Supplementary Information

Pharmacological complementation remedies an inborn error of lipid metabolism

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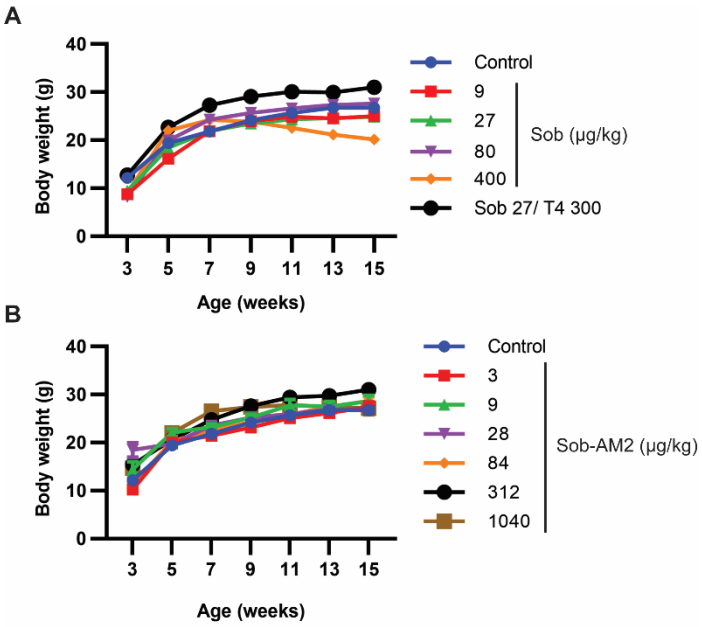

Figure S1 (related to Figures 1-5). Body weights during sobetirome and Sob-AM2 dosing.

Male *Abcd1* KO mice were administered chow containing sobetirome or Sob-AM2 from 3-15 weeks of age. The chow was compounded with (A) sobetirome or (B) Sob-AM2 at the concentration required to administer the estimated daily dose shown in the figure. Body weights were recorded every two weeks. All data are represented as the mean, and the error bars represent SEM. Only mice administered sobetirome at 400 µg/kg showed significant weight loss during the 12-week dosing period.

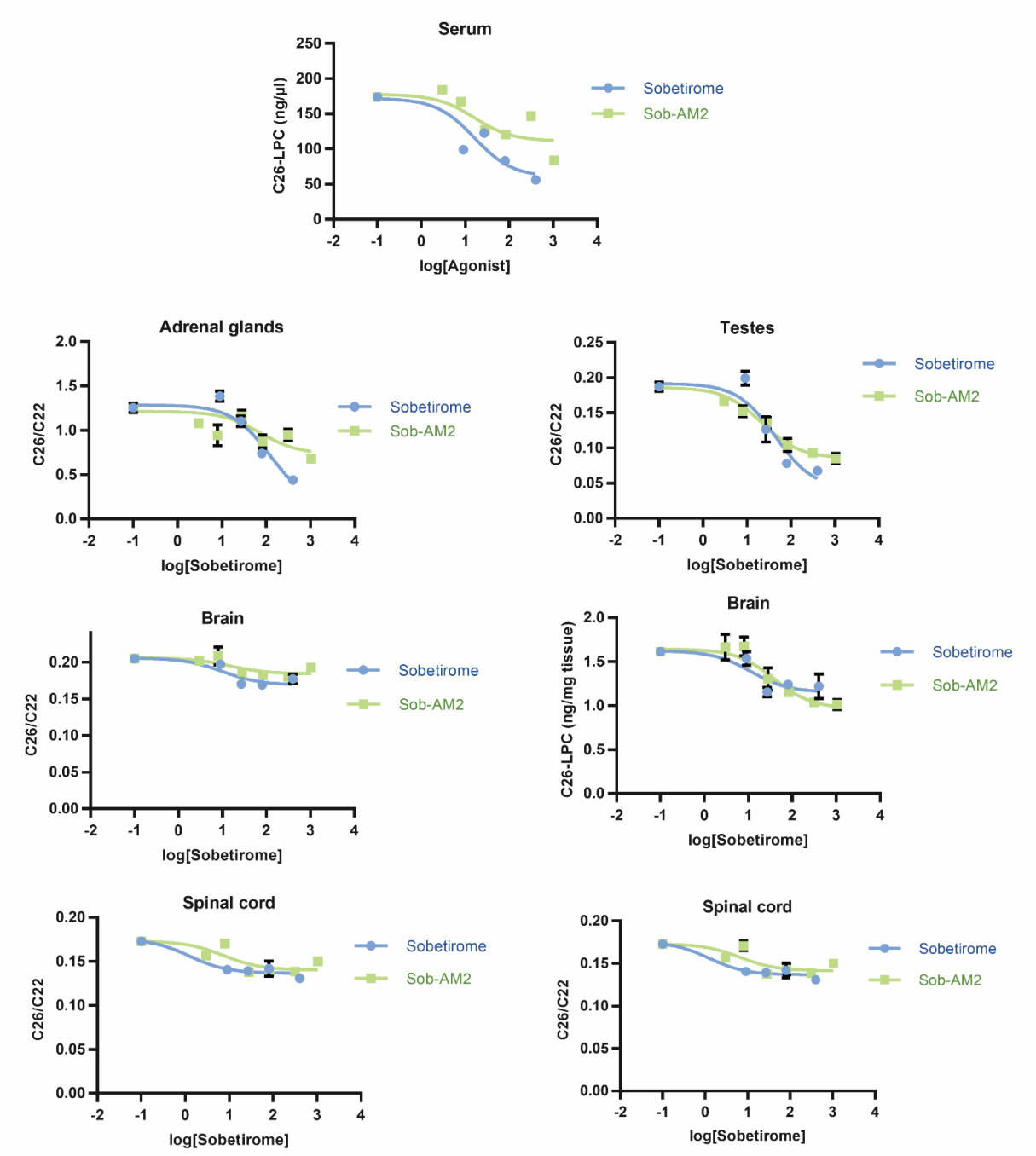

Figure S2 (related to Figures 1-5). Dose-response curves for sobetirome and Sob-AM2.

Male *Abcd1* KO mice were administered chow containing sobetirome or Sob-AM2 from 3-15 weeks of age. The chow was compounded with sobetirome or Sob-AM2 at the concentration required to administer the estimated daily dose shown in the figure. C26-lysophosphatidylcholine (C26-LPC) was measured by LC-MS/MS in serum, brain, and spinal cord. Total C26 and C22 were measured by GC-MS and the C26/C22 ratio is reported for adrenal glands, testes, brain, and spinal cord. All data are represented as the mean, and the error bars represent SEM.

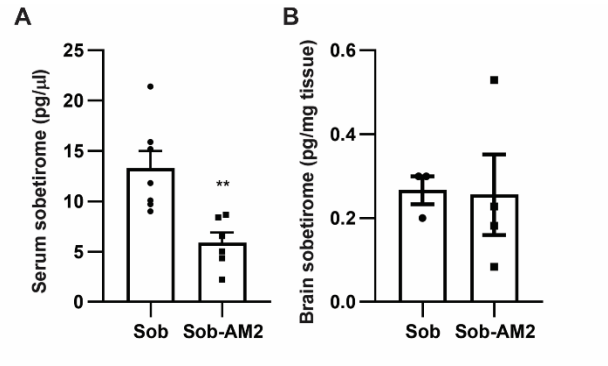

Figure S3 (related to Figures 1-5). Sobetirome and Sob-AM2 dosing results in reduced sobetirome exposure in serum and similar levels in brain.

Male *Abcd1* KO mice were administered chow containing sobetirome (80 µg/kg/day) or Sob-AM2 (84 µg/kg/day) from 3-15 weeks of age. Sobetirome levels in (A) serum and (B) brain were measured by LC-MS/MS. All data are represented as the mean, and the error bars represent SEM. Statistical analysis was performed using an unpaired t-test (**P < 0.01).

Table S1 (related to Figures 1-5 and 7). Percent changes in peripheral VLCFA levels relative to control.

Drug (µg/kg)	Serum C26-LPC	n	Adrenal glands C26/C22	n	Testes C26/C22	n
Sobetirome (9)	-43 ± 3	6	10 ± 5	6	7 ± 5	6
Sobetirome (27)	-29 ± 3	7	-12 ± 5	7	-32 ± 10	7
Sobetirome (80)	-52 ± 2	5	-41 ± 2	5	-58 ± 2	5
Sobetirome (400)	-68 ± 4	5	-65 ± 3	5	-64 ± 1	4
Sob-AM2 (3)	6 ± 5	6	-14 ± 4	6	-11 ± 3	6
Sob-AM2 (9)	-4 ± 2	5	-25 ± 9	5	-19 ± 4	6
Sob-AM2 (28)	-27 ± 5	9	-8 ± 5	9	-27 ± 4	9
Sob-AM2 (84)	-31 ± 3	6	-31 ± 6	6	-44 ± 5	6
Sob-AM2 (312)	-15 ± 8	7	-24 ± 5	7	-50 ± 3	7
Sob-AM2 (1040)	-52 ± 3	7	-46 ± 2	7	-55 ± 4	6
Sobetirome (27) and T4 (300)	-55 ± 5	8	-59 ± 6	8	-45 ± 4	8

Table S2 (related to Figures 1-5 and 7). Percent changes in CNS VLCFA levels relative to control.

Drug (µg/kg)	Brain C26/C22	n	Brain C26-LPC	n	Spinal cord C26/C22	n	Spinal cord C26-LPC	n
Sobetirome (9)	-4 ± 1	6	-5 ± 5	6	-19 ± 1	6	-20 ± 3	6
Sobetirome (27)	-17 ± 3	7	-28 ± 3	7	-20 ± 3	7	-36 ± 2	7
Sobetirome (80)	-17 ± 2	5	-23 ± 2	5	-18 ± 5	5	-41 ± 1	5
Sobetirome (400)	-13 ± 3	5	-24 ± 9	4	-24 ± 2	4	-47 ± 1	5
Sob-AM2 (3)	-1 ± 2	6	3 ± 9	6	-9 ± 3	6	-19 ± 3	6
Sob-AM2 (9)	2 ± 6	6	4 ± 7	6	-1 ± 3	6	-3 ± 9	6
Sob-AM2 (28)	-9 ± 1	9	-19 ± 8	9	-20 ± 2	9	-36 ± 2	9
Sob-AM2 (84)	-11 ± 1	5	-29 ± 2	6	-18 ± 4	6	-37 ± 2	5
Sob-AM2 (312)	-12 ± 2	5	-36 ± 3	7	-20 ± 3	7	-35 ± 3	7
Sob-AM2 (1040)	-6 ± 2	7	-37 ± 4	7	-13 ± 2	7	-38 ± 3	7
Sobetirome (27) and T4 (300)	-3 ± 3	8	-26 ± 6	8	-20 ± 2	8	-17 ± 6	8