

**Supplementary Table 1** Imaging Brain Regions of Interest (ROI)

<b>Frontal Lobe</b>	<b>Frontal/Parietal</b>	<b>Parietal</b>	<b>Temporal</b>	<b>Basal Ganglia</b>	<b>Limbic and Limbic Interacting</b>	<b>Occipital Lobe</b>
Caudal Middle Frontal	Paracentral	Inferior Parietal	Inferior Temporal	Caudate	Amygdala	Cuneus
Medial Orbito Frontal		Superior Parietal	Middle Temporal	Putamen	Caudal Anterior Cingulate	Lateral Occipital
Pars Opercularis		Postcentral	Superior Temporal	Pallidum	Rostral Anterior Cingulate	Lingual
Pars Orbitalis		Precuneus	Transverse Temporal		Posterior Cingulate	Pericalcarine
Pars Triangularis		Supramarginal			Hippocampus	
Precentral					Thalamus	
Rostral Middle Frontal						
Superior Frontal						

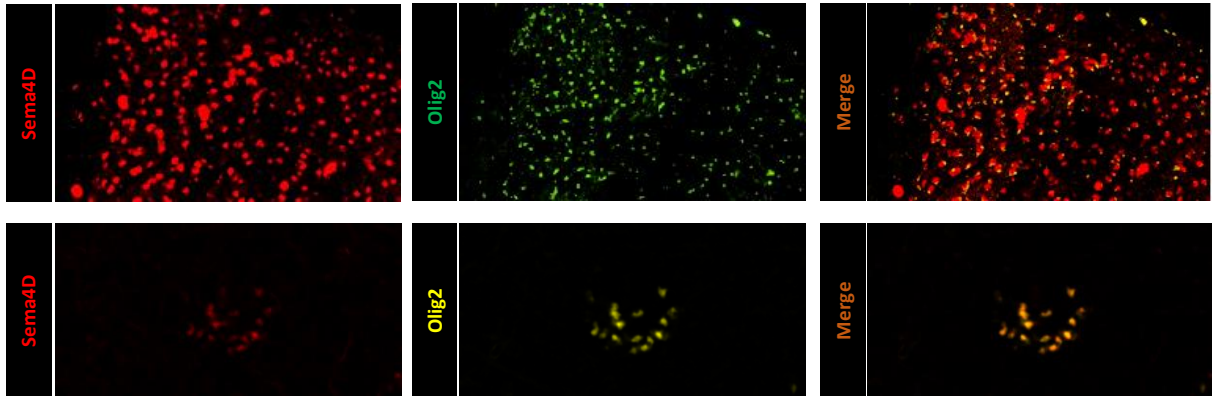
**Supplementary Table 2** Analyses of the Percent Change from Baseline in SUVR in Cortical Brain Regions of Interest for Double-Blind and Open-Label Treatment Periods in Participants with Huntington's Disease (SIGNAL Cohort A Study)

		Baseline		LS mean change				% Change: 6 mo		% Change: VX15 - Placebo			
		Placebo P(0)	VX15 V(0)	Placebo P(7-0)	VX15 V(7-0)	VX15- placebo V(7-0) – P(7-0)	SEM	Placebo P(7-0)	VX15 V(7-0)	V(7-0) – P(7-0)	p- value	PV(12-7) – P(7-0)	p-value
<b>Frontal</b>	<b>Caudal middle frontal gyrus</b>	1.610	1.482	-0.128	0.185	0.313	0.148	-7.93%	12.48%	20.41%	0.051	23.51%	0.084
	<b>Medial Orbito Frontal</b>	1.501	1.422	-0.056	0.099	0.155	0.065	-3.72%	6.94%	10.67%	0.030	10.35%	0.086
	<b>Parsopercularis</b>	1.586	1.510	-0.074	0.153	0.227	0.095	-4.69%	10.14%	14.83%	0.029	13.84%	0.081
	<b>Parsorbitalis</b>	1.641	1.469	-0.109	0.174	0.283	0.139	-6.62%	11.87%	18.49%	0.059	22.62%	0.046
	<b>Parstriangularis</b>	1.626	1.499	-0.061	0.157	0.218	0.102	-3.73%	10.49%	14.22%	0.049	13.51%	0.089
	<b>Precentral gyrus</b>	1.459	1.389	-0.093	0.182	0.275	0.110	-6.35%	13.11%	19.46%	0.023	20.10%	0.070
	<b>Rostral middle frontal gyrus</b>	1.691	1.565	-0.100	0.171	0.271	0.123	-5.92%	10.90%	16.82%	0.042	17.94%	0.084
	<b>Superior Frontal gyrus</b>	1.559	1.582	-0.050	0.081	0.132	0.057	-3.22%	5.14%	8.36%	0.033	6.28%	0.303
<b>Frontal / Parietal</b>	<b>Paracentral lobule</b>	1.525	1.308	-0.062	0.143	0.204	0.141	-4.06%	10.90%	14.96%	0.170	22.32%	0.109
<b>Parietal</b>	<b>Post-central gyrus</b>	1.363	1.325	-0.083	0.187	0.270	0.101	-6.08%	14.09%	20.17%	0.016	17.94%	0.096
	<b>Supramarginal gyrus</b>	1.428	1.412	-0.078	0.143	0.221	0.085	-5.45%	10.16%	15.61%	0.019	14.70%	0.057
	<b>Precunues cortex</b>	1.836	1.628	-0.057	0.102	0.159	0.114	-3.11%	6.24%	9.35%	0.181	15.68%	0.064
	<b>Inferior Parietal</b>	1.630	1.621	-0.037	0.057	0.094	0.044	-2.26%	3.53%	5.79%	0.047	7.47%	0.069

	<b>Superior parietal</b>	1.496	1.491	-0.040	0.058	0.098	0.046	-2.68%	3.89%	6.58%	0.051	7.25%	0.058
<b>Temporal</b>	<b>Superior temporal gyrus</b>	1.340	1.393	-0.035	0.056	0.091	0.033	-2.62%	4.01%	6.63%	0.015	7.62%	0.055
	<b>Transverse Temporal gyrus</b>	1.656	1.567	-0.043	0.120	0.163	0.082	-2.61%	7.67%	10.28%	0.063	8.09%	0.154
	<b>Middle temporal gyrus</b>	1.478	1.522	-0.039	0.059	0.098	0.036	-2.65%	3.89%	6.54	0.015	8.36%	0.093
<b>Cingulate</b>	<b>Caudal anterior cingulate</b>	1.533	1.335	-0.049	0.111	0.159	0.094	-3.19%	8.28%	11.47	0.109	15.52%	0.090
	<b>Posterior cingulate</b>	1.658	1.447	-0.070	0.127	0.198	0.141	-4.23	8.81	13.04	0.180	21.01	0.099
	<b>Rostral anterior cingulate</b>	1.393	1.330	-0.040	0.086	0.126	0.056	-2.88	6.47	9.35	0.038	9.06	0.152

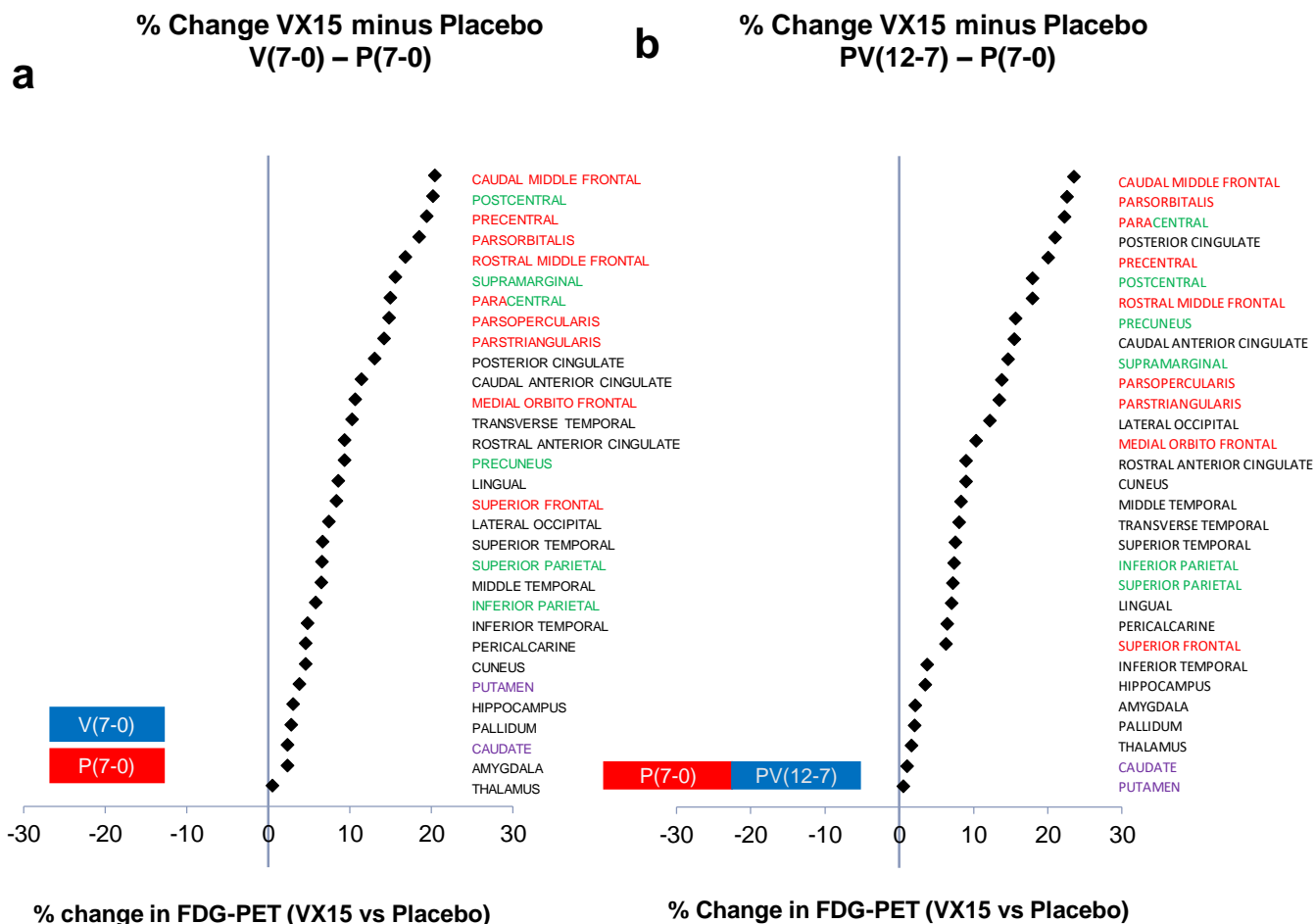
FDG-PET Signals in Brain ROI. Baseline SUVR values for each ROI are indicated for placebo, P(0), and pepinemab, V(0) for 6-month double-blind and V(7) for 5-month open label. Change ( $\Delta$ ) in SUVR is the average of left and right hemispheres during the respective double-blind or open-label treatment periods. Least square mean (LSM) change was calculated over the treatment period by subtracting baseline SUVR from SUVR at 7 month visit (double-blind period) or SUVR at 7 month visit from SUVR at 12 month visit (open-label period). In all cases SUVR change in placebo is that determined for the P(7-0) period. Calculations are shown for the 20 brain ROI with the greatest double-blind treatment change. P-values <0.05 were considered statistically significant and indicated as \* in the graphical depiction of % change of LS means from baseline depicted in figure 5.

# Supplementary Data 1



**Supplementary Data 1: SEMA4D is expressed on Olig2-positive oligodendrocytes of dentate gyrus regions in HD mice at 9.3 months of age.** **A.** Plan-Apochromat 40x/0.95 objective SEMA4D is expressed on both oligodendrocytes (SEMA4D+Oligo2+, yellow) and the closely associated neurons (SEMA4D+ but Olig2-, red). See also Fig. 1,4). **B.** Higher magnification images of SEMA4D+ oligodendrocytes: Plan-Apochromat 63x/1.4, oil objective and ApoTome system (Carl Zeiss) with AxioCam 702 Monochrome Camera.

# Supplementary Data 2



**Supplementary Data 2. Rank Order of FDG-PET Brain ROI: Group Comparisons.** **a.** FDG-PET treatment effect in the pepinemab group minus change in the contemporaneous placebo control, V(7-0) – P(7-0). **b.** Within-Group treatment effect of 6 months of “cross-over” pepinemab treatment minus change in 6 months of placebo: VX15 following Placebo (12-7) – Placebo (7-0). Difference between pepinemab (n=11) and placebo (n=8) groups in least square (LS) mean change in FDG-PET signal for each brain region of interest (ROI) are shown as a percent change from baseline with 95% confidence limits (bars that bracket each point) for each ROI. Each point represents one of 31 ROI, as indicated. Regions of Frontal lobe (red), parietal lobe (green), and striatum (purple) are color coded.