SUPPLEMENTAL INFORMATION

Table S1: Complete Blood Count (mean values and standard deviation) - baseline and after three months of treatment

Parameter	Units	Normal Range	Placebo		RD2 acetate 3 mg/kg		RD2 acetate 30 mg/kg	
			baseline	treatment	baseline	treatment	baseline	treatment
WBC	10^9/l	4.0-16	6.4 ± 3.9	5.7 ± 3.1	4.6 ± 1.9	5.1 ± 1.4	4.4 ± 1.4	4.0 ± 1.2
RBC	10^{12}/l	4.8-9.3	5.3 ± 0.45	5.4 ± 0.38	5.4 ± 0.31	5.4 ± 0.35	5.5 ± 0.67	5.6 ± 0.65
Hemoglobin	g/l	121-203	123 ± 11	123 ± 9.4	128 ± 8.8	128 ± 8.2	131 ± 16	132 ± 16
Hematocrit	%	36-60	37 ± 3.1	38 ± 2.7	47 ± 28	47 ± 28	40 ± 4.6	41 ± 4.7
MCV	Fl	58-79	71 ± 1.7	72 ± 2.6	70 ± 9.3	70 ± 9.3	72 ± 2.1	73 ± 1.7
MCH	Pg	19-28	23 ± 0.86	23 ± 0.97	28 ± 15	28 ± 15	24 ± 0.47	24 ± 0.42
MCHC	g/l	300-380	329 ± 8.6	321 ± 3.8	301 ± 88	299 ± 87	332 ± 8.1	324 ± 5.3
Platelet count	10^9/l	170-400	394 ± 165	384 ± 146	343 ± 94	335 ± 85	301 ± 111	327 ± 108
Neutrophils	10^9/l	2.06-10.60	4.5 ± 3.4	4.0 ± 2.5	2.8 ± 1.6	3.5 ± 1.1	2.8 ± 1.0	2.6 ± 0.92
Lymphocytes	10^9/l	0.69-4.50	1.3 ± 0.30	1.2 ± 0.36	1.2 ± 0.45	1.2 ± 0.36	1.2 ± 0.36	1.1 ± 0.28
Monocytes	10^9/l	0-0.84	0.29 ± 0.23	0.28 ± 0.18	0.18 ± 0.08	0.23 ± 0.09	0.19 ± 0.07	0.19 ± 0.05
Eosinophils	10^9/l	0-1.20	0.29 ± 0.19	0.26 ± 0.17	0.27 ± 0.11	0.18 ± 0.08	0.21 ± 0.10	0.22 ± 0.19
Basophils	10^9/l	0-0.15	0	0	0	0	0	0
Total Protein	g/l	50-74	54 ± 3.1	57 ± 6.6	53 ± 2.1	56 ± 2.9	54 ± 5.3	57 ± 6.0
Albumin	g/l	27-44	31 ± 2.1	31 ± 2.8	30 ± 2.7	30 ± 2.5	29 ± 2.3	30 ± 2.6
Globulin	g/l	16-36	23 ± 3.3	25 ± 4.1	24 ± 2.0	26 ± 2.6	25 ± 3.8	28 ± 4.5
A/G Ratio		0.8-2.0	1.4 ± 0.25	1.3 ± 0.27	1.3 ± 0.20	1.2 ± 0.18	1.2 ± 0.14	1.1 ± 0.18

Table S2: Clinical chemistry (mean values and standard deviation) - baseline and after three months of treatment. Mean results of the clinical chemistry for placebo and RD2 treated animals. There were no significant changes in any of the listed measures except for the triglyceride concentration, which was significantly increased after dosing with 3 mg/kg or 30 mg/kg, but still in the normal range of historical controls.

Parameter	Units	Normal Range	Placebo		RD2 acetate 3 mg/kg		RD2 acetate 30 mg/kg	
			baseline	treatment	baseline	treatment	baseline	treatment
Phosphorus	mmol/l	0.81-1.9	1.3 ± 0.21	1.7 ± 0.95	1.4 ± 0.27	1.5 ± 0.25	1.4 ± 0.32	1.6 ± 0.35
Glucose	mmol/l	3.9-7.7	5.0 ± 0.52	5,3 ± 0.49	4.9 ± 0,29	5.2 ± 0.33	5.0 ± 0.41	5.1 ± 0.54
Calcium	mmol/l	2.2-2.9	2.4 ± 0.06	2.4 ± 0.04	2.3 ± 0.08	2.4 ± 0.11	2.3 ± 0.11	2.4 ± 0.12

Magnesium	mmol/l	0.7-1.3	0.70 ± 0.05	0.77 ± 0.06	0.74 ± 0.05	0.78 ± 0.06	0.73 ± 0.07	0.76 ± 0.05
Sodium	mmol/l	139-154	145 ± 3.9	147 ± 1.0	146 ± 3.8	147 ± 1.5	145 ± 3.6	148 ± 2.3
Potassium	mmol/l	3.6-5.5	4.3 ± 0.31	4.4 ± 0.28	4.2 ± 0.29	4.3 ± 0.25	4.1 ± 0.32	4.3 ± 0.40
Sodium/Potassium Ratio		27-38	34 ± 2.5	34 ±2.1	35 ± 2.0	34 ± 1.8	35 ± 2.7	35 ± 3.1
Chloride	mmol/l	102-120	112 ± 3.9	113 ± 1.7	113 ± 2.3	113 ± 2.5	112 ± 3.7	113 ± 2.8
Cholesterol	mmol/l	2.4-10	4.9 ± 0.95	5.2 ± 0.68	5.2 ± 0.83	5.5 ± 0.86	5.3 ± 1.2	5.4 ± 1.2
Triglycerides	mmol/l	0.33-3.3	2.0 ± 0.33	2.0 ± 0.47	2.7 ± 1.4	3.2 ± 1.8	2.2 ± 0.37	2.6 ± 0.39
Amylase	U/l	290-1125	475 ± 203	503 ± 229	494 ± 164	511 ± 159	434 ± 142	465 ± 182
Precision PSL	U/l	24-140	60 ± 21	44 ± 16	68 ± 50	52 ± 31	66 ± 29	57 ± 26
CPK total	U/l	59-895	84 ± 18	88 ± 13	96 ± 33	92 ± 32	92 ± 21	103 ± 43

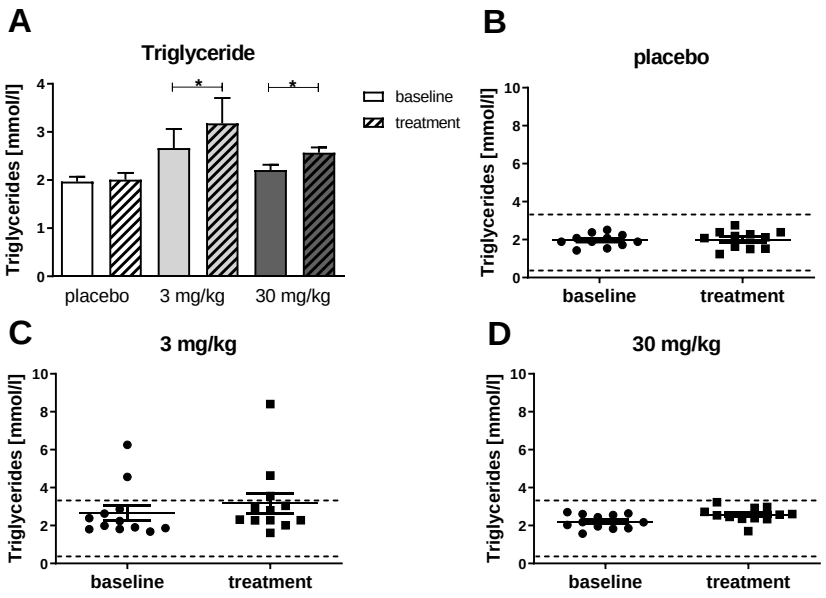

Figure S1: Blood concentration of triglycerides of placebo (B), 3 mg/kg RD2 (C) and 30 mg/kg RD2 (D) treated animals was analyzed using a paired t-test with timepoints serving as a within-subject measure. A significantly increased concentration of triglycerides was detected after three-month RD2 treatment (3 mg/kg and 30 mg/kg) compared to baseline, but not in the placebo treated animals (A). With two exceptions (in 3 mg/kg group), all measured values are within the normal reference range. Without these two animals, which are already out of the normal range at baseline, there is no significant difference between baseline and treatment any more in the 3 mg/kg group. Area between the dashed lines represent the normal reference range. (*$p < 0.05$). Data is presented as mean ± SEM; n = 11 to 12

Table S3: Liver function blood test. To assess potential effects of RD2 on liver function, aspartate aminotransferase (AST), alanine transaminase (ALT), alkaline phosphatase (Alk), gamma-glutamyl transpeptidase (GGTP), albumin, and total bilirubin were determined. There were no significant treatment related changes in any of the listed measures.

Parameter	Units	Normal Range	Placebo		RD2 acetate 3 mg/kg		RD2 acetate 30 mg/kg	
			baseline	treatment	baseline	treatment	baseline	treatment
AST	U/l	15-66	22 ± 5.2	22 ± 4.7	23 ± 4.5	22 ± 7.3	25 ± 4.1	25 ± 3.2
ALT	U/l	12-118	45 ± 25	98 ± 132	33 ± 23	29 ± 13	32 ± 15	32 ± 19
Alk	U/l	5-131	53 ± 30	134 ± 200	113 ± 136	121 ± 140	93 ± 91	84 ± 77
GGTP	U/l	1-12	3.9 ± 1.3	9.0 ± 6.4	3.5 ± 4.5	6.4 ± 2.0	3.6 ± 1.2	6.1 ± 1.5
Bilirubin	µmol/l	0.0-5.1	2.5 ±0.53	3.1 ± 1.2	2.5 ± 0.63	2.4 ± 0.57	2.2 ± 0.44	2.4 ± 0.54
BUN	mmol/l	2.1-11	5.2 ± 1.7	5.7 ± 4.0	5.4 ± 0.79	5.8 ± 0.99	5.2 ± 1.1	5.9 ± 1.6
Creatinine	µmol/l	44-141	56 ± 20	59 ± 26	51 ± 9.3	54 ± 11	54 ± 10	61 ± 12
Creatinine/BUN ratio			96 ± 23	93 ± 22	108 ± 18	110 ± 16	97 ± 15	96 ± 8.7

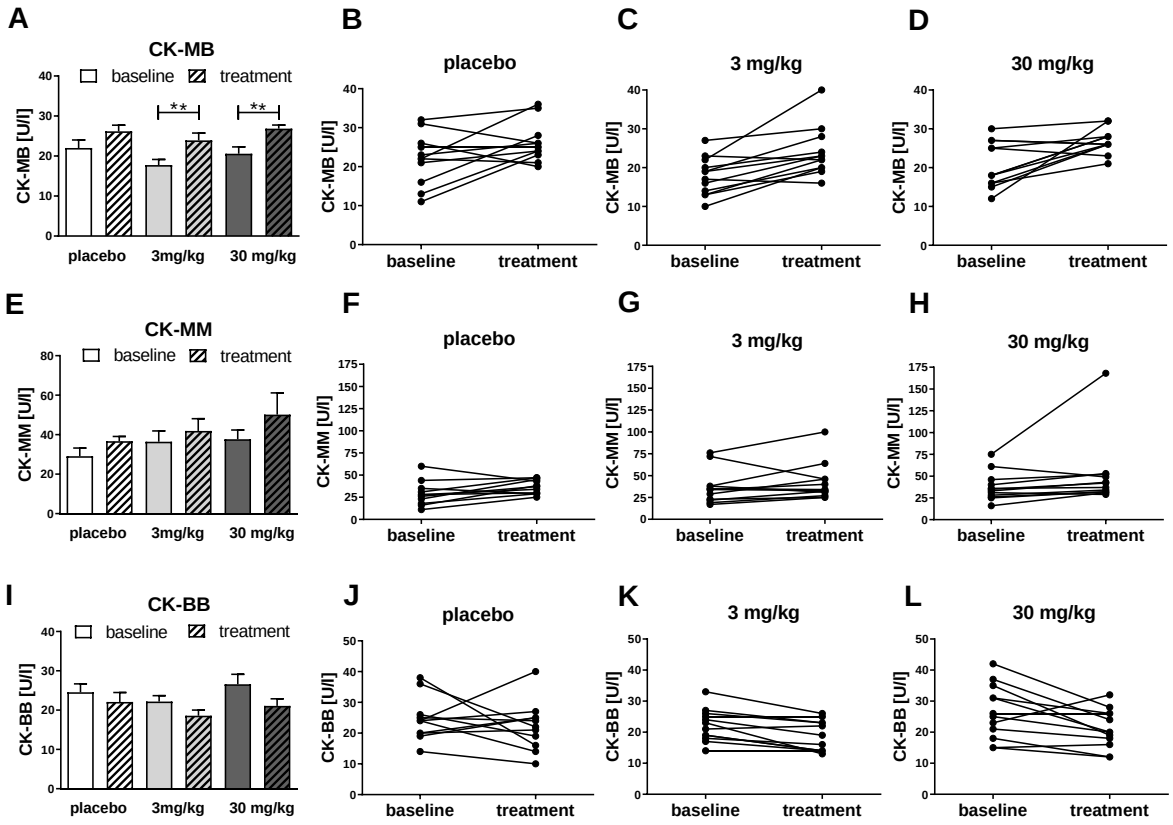

Figure S2: Blood concentration of the creatinine kinase isoenzymes (CK-MB (A-D), CK-MM (E-F) and CK-BB (I-L) were each analyzed using a paired t-test with timepoints serving as a within-subject measure. A significantly increased concentration of CK-MB was detected after three-month treatment

with RD2 (3 mg/kg and 30 mg/kg) compared to baseline, but not in the placebo treated animals. (**p < 0.01) (A). Data are presented as mean ± SEM; n = 11 to 12.

Other correlations

We found a significant and positive correlation between the results of the DNMP and the selective attention tests in the dogs of the placebo cohort at all time points available (Fig. S3F). This indicates that both tests are robustly measuring memory and cognition deficits in dogs. We found a positive and significant correlation between selective attention accuracy and total Aβ42 concentration in CSF (Fig. S3D). We examined the correlation of changes (after three months treatment versus baseline) of CSF Aβ42 total concentrations with changes (after three months treatment versus baseline) of CSF Aβ oligomer concentrations and found a significant and inverse correlation (Fig. S3F, Pearson -0.496 p-value 0.00287). This does not necessarily mean that Aβ42 levels are increased due to Aβ oligomer disassembly. Disassembly of 100 fM Aβ oligomers, even if we anticipate 100 monomer building blocks per oligomer, would yield 10 pM amounts of additional Aβ monomers equal to 40 pg/ml, a concentration increase that may not contribute significantly to the total Aβ42 concentration (Fig. S3E).

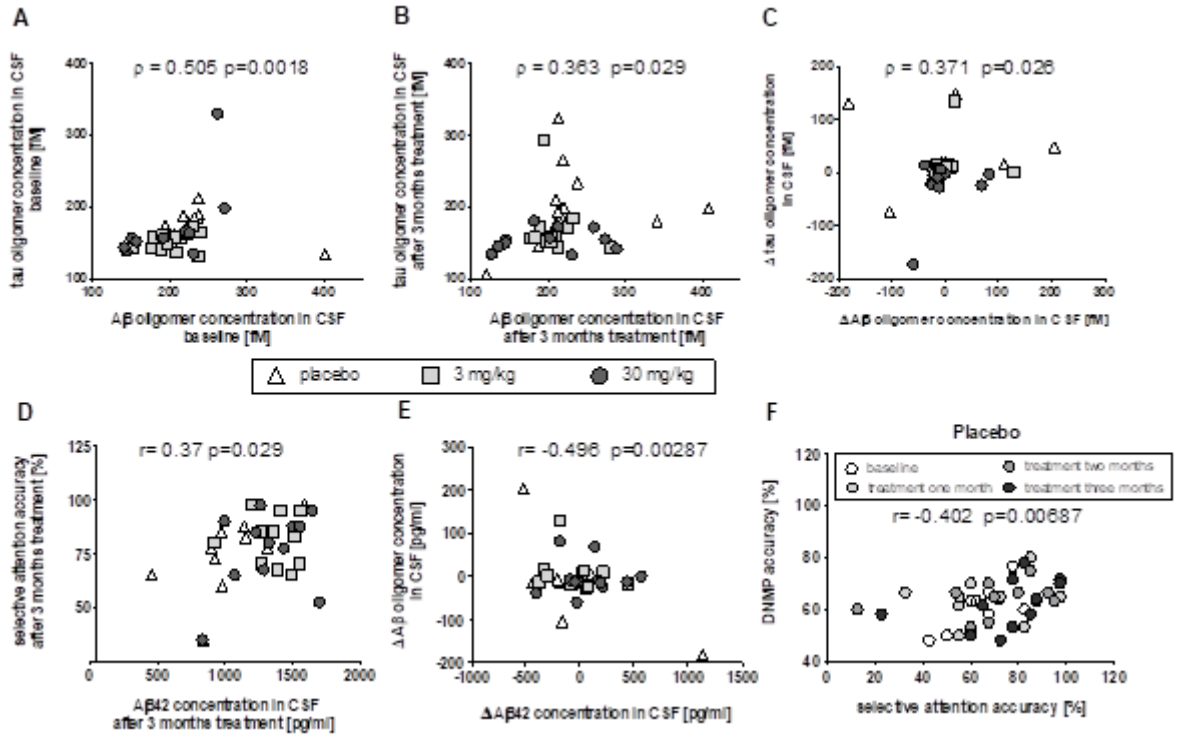

Figure S3: Correlations between Aβ42 and Aβ oligomer concentrations as well as with cognitive testing. A: Correlation of CSF Aβ oligomer concentration vs. CSF tau oligomer concentration at baseline. B: Correlation of CSF Aβ oligomer concentration vs. CSF tau oligomer concentration after 3 months treatment with RD2. C: Correlation of changes of CSF Aβ oligomer concentration vs. changes of CSF tau oligomer concentration. Changes (Δ) were calculated by subtracting baseline value from three-month treatment value. D: Correlation of CSF Aβ42 concentration with selective attention accuracy after 3 months treatment. E: Correlation of changes of CSF Aβ42 concentration with changes of CSF Aβ oligomer concentration. Changes (Δ) were calculated by subtracting baseline value from

three-month treatment value. F: Correlation of selective attention accuracy and DNMP accuracy of the placebo group from all available different time points. Correlations were performed with Pearson (r) and Spearman (ρ) analysis at alpha level 0.05 with n = 11 to 12.