Table e-1: Demographics and baseline clinical characteristics of study cohorts

	Cohort 1 0 01mg/kg/hr N=9	**Cohort 2 0 10mg/kg/hr N=9**	**Cohort 3 0 25mg/kg/hr N=9**	**Placebo 0mg/kg/hr N=9**	**All N=36**
Age (Years)*	41 ± 11	45 ± 14	42 ± 17	42 ± 16	43 ± 14
Sex					
Female	7	8	6	9	30
Male	2	1	3	0	6
Weight (kg)*	71 ± 21	64 ± 8	59 ± 8	56 ± 6	62 ± 13
BMI (kg/m2)*	26 ± 7	24 ± 3	22 ± 5	21 ± 2	23 ± 5
Symptom					
Fatigue	9	9	9	8	
Exercise Intolerance	9	7	9	9	
Muscle weakness	8	8	8	7	
Muscle cramps	2	3	3	4	
Muscle atrophy	1	2	3	3	
Fasiculations	2	1	0	1	
Genetic Findings					
Mitochondrial DNA deletions	2	3	5	3	13
Mitochondrial DNA missense mutations	2	5	3	5	15
Nuclear DNA mutations	5	1	1	1	8

*Means ± SD are shown

Table e-2: Genetic findings in the mitochondrial disease cohorts

Characteristic	Elamipretide			Placebo (N = 9)	All participants (N = 36)
	0.01 mg/kg/hr (N = 9)	0.10 mg/kg/hr (N = 9)	0.25 mg/kg/hr (N = 9)		
MT Deletion Syndrome (20-60% heteroplasmy in muscle)	2	1	5	3	11
MT-tRNA mutations (A3243G, A8344G,T 12148C) (22.5-83% heteroplasmy in blood)	0	3	3	2	8
POLG-related Disorder	3	0	0	1	4
LHON Plus	0	2	0	1	3
Kearns-Sayre Syndrome (KSS)	0	2	0	0	2
Multi-system Mitochondrial Disorder (OPA1)	1	1	0	0	2
Leigh Syndrome (NDUFV1)	1	0	0	0	1
MEGDEL	0	0	1	0	1
Mitochondrial Myopathy (MT-CYB)	0	0	0	1	1
Multi-system Mitochondrial Disorder (MT-COX1) (85% heteroplasmy in blood)	1	0	0	0	1
Multi-system Mitochondrial Disorder (MT-ND1) (100% homoplasmy in blood)	0	0	0	1	1
Multi-system Mitochondrial Disorder (MT-ND3) (21% heteroplasmy in blood)	1	0	0	0	1

Details of the genetic mutations for participants enrolled in the trial grouped by gene or syndrome.

Table e-3: Change in NMDAS scores, participants-reported symptom changes and biomarker findings at Day 5.

		Elamipretide			
		0.01 mg/kg/hr (n=9)	**0.10 mg/kg/hr (n=9)**	**0.25 mg/kg/hr (n=9)**	**Placebo (n=9)**
Participants Reported Symptoms					
NMDAS Current Function	**Baseline Mean (SD)**	12.1 (5.90)	16.3 (6.34)	16.2 (5.85)	16.2 (6.59)
	Change on Day 5[1] LS Mean LSM Diff[2] (90% CI)[3]	-3.1 0.1 (-3.8, 4.0)	-5.4 -2.2 (-6.0, 1.6)	-3.8 -0.6 (-4.3, 3.2)	-3.2
Daily Symptom Questionnaire					
Limitations on Activities	**Baseline Mean (SD)**	4.0 (3.46)	3.9 (3.14)	4.3 (3.39)	4.8 (2.64)
	Change on Day 5[1] LS Mean LSM Diff[2] (90% CI)[3]	-1.5 -0.8 (-2.4, 0.8)	-1.7 -1.1 (-2.7, 0.5)	-1.6 -1.0 (-2.6, 0.6)	-0.7
Muscle Weakness	**Baseline Mean (SD)**	2.9 (3.33)	4.6 (1.94)	4.8 (3.35)	4.9 (2.42)
	Change on Day 5[1] LS Mean LSM Diff[2] (90% CI)[3]	-2.1 -0.8 (-2.6, 0.9)	-2.2 -0.9 (-2.5, 0.8)	-2.4 -1.1 (-2.7, 0.6)	-1.3
Physical Fatigue	**Baseline Mean (SD))**	4.6 (3.17)	4.1 (2.47)	3.3 (3.32)	5.3 (1.73)
	Change on Day 5[1] LS Mean LSM Diff[2] (90% CI)[3]	-2.5 -1.5 (-3.3, 0.3)	-2.3 -1.2 (-3.0, 0.6)	-1.3 -0.3 (-2.1, 1.6)	-1.0
Muscle Pain	**Baseline Mean (SD)**	3.2 (3.63)	3.1 (3.22)	2.1 (2.32)	3.2 (2.59)
	Change on Day 5[1] LS Mean LSM Diff[2] (90% CI)[3]	-1.3 0.2 (-1.3, 1.8)	-2.2 -0.7 (-2.3, 0.8)	-0.8 0.7 (-0.9, 2.3)	-1.5
Mental Fatigue	**Baseline Mean (SD)**	2.0 (3.32)	4.0 (3.46)	3.1 (3.30)	4.0 (2.83)
	Day 5[1] LS Mean LSM Diff[2] (90% CI)[3]	-1.8 -1.3 (-2.9, 0.3)	-1.8 -1.2 (-2.8, 0.4)	-1.4 -0.9 (-2.5, 0.7)	-0.5
Abdominal Pain	**Baseline Mean (SD)**	0.9 (1.83)	1.0 (1.50)	0.3 (1.00)	2.0 (3.04)

	Day 5[1] LS Mean LSM Diff[2] (90% CI)[3]	-0.8 -0.1 (-0.6, 0.4)	-0.1 0.5 (0.1, 1.0)	-0.6 0.1 (-0.4, 0.6)	-0.7
Biomarkers					
FGF-21 (ng/L)	**Baseline Mean (SD)**	161.59 (146.53)	116.55 (51.82)	218.23 (263.08)	80.58 (49.94)
	Day 5 Mean Diff[2] (SD)	-6.38 (35.80)	2.27 (51.11)	-32.08 (87.37)	1.30 (36.61)
Glutathione (ug/L)	**Baseline Mean (SD)**	3.65 (3.57)	1.72 (1.42)	2.05 (0.88)	3.91 (7.24)
	Day 5 Mean Diff[2] (SD)	-0.94 (1.38)	0.58 (1.18)	0.24 (0.87)	-0.68 (2.06)
8 Isoprostane/ Creatinine (pg/mg)	**Baseline Mean (SD)**	1633.1 (1552.32)	2138.9 (889.75)	1469.6 (713.41)	1875.9 (1252.38)
	Day 5 Mean Diff[2] (SD)	-370.9 (997.58)	-159.1 (802.10)	15.0 (726.35)	-279.1 (1459.94)
8 hydroxy-2 deoxyguanosine/Creatinine ug/g	**Baseline Mean (SD)**	17.42 (6.99)	24.82 (16.22)	21.73 (16.89)	21.28 (13.43)
	Day 5 Mean Diff[2] (SD)	5.87 (8.08)	7.70 (24.53)	3.71 (25.12)	-3.54 (11.78)

*Means ± SD are shown for each variable

**Score based on a modified Newcastle Mitochondrial Disease Scale which included the 10 elements in Section I (Current Function) and the 9 elements in Section III (Current Clinical Assessment minus question 10 cognition). Total score per participants ranges from 0 to 78.