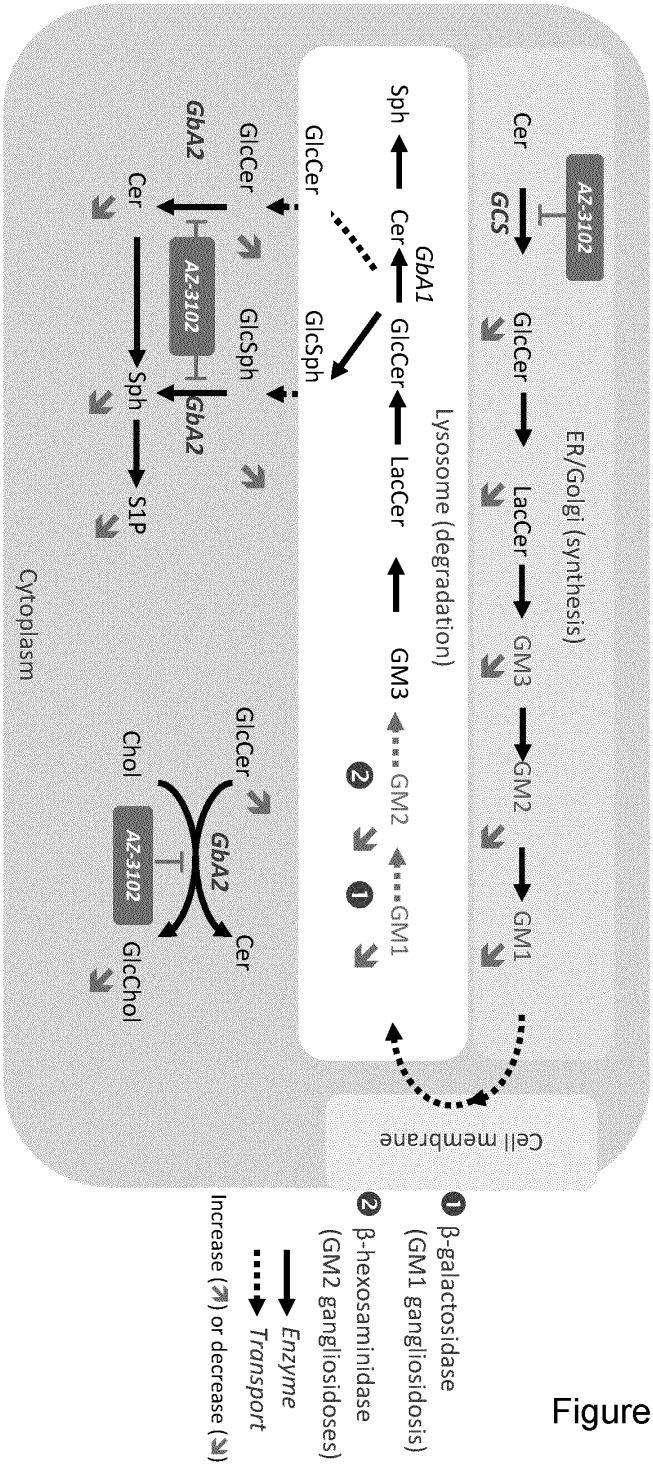

ER/Golgi (synthesis)
Cer
AZ-3102
GCS
GlcCer
LacCer
GM3
GM2
GM1
Lysosome (degradation)
Sph
GbA1
Cer
GlcCer
LacCer
GM3
GM2
GM1
GlcCer
GlcSph
GlcCer
GbA2
Cer
AZ-3102
GlcSph
GbA2
Sph
S1P
Cytoplasm
GlcCer
Chol
GbA2
Cer
AZ-3102
GlcChol
Cell membrane
❶ β-galactosidase (GM1 gangliosidosis)
❷ β-hexosaminidase (GM2 gangliosidoses)
Enzyme
Transport
Increase (↗) or decrease (↘)

Figure 1

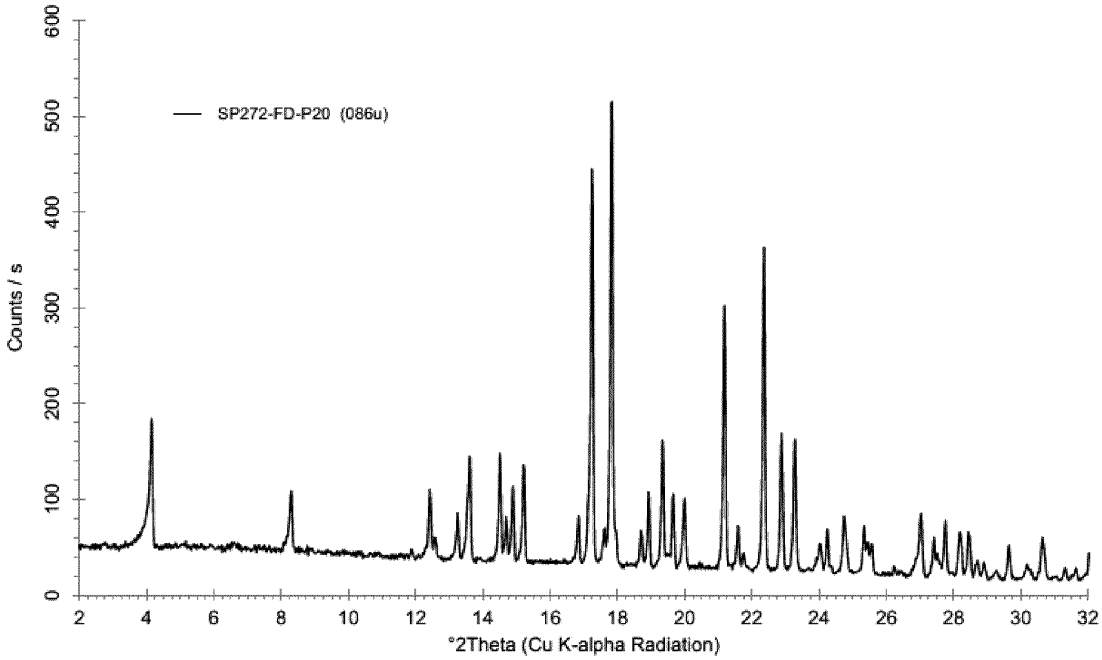


Figure 2A

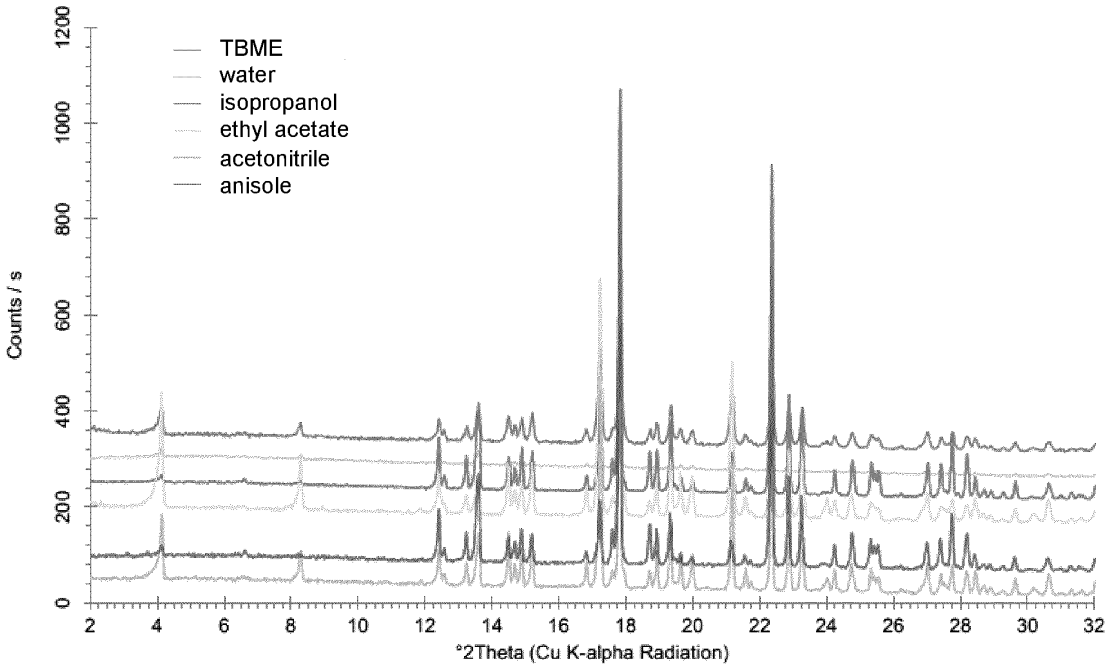


Figure 2B

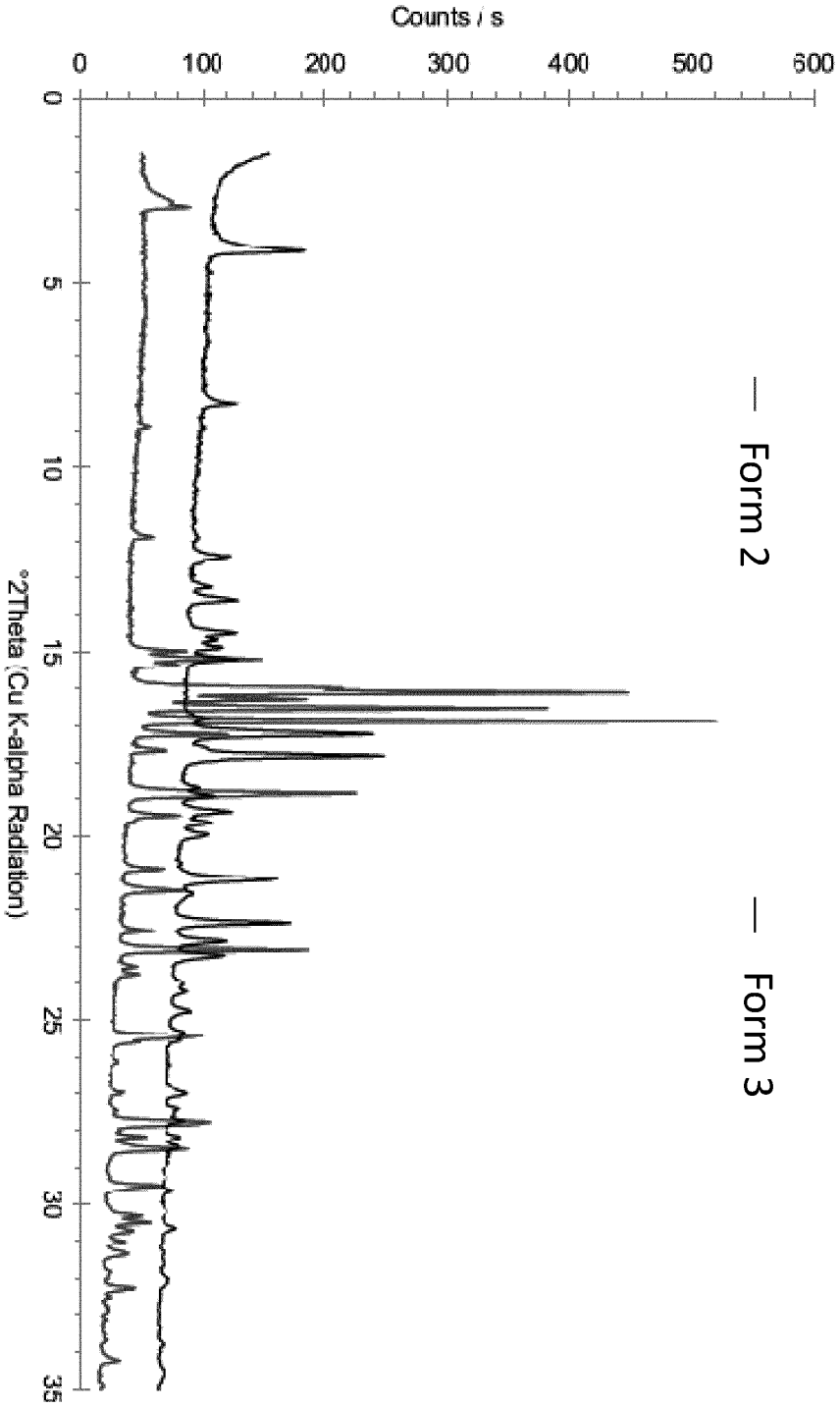

Counts / s
0
100
200
300
400
500
600
0
5
10
15
20
25
30
35
°2Theta (Cu K-alpha Radiation)
Form 2
Form 3

Figure 3

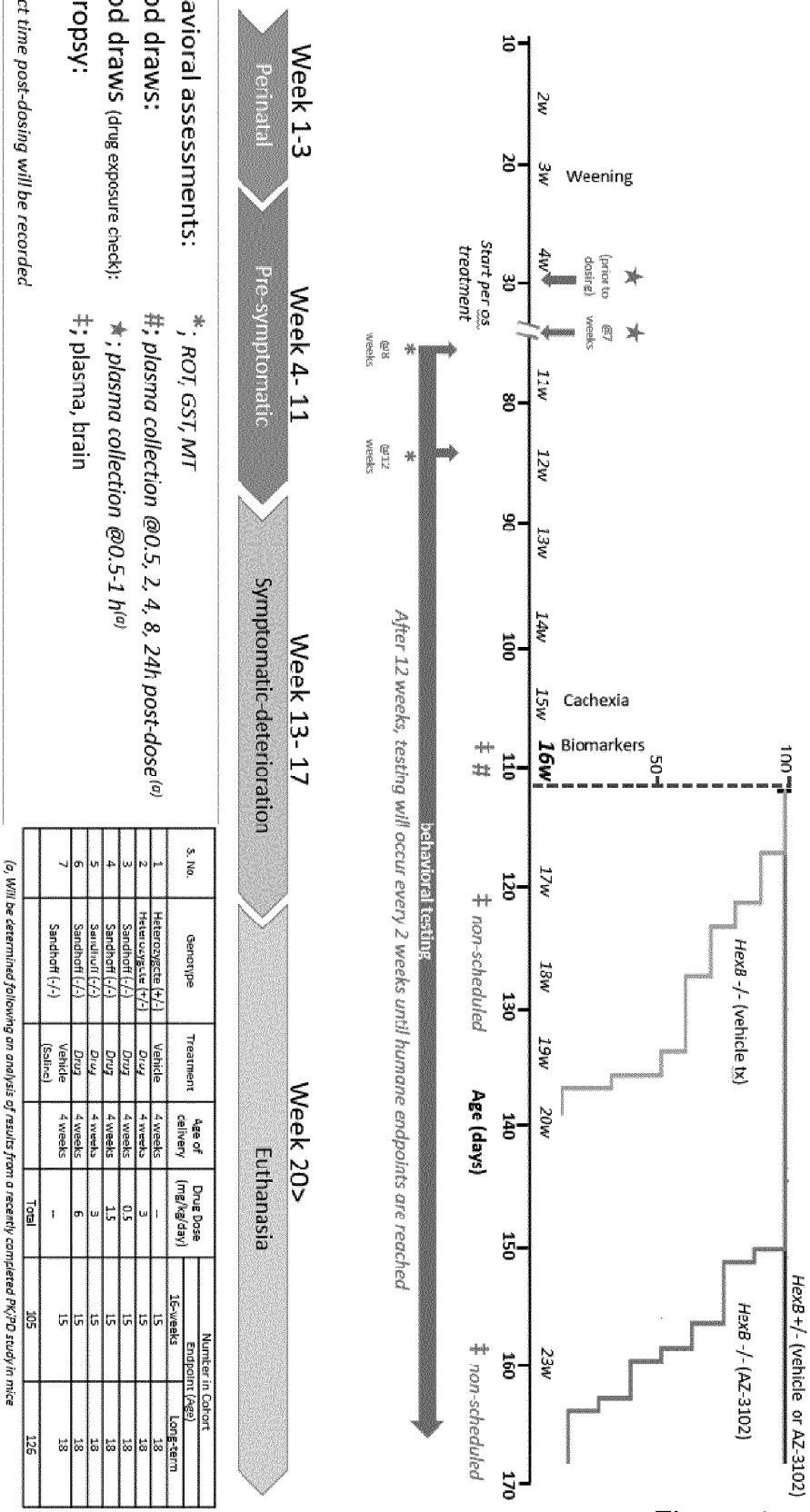


Figure 4

Behavioral assessments: *; *ROT, GST, MT*

Blood draws: #; *plasma collection @0.5, 2, 4, 8, 24h post-dose* [a]

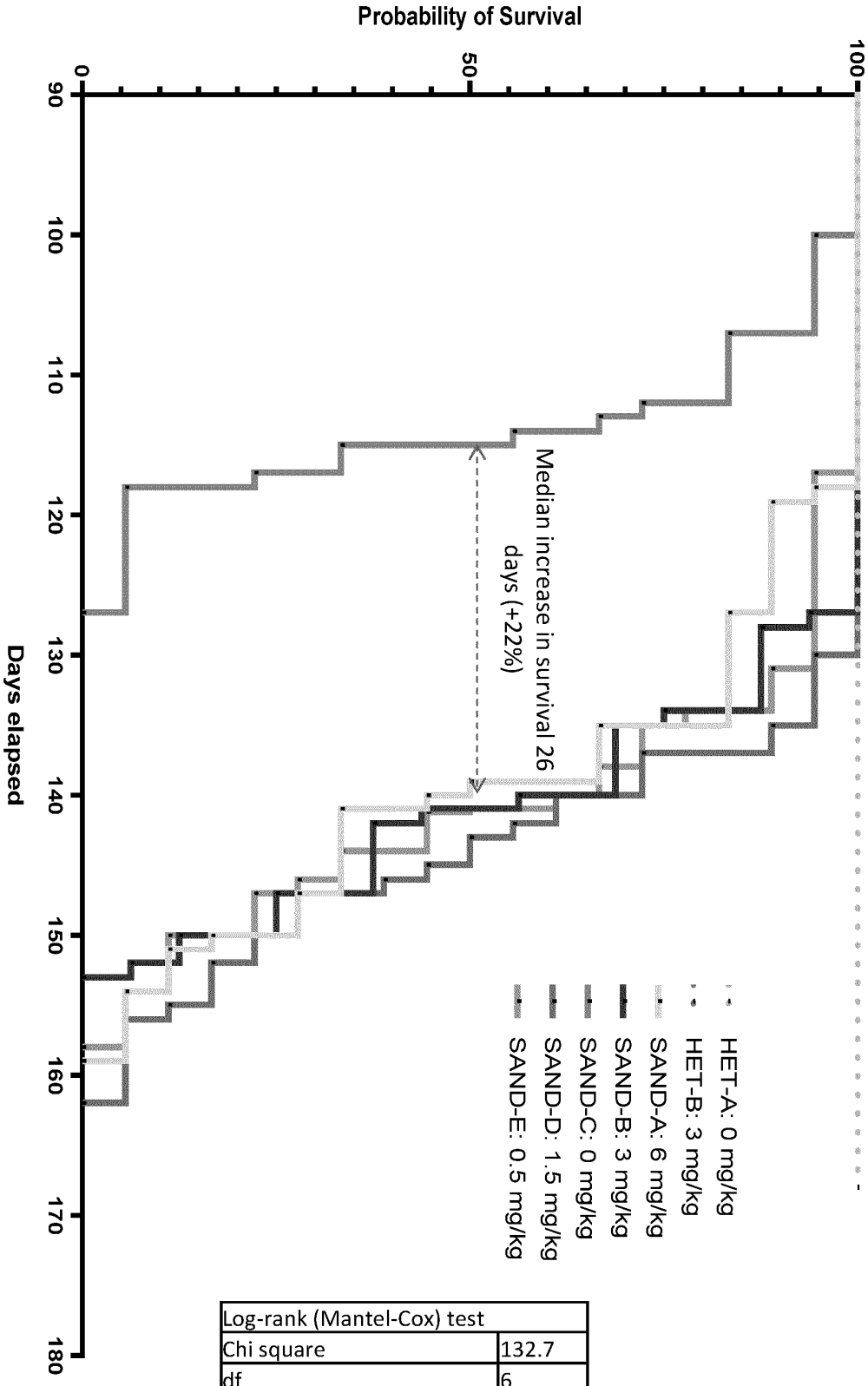
Blood draws (drug exposure check): ★; *plasma collection @0.5-1 h* [a]

Necropsy: ‡; plasma, brain

[a] *Exact time post-dosing will be recorded*

S. No.	Genotype	Treatment	Age of delivery	Drug Dose (mg/kg/day)	Number in Cohort	
					Endpoint (Age)	
					16-weeks	Long-term
1	Heterozygote (+/-)	Vehicle	4 weeks	--	15	18
2	Heterozygote (+/-)	*Drug*	4 weeks	3	15	18
3	Sandhoff (-/-)	*Drug*	4 weeks	0.5	15	18
4	Sandhoff (-/-)	*Drug*	4 weeks	1.5	15	18
5	Sandhoff (-/-)	*Drug*	4 weeks	3	15	18
6	Sandhoff (-/-)	*Drug*	4 weeks	6	15	18
7	Sandhoff (-/-)	Vehicle (Saline)	4 weeks	--	15	18
				Total	105	126

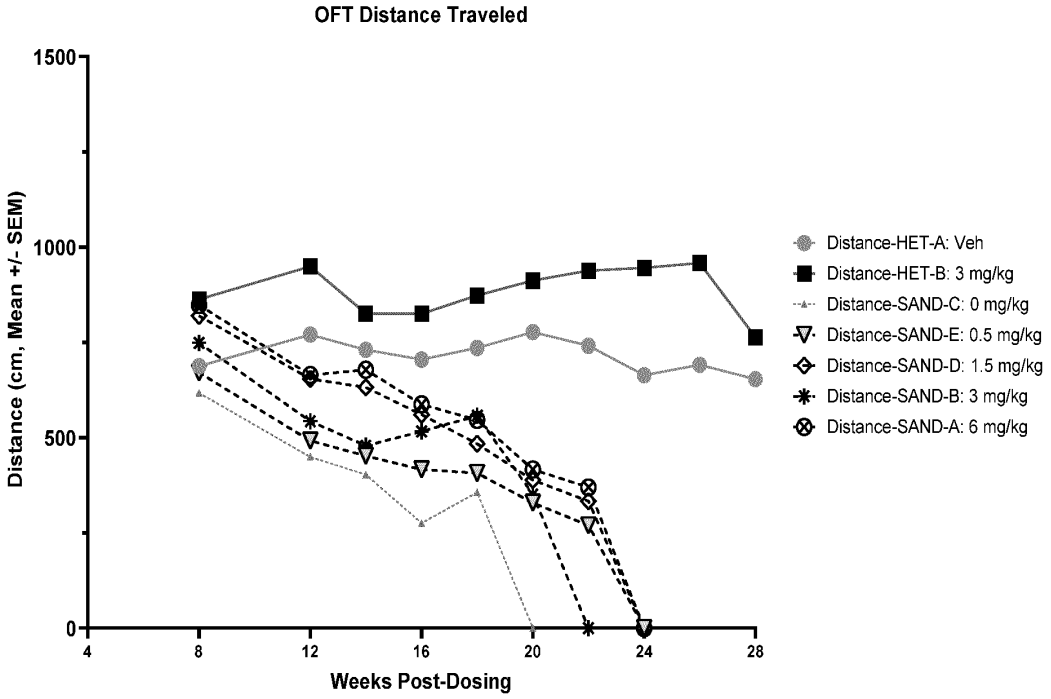
[a] *Will be determined following an analysis of results from a recently completed PK/PD study in mice*



Log-rank (Mantel-Cox) test	
Chi square	132.7
df	6
P value	<0.0001
P value summary	****

Figure 5

Total distance traveled



Total distance traveled at 16 weeks

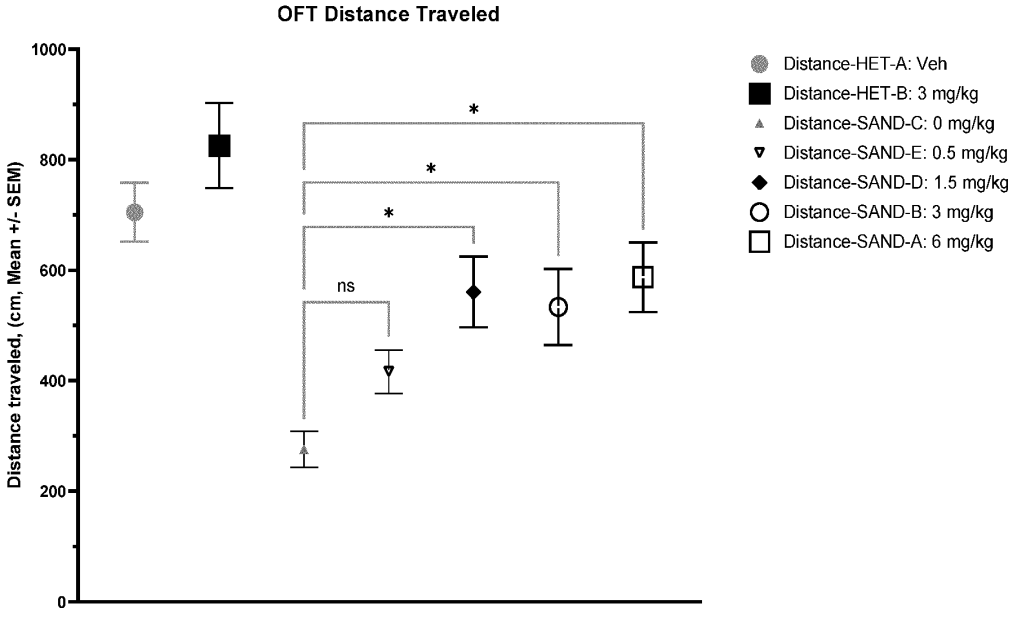
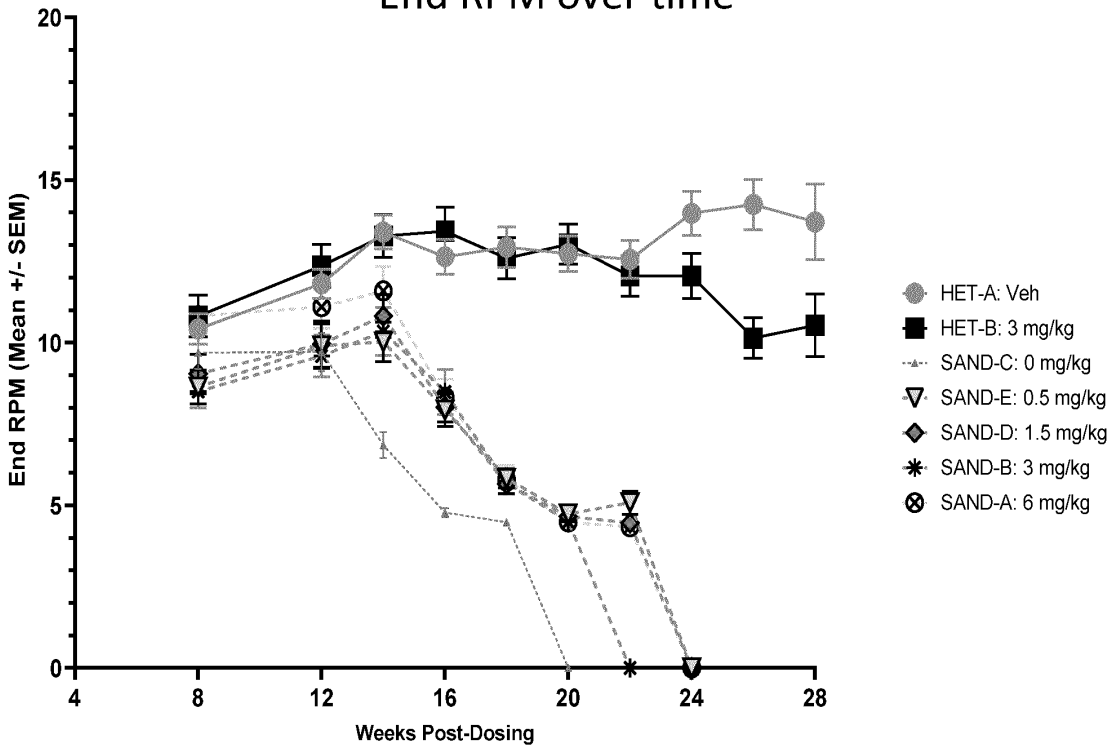


Figure 6

End RPM over time



End RPM at 16 weeks

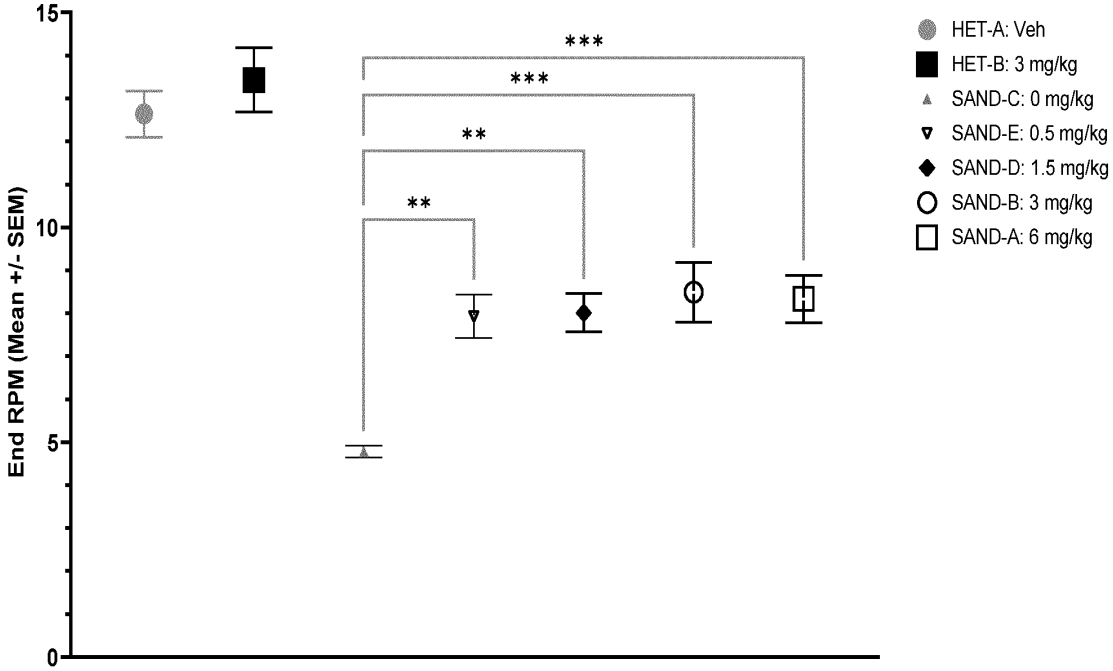
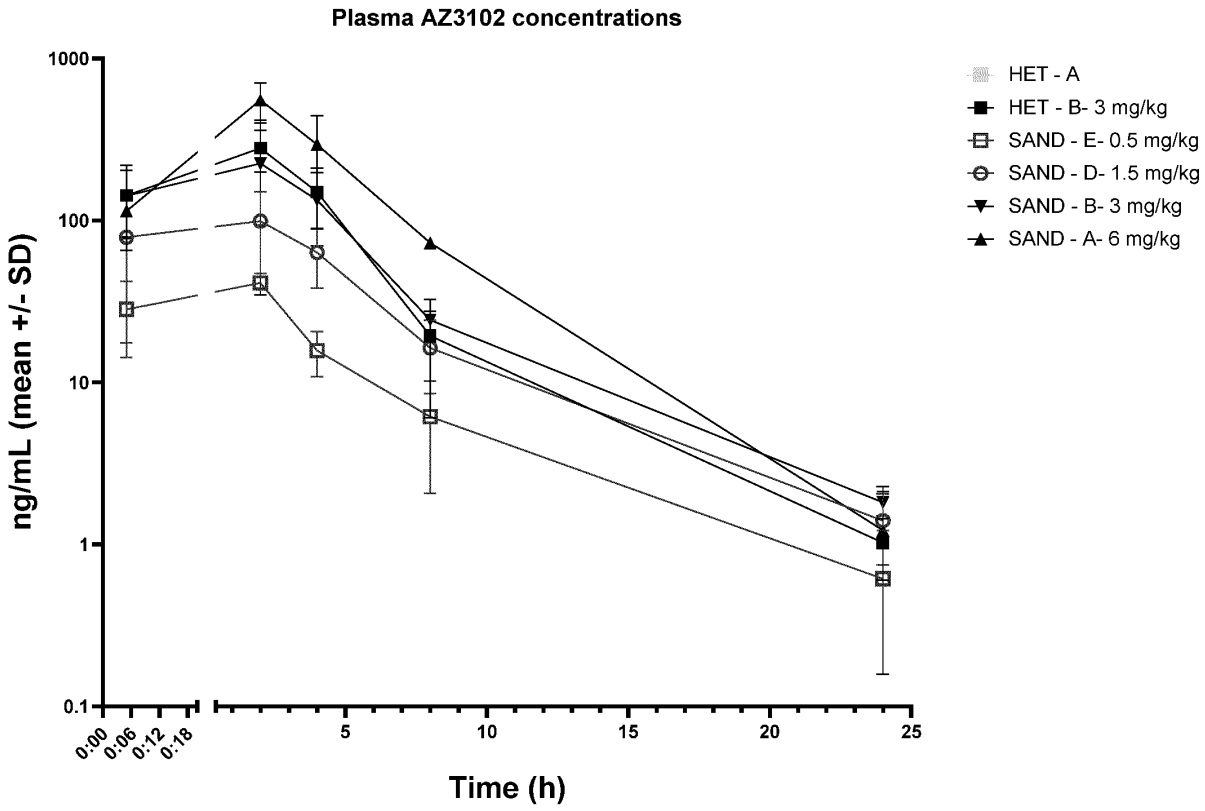


Figure 7


Plasma AZ3102 concentrations
ng/mL (mean +/- SD)
1000
100
10
1
0.1
0:00
0:06
0:12
0:18
5
10
15
20
25
Time (h)
HET - A
HET - B- 3 mg/kg
SAND - E- 0.5 mg/kg
SAND - D- 1.5 mg/kg
SAND - B- 3 mg/kg
SAND - A- 6 mg/kg

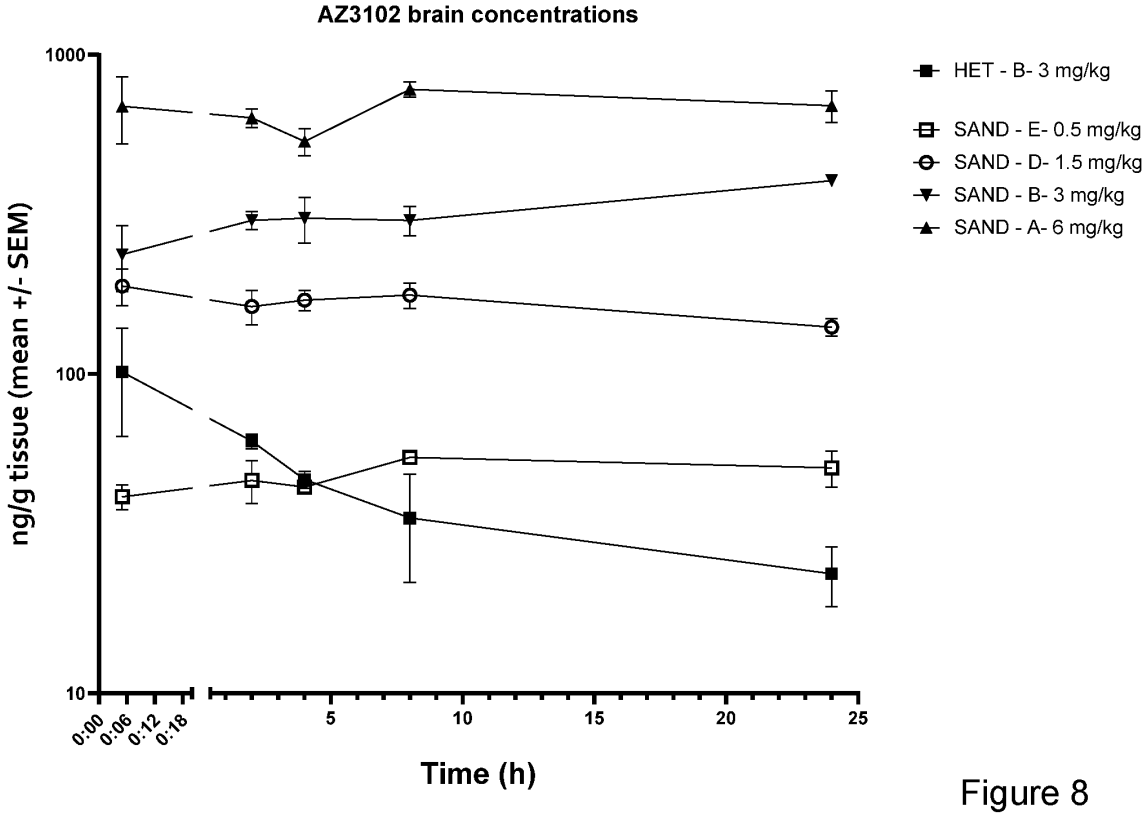

AZ3102 brain concentrations
ng/g tissue (mean +/- SEM)
1000
100
10
0:00
0:06
0:12
0:18
5
10
15
20
25
Time (h)
HET - B- 3 mg/kg
SAND - E- 0.5 mg/kg
SAND - D- 1.5 mg/kg
SAND - B- 3 mg/kg
SAND - A- 6 mg/kg

Figure 8

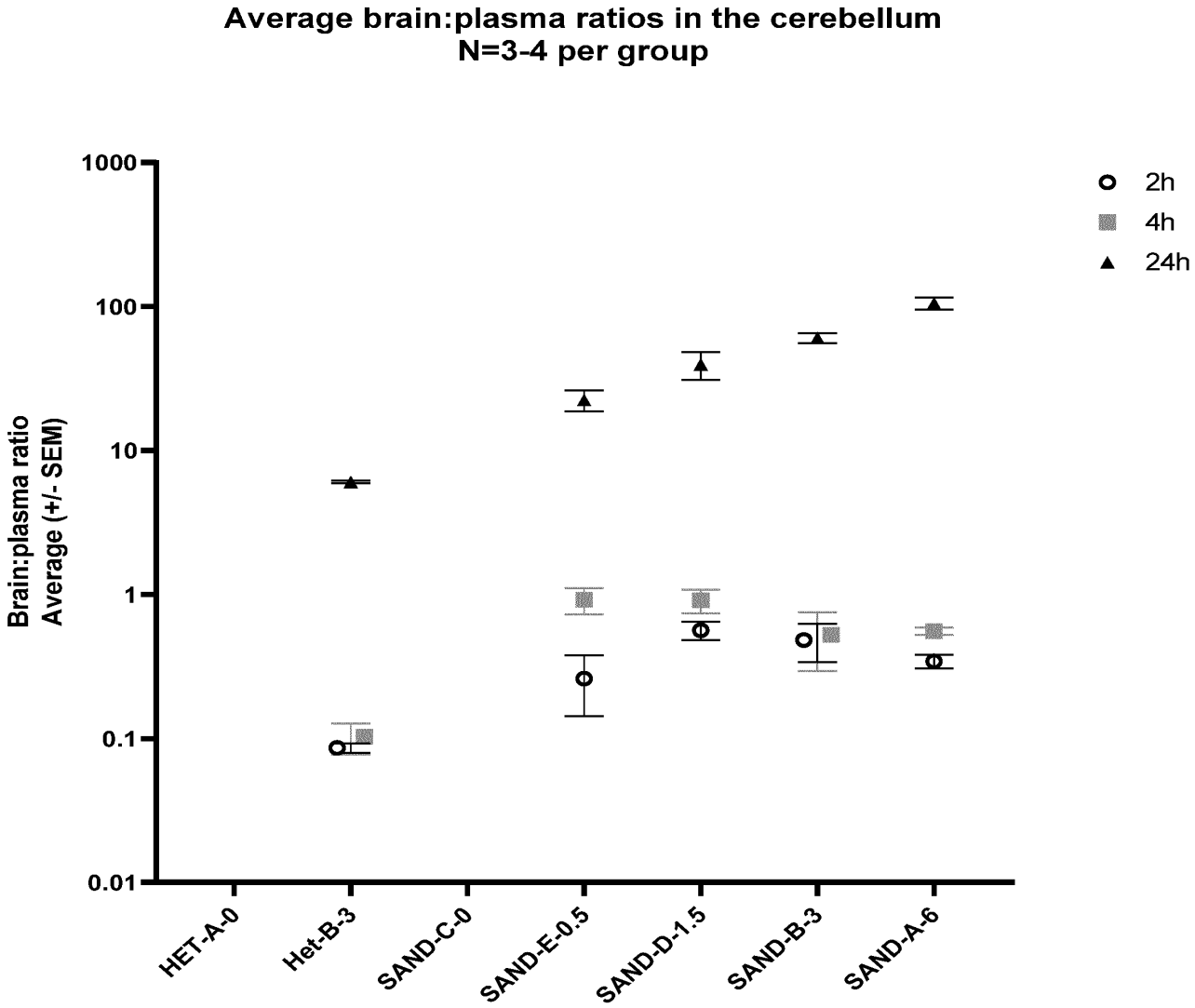
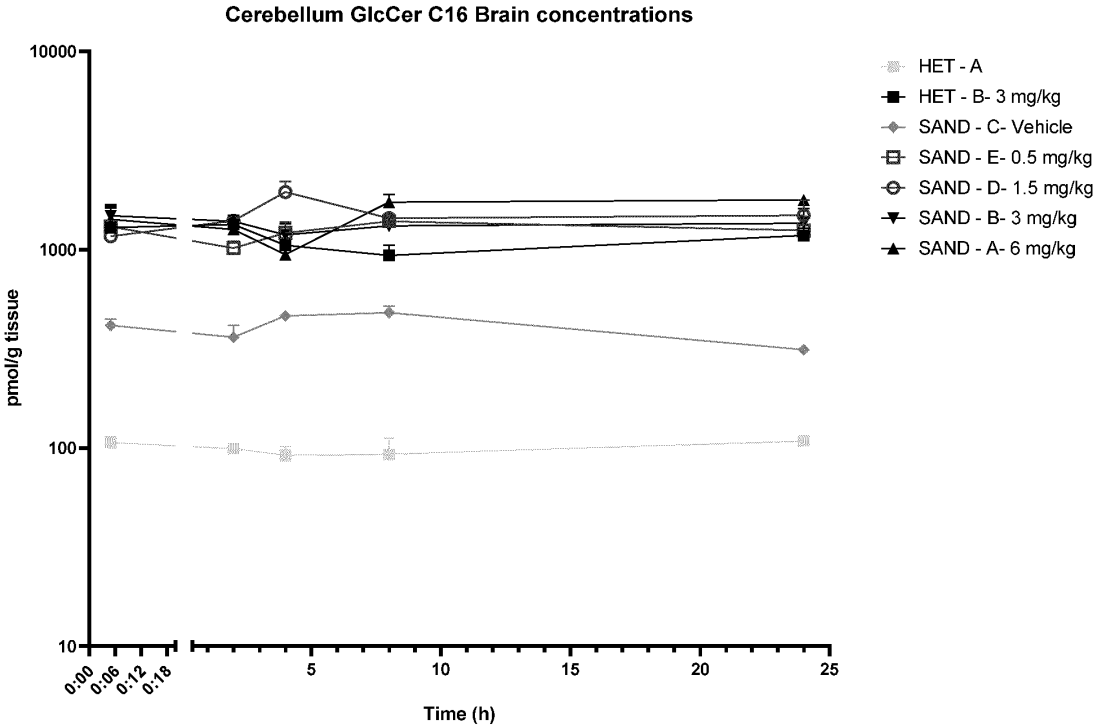

Average brain:plasma ratios in the cerebellum
N=3-4 per group
Brain:plasma ratio
Average (+/- SEM)
1000
100
10
1
0.1
0.01
2h
4h
24h
HET-A-0
Het-B-3
SAND-C-0
SAND-E-0.5
SAND-D-1.5
SAND-B-3
SAND-A-6

Figure 9


Cerebellum GlcCer C16 Brain concentrations
10000
1000
100
10
pmol/g tissue
0:00
0:06
0:12
0:18
5
10
15
20
25
Time (h)
HET - A
HET - B- 3 mg/kg
SAND - C- Vehicle
SAND - E- 0.5 mg/kg
SAND - D- 1.5 mg/kg
SAND - B- 3 mg/kg
SAND - A- 6 mg/kg

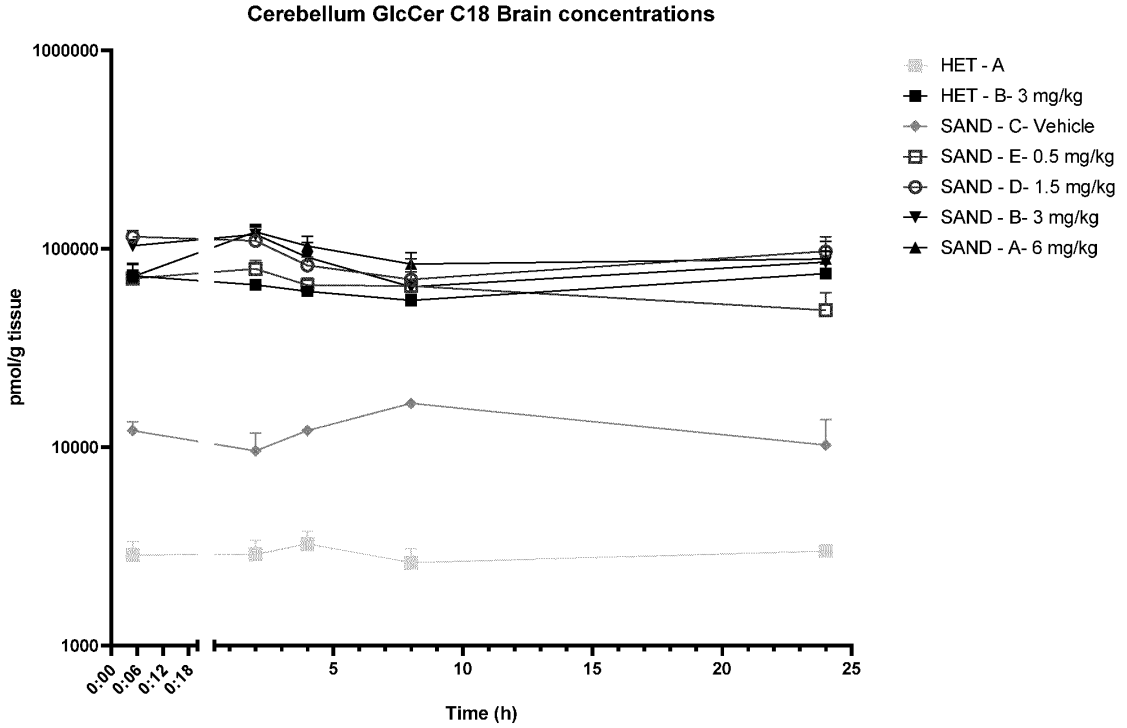
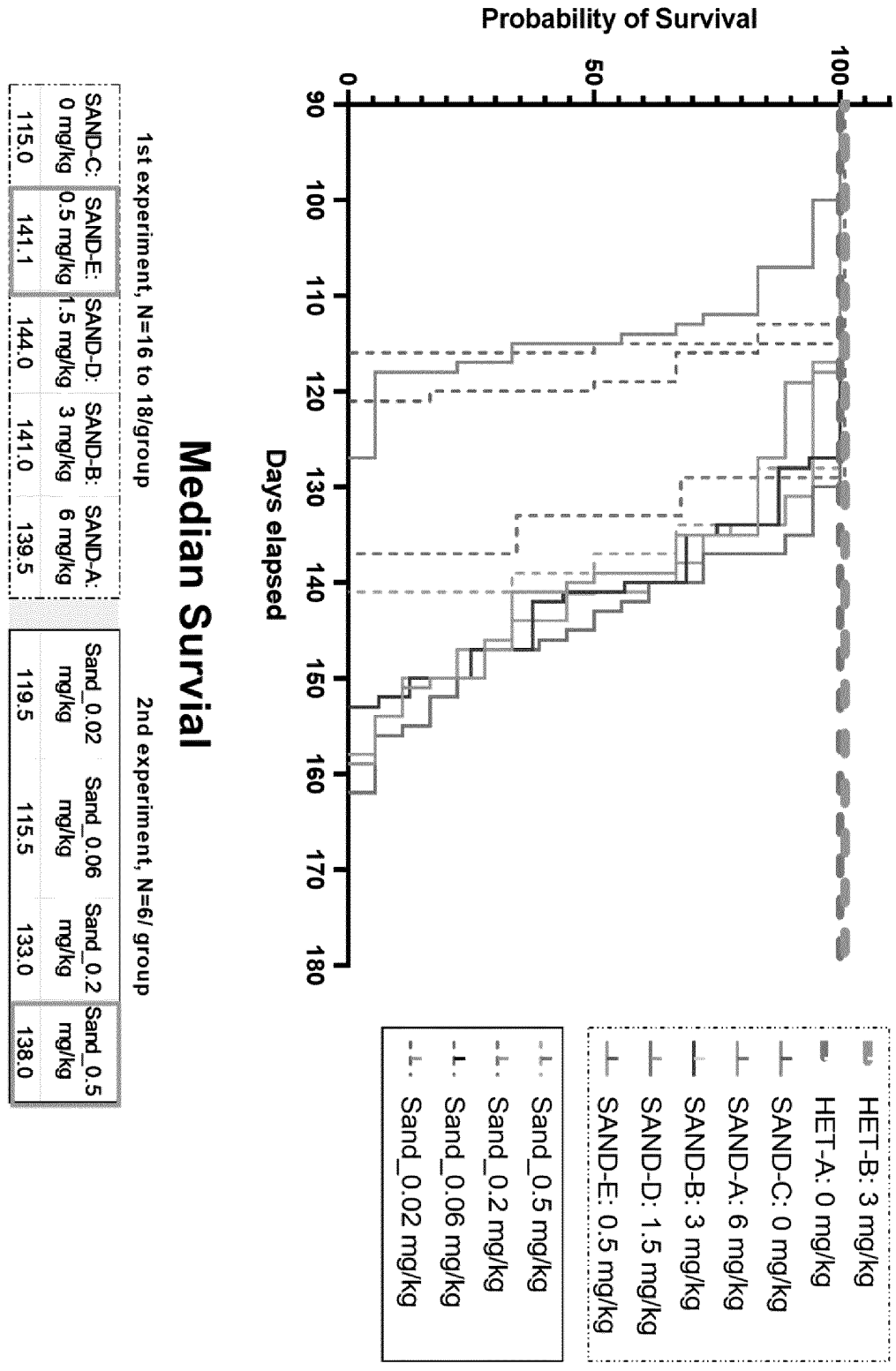

Cerebellum GlcCer C18 Brain concentrations
1000000
100000
10000
1000
pmol/g tissue
0:00
0:06
0:12
0:18
5
10
15
20
25
Time (h)
HET - A
HET - B- 3 mg/kg
SAND - C- Vehicle
SAND - E- 0.5 mg/kg
SAND - D- 1.5 mg/kg
SAND - B- 3 mg/kg
SAND - A- 6 mg/kg

Figure 10



Median Survial

1st experiment, N=16 to 18/group

SAND-C: 0 mg/kg	SAND-E: 0.5 mg/kg	SAND-D: 1.5 mg/kg	SAND-B: 3 mg/kg	SAND-A: 6 mg/kg
115.0	141.1	144.0	141.0	139.5

2nd experiment, N=6/ group

Sand_0.02 mg/kg	Sand_0.06 mg/kg	Sand_0.2 mg/kg	Sand_0.5 mg/kg
119.5	115.5	133.0	138.0

Figure 11

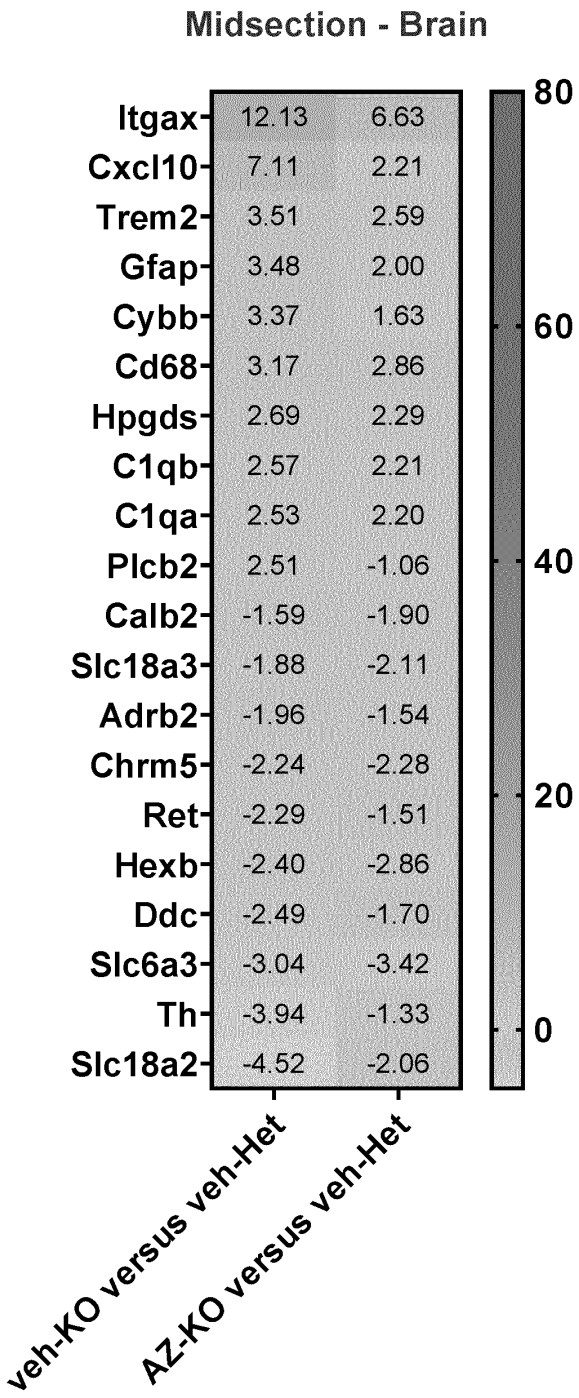
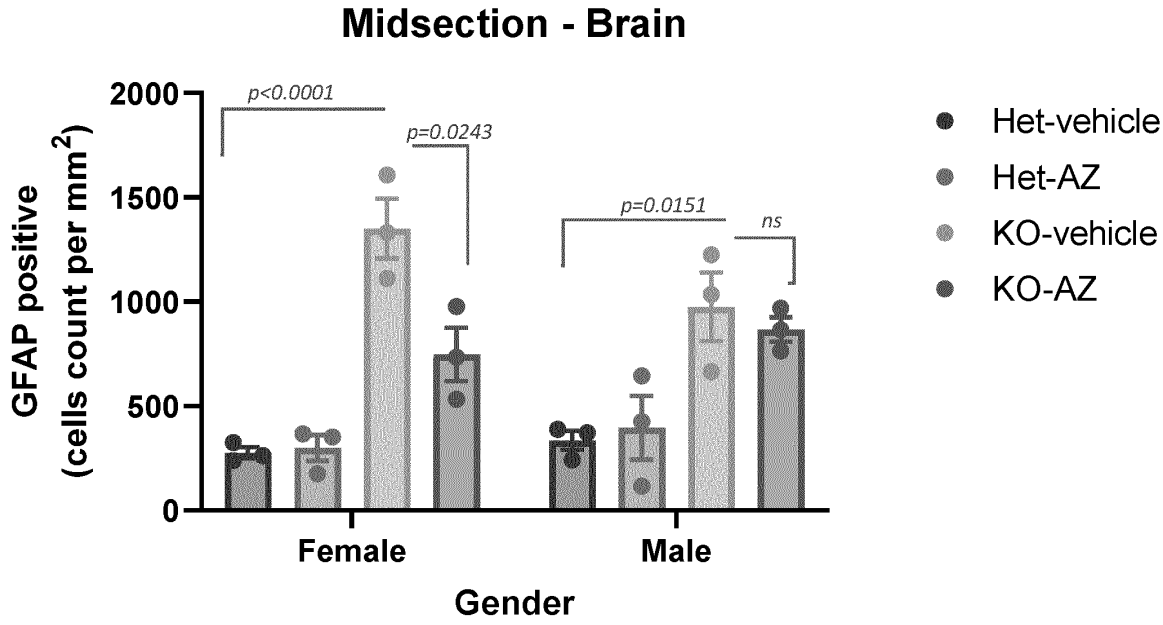

Midsection - Brain
Itgax 12.13 6.63
Cxcl10 7.11 2.21
Trem2 3.51 2.59
Gfap 3.48 2.00
Cybb 3.37 1.63
Cd68 3.17 2.86
Hpgds 2.69 2.29
C1qb 2.57 2.21
C1qa 2.53 2.20
Plcb2 2.51 -1.06
Calb2 -1.59 -1.90
Slc18a3 -1.88 -2.11
Adrb2 -1.96 -1.54
Chrm5 -2.24 -2.28
Ret -2.29 -1.51
Hexb -2.40 -2.86
Ddc -2.49 -1.70
Slc6a3 -3.04 -3.42
Th -3.94 -1.33
Slc18a2 -4.52 -2.06
80
60
40
20
0
veh-KO versus veh-Het
AZ-KO versus veh-Het

Figure 12



Tukey's multiple comparisons test	Mean Diff.	95.00% CI of diff.	Below threshold?	Summary	Adjusted P Value
Female: Het-vehicle vs. Female: KO-vehicle	-1074	-1617 to -531.1	Yes	****	<0.0001
Female: KO-vehicle vs. Female: KO-AZ	602.3	59.47 to 1145	Yes	*	0.0243
Male: Het-vehicle vs. Male: KO-vehicle	-640.7	-1183 to -97.83	Yes	*	0.0151
Male: KO-vehicle vs. Male: KO-AZ	109.4	-433.4 to 652.2	No	ns	0.9959

Figure 13