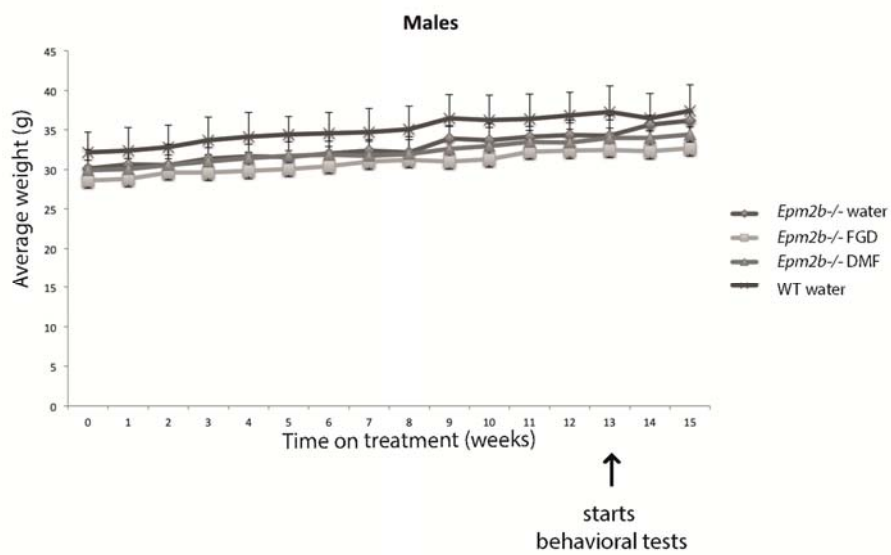
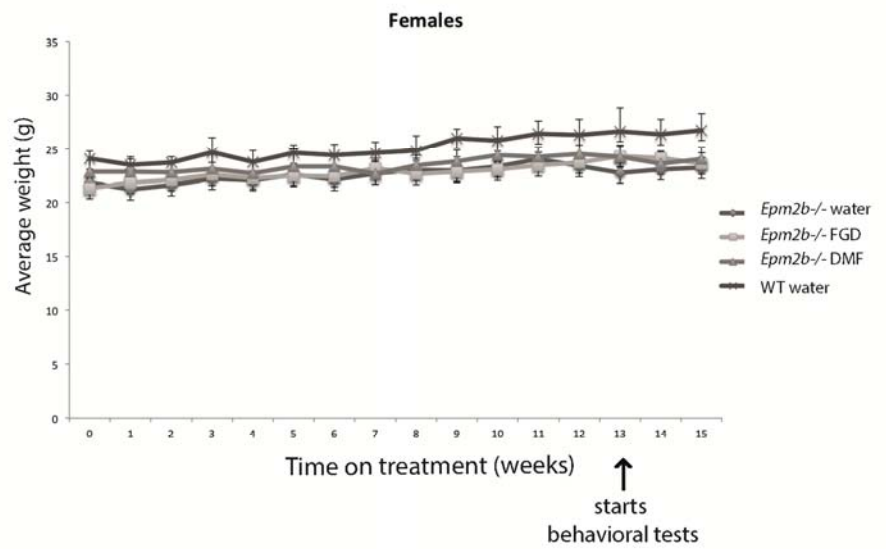


Supplementary Material

Supplementary Fig. S1. Fingolimod and dimethylfumarate did not affect the body weight of the mice during the treatment period. Average weight in grams (g) for female **(A)** or male **(B)** mice is represented as mean \pm standard deviation of the mean (SD) for each group of mice (WT in water, *Epm2b*^{-/-} in water, fingolimod or dimethylfumarate) for each time point (weeks of treatment).

Supplementary Figure S1



Supplementary Table S1: Statistical summary table of behavioral and histopathological variables analyzed throughout this study. The table details the behavioral test (analyzed by two-way ANOVA) or histological analysis (analyzed by one-way ANOVA) with the variable name and the mean \pm SD for each variable with the significance (P-value). (a) P-values of *Epm2b*^{-/-} variables respect to the WT control, both in water; (b) P-values of variables from treated mice respect to the corresponding mice group treated with water. nd: not determined.

Variable	Genotype	Water ^a	Fingolimod	P-value FGD ^b	Dimethyl Fumarate	P-value DMF ^b
Openfield Traveled distance in the peripheral area (cm)	WT	1845.36 \pm 408.02	2275.25 \pm 324.34	P=0.106	1980.49 \pm 557.66	P=0.970
Openfield Traveled distance in the peripheral area (cm)	Epm2b ^{-/-}	2291.90 \pm 526.02 P=0.121	1821.76 \pm 200.99	P=0.043	2021.65 \pm 331.12	P=0.553
Openfield Travelled distance in center (cm)	WT	256.59 \pm 157.31	196.07 \pm 85.60	P=0.731	355.66 \pm 110.59	P=0.227
Openfield Travelled distance in center (cm)	Epm2b ^{-/-}	273.35 \pm 126.30 P=0.993	126.97 \pm 88.00	P=0.015	241.45 \pm 101.00	P=0.980
Openfield Number entries in center	WT	9.10 \pm 4.91	8.00 \pm 3.43	P=0.985	11.87 \pm 5.12	P=0.574
Openfield Number entries in center	Epm2b ^{-/-}	10.00 \pm 5.23 P=0.996	5.18 \pm 2.71	P=0.049	7.64 \pm 3.25	P=0.732
OLM Discrimination index	WT	5.76 \pm 5.59	34.21 \pm 27.08	P=0.946	18.20 \pm 31.04	P=0.998
OLM Discrimination index	Epm2b ^{-/-}	19.77 \pm 37.92 P=0.998	6.77 \pm 20.13	P=0.998	1.57 \pm 15.05	P=0.999
OLM Activity time (s)	WT	298.63 \pm 13.68	239.46 \pm 52.18	P<0.0001	301.01 \pm 6.43	P=0.999
OLM Activity time (s)	Epm2b ^{-/-}	297.31 \pm 11.57 P=0.999	190.69 \pm 48.69	P<0.0001	290.13 \pm 15.58	P=0.995
Neurodegenerative signs Hindlimb clasping (Absent, Mild,	WT	56, 25, 19, 0	90, 5, 5, 0	P<0.0001	73, 20, 7, 0	P<0.05

Moderate, Severe)						
Neurodegenerative signs Hindlimb claspings (Absent, Mild, Moderate, Severe)	Epm2b-/-	56, 38, 6, 0 P<0.01	75, 25, 0, 0	P<0.01	85, 15, 0, 0	P<0.0001
PGs inclusions %PG numbers vs Epm2b-/- water	WT	1.87 ± 1.14	nd	nd	nd	nd
PGs inclusions %PG numbers vs Epm2b-/- water	Epm2b-/-	100.00 ± 24.68 P<0.0001	126.36 ± 19.11	P=0.093	109.20 ± 18.60	P=0.387
Astrogliosis % GFAP intensity signal	WT	100.00 ± 15.58	nd	nd	nd	nd
Astrogliosis % GFAP intensity signal	Epm2b-/-	156.92 ± 26.24 P<0.001	127.09 ± 10.90	P<0.05	117.83 ± 13.38	P<0.05
Microgliosis % IBA1 intensity signal	WT	100.00 ± 24.75	nd	nd	nd	nd
Microgliosis % IBA1 intensity signal	Epm2b-/-	116.65 ± 27.59 P=0.247	111.91 ± 21.48	P=0.900	101.65 ± 25.03	P=0.532
Relative gasdermin-D levels/Actin	WT	39.49 ± 2.30	nd	nd	nd	nd
Relative gasdermin-D levels/Actin	Epm2b-/-	80.03 ± 16.26 P<0.05	35.23 ± 17.95	P<0.05		
Relative gasdermin-D levels/GAPDH	WT	40.40 ± 0.87	nd	nd	nd	nd
Relative gasdermin-D levels/GAPDH	Epm2b-/-	64.46 ± 29.48 P<0.05			78.54 ± 17.37	P=0.199
Relative P65/NFkB levels/Actin	WT	8.31 ± 6.26	nd	nd	nd	nd
Relative P65/NFkB levels/Actin	Epm2b-/-	16.96 ± 4.36 P=0.200	5.92 ± 3.63	P<0.05		
Relative P65/NFkB levels/GAPDH	WT	0.96 ± 0.61	nd	nd	nd	nd
Relative P65/NFkB levels/GAPDH	Epm2b-/-	2.53 ± 0.39			1.22 ± 1.42	P=0.700

		P=0.200				
Relative SOCS3 levels/Actin	WT	42.14 ± 41.76	nd	nd	nd	nd
Relative SOCS3 levels/Actin	Epm2b ^{-/-}	75.61 ± 21.52	21.57 ± 10.91	P<0.05		
		P=0.200				
Relative SOCS3 levels/GAPDH	WT	0.83 ± 0.31	nd	nd	nd	nd
Relative SOCS3 levels/GAPDH	Epm2b ^{-/-}	1.16 ± 0.29			1.17 ± 0.33	P=0.900
		P=0.200				
Relative CXCL10 expression	WT	1.19 ± 0.42	nd	nd	nd	nd
Relative CXCL10 expression	Epm2b ^{-/-}	11.06 ± 4.05	6.11 ± 1.09	P<0.05	11.69 ± 9.35	P=0.629
		P<0.01				
T-Lymphocyte infiltration Number of cells in 300µm ²	WT	CD3 0.6 ± 0.8 CD4 0.1 ± 0.3 CD8 0.7 ± 1.0	nd	nd	nd	nd
T-Lymphocyte infiltration Number of cells in 300µm ²	Epm2b ^{-/-}	CD3 5.0 ± 2.9 CD4 1.3 ± 1.0 CD8 4.3 ± 2.0 CD3 P<0.01 CD4 P<0.01 CD8 P<0.01	CD3 2.3 ± 2.3 CD4 0.3 ± 0.5 CD8 1.5 ± 1.6	P<0.05 P<0.01 P<0.05	CD3 3.9 ± 2.7 CD4 0.6 ± 0.5 CD8 3.3 ± 1.2	P=0.252 P=0.119 P=0.145