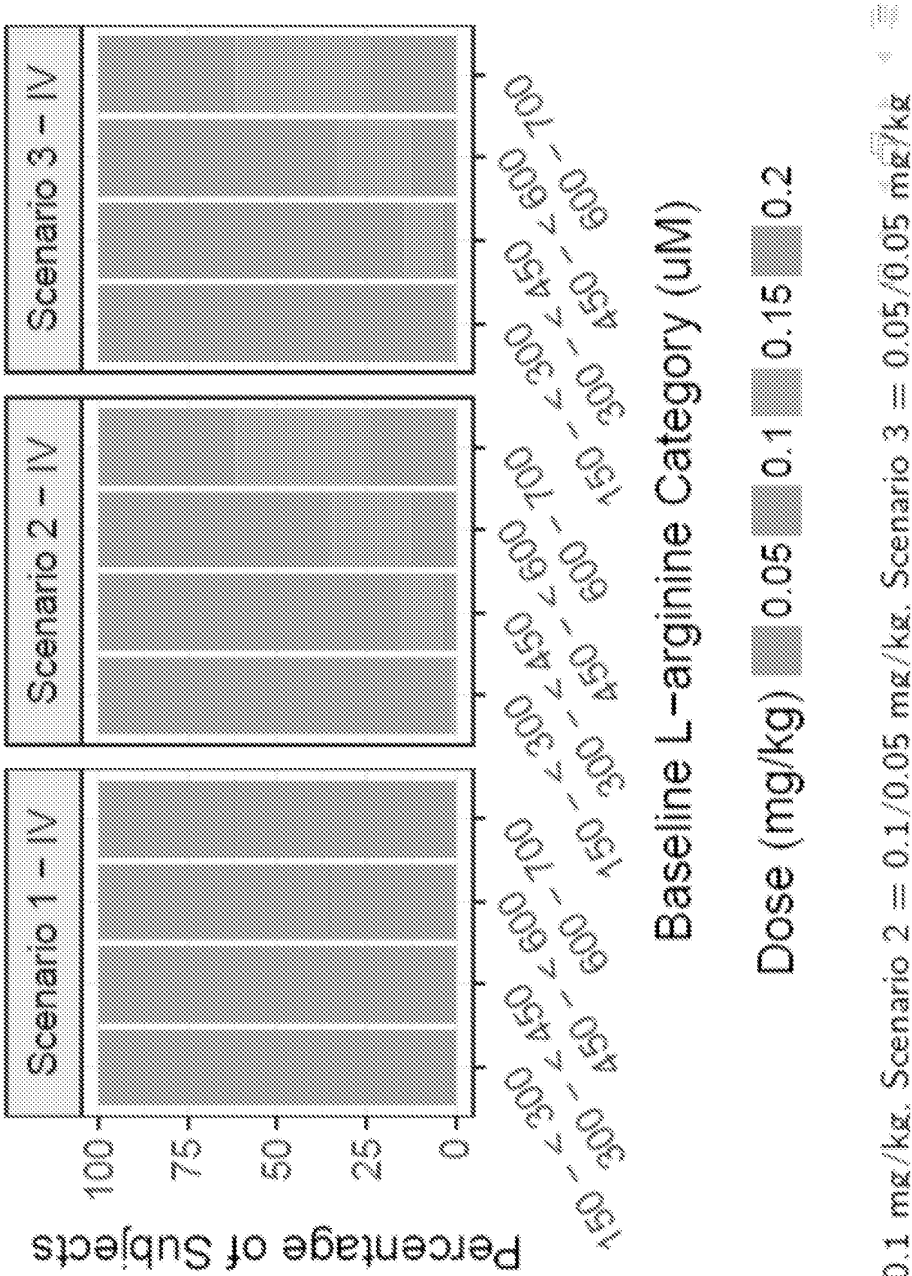
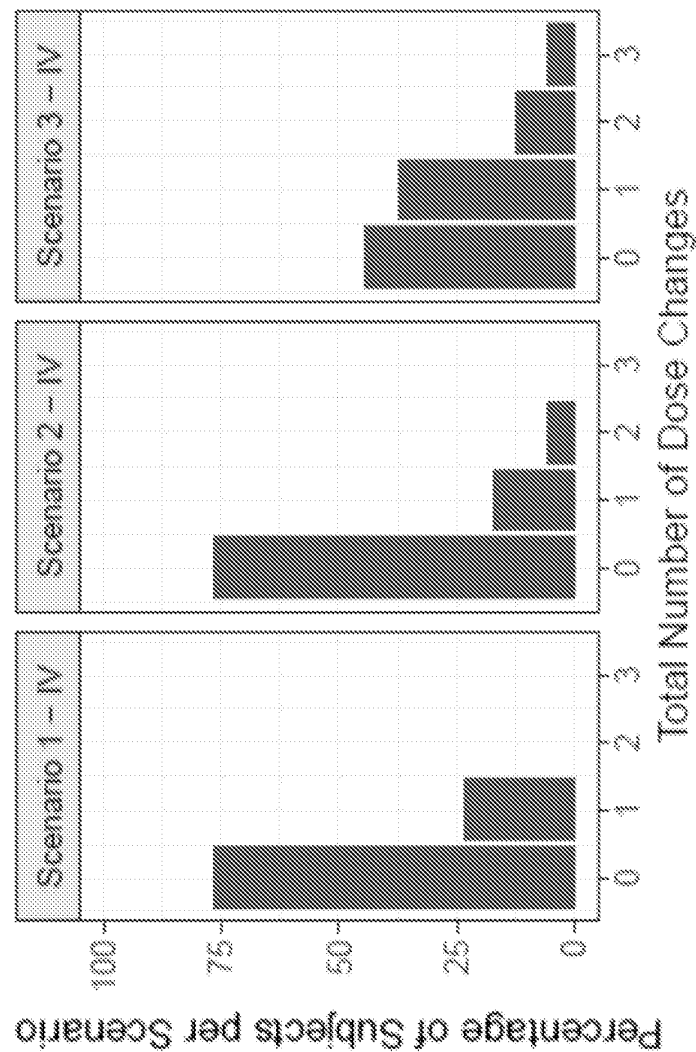


Figure 19



Scenario 1 = 0.1/0.1 mg/kg, Scenario 2 = 0.1/0.05 mg/kg, Scenario 3 = 0.05/0.05 mg/kg

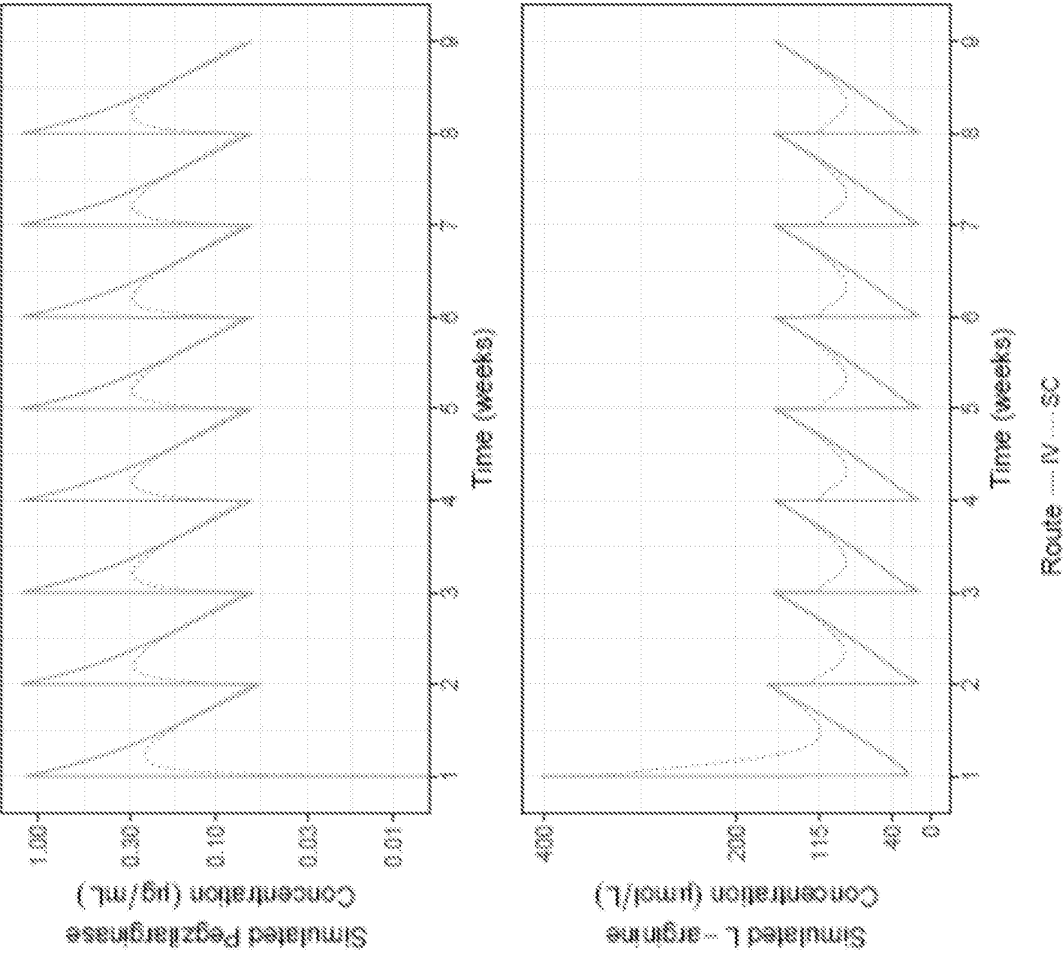


Figure 20

Figure 21

Scenario	L-Arginine Range			
	<40 μ M	40 – $\leq$ 115 μ M	40 – $\leq$ 200 μ M	$\leq$ 200 μ M
	Median Percentage of Time Within a Dosing Interval (90% PI, %)			
Scenario 1 - IV	41.6 (24.1 – 71.5)	51.7 (27.6 – 63.1)	57.1 (28.5 – 73.9)	99.7 (96.7 – 100)
Scenario 2 - IV	39.9 (22.7 – 71.5)	52.1 (27.6 – 63.1)	59.2 (28.5 – 75.2)	99.7 (96.7 – 100)
Scenario 3 - IV	30 (15.5 – 50.7)	55.4 (43.7 – 68.9)	67.3 (48.8 – 82.4)	98.3 (93.5 – 100)
Scenario 1 - SC	3 (0 – 73.1)	79 (26.2 – 99.2)	95.3 (26.7 – 99.8)	99.7 (98.1 – 100)
Scenario 2 - SC	0 (0 – 73.1)	78.4 (26.2 – 99.2)	96.9 (26.7 – 99.8)	99.7 (98.1 – 100)
Scenario 3 - SC	0 (0 – 39)	79.1 (45.3 – 99.1)	98.4 (60.9 – 100)	99.3 (89.5 – 100)
Data represents the average time that L-arginine remained in each of the ranges over 24 weeks. The median and 90% PI are shown for each scenario. The time in range are presented as a percentage of the dosing interval (168 h). Scenario 1 - 0.1/0.1 mg/kg, Scenario 2 - 0.1/0.05 mg/kg, Scenario 3 - 0.05/0.05 mg/kg.				