

## Supplementary Online Content

Edwards AL, Collins JA, Junge C, et al. Exploratory tau biomarker results from a multiple ascending-dose study of BIIB080 in Alzheimer disease: a randomized clinical trial. *JAMA Neurol*. Published online October 30, 2023. doi:10.1001/jamaneurol.2023.3861

**eMethods.** Partial volume corrected tau PET analysis

**eTable 1.** MAD baseline characteristics: All study participants

**eTable 2.** MAD baseline characteristics: Tau PET substudy participants with baseline and end-of-MAD scans

**eTable 3.** MAD baseline characteristics: Tau PET substudy participants with baseline and end-of-LTE scans

**eTable 4.** MAD baseline characteristics: LTE participants

**eTable 5.** Number of participants in each treatment group analyzed at each timepoint for CSF t-tau and p-tau181

**eTable 6.** Summary statistics for % change from baseline of CSF t-tau

**eTable 7.** Summary statistics for % change from baseline of CSF p-tau181

**eTable 8.** Summary statistics for change from baseline of tau PET SUVR at Week 25 by composite region

**eTable 9.** Summary statistics for change from baseline of tau PET SUVR at Week 100 by composite region

**eTable 10.** Summary statistics for change from baseline of partial volume-corrected tau PET SUVR at Week 25 by composite region

**eTable 11.** Summary statistics for change from baseline of partial volume-corrected tau PET SUVR at Week 100 by composite region

**eTable 12.** Ventricle, Hippocampus and Whole Brain Volumes

**eFigure 1.** Dosing, CSF sampling, and tau PET scan schedule for the MAD and LTE

**eFigure 2.** Change from baseline on CSF t-tau and p-tau181 in the MAD and LTE

**eFigure 3.** Longitudinal tau PET for individual participants

**eFigure 4.** Change from baseline on partial volume corrected tau PET in the MAD and LTE

**eFigure 5.** Baseline tau PET vs change from baseline tau PET

**eFigure 6.** Relationship between model-predicted CSF PK and tau PET change from baseline

### **eReferences**

This supplemental material has been provided by the authors to give readers additional information about their work.

**eMethods.** Partial volume corrected tau PET analysis.

Post-hoc partial volume corrected SUVRs were calculated for lobar composite ROIs, using the following steps. Each participants tau PET scan was spatially smoothed to 8mm FWHM, motion-corrected, averaged, and co-registered to their 3D-T1-weighted MRI. Partial volume correction was then performed with FreeSurfer using the region-based voxel-wise method<sup>1,2</sup>, and resampled to the participants MRI volume. Each participant's MRI was co-registered to an AD-specific MNI template<sup>3</sup>, and the Hammers atlas<sup>4</sup> ROIs were resampled to the subjects' MRI-space and eroded by 1mm to account for potential misalignment. Partial volume corrected SUVRs were then calculated for each lobar composite ROI<sup>5</sup> using the ventral cerebellum as a reference region.

**eTable 1.** MAD baseline characteristics: All study participants

Values are presented as mean  $\pm$  standard deviation. Percentages may not total 100 due to rounding.

	Placebo	BIIB080				
	(N=12)	Cohort A, 10mg every 4 wks (N=6)	Cohort B, 30mg every 4 wks (N=6)	Cohort C, 60mg every 4 wks (N=9)	Cohort D, 115mg every 12 wks (N=13)	BIIB080 combined (N=34)
Age (years)	66 $\pm$ 4.6	64 $\pm$ 5.2	65 $\pm$ 6.1	66 $\pm$ 6.8	67 $\pm$ 6.3	66 $\pm$ 6.1
Sex						
Female (%)	6 (50)	2 (33)	4 (67)	5 (56)	6 (46)	17 (50)
Male (%)	6 (50)	4 (67)	2 (33)	4 (44)	7 (54)	17 (50)
Race – white (%)	12 (100)	6 (100)	6 (100)	9 (100)	13 (100)	34 (100)
MMSE Total Score	24.2 $\pm$ 1.7	21.5 $\pm$ 1.6	24.5 $\pm$ 1.4	24.6 $\pm$ 2.5	23.2 $\pm$ 2.5	23.5 $\pm$ 2.4
RBANS Total Score	64.9 $\pm$ 10.2	58.8 $\pm$ 11.2	69.2 $\pm$ 12.1	69.9 $\pm$ 9.1	70.9 $\pm$ 13.4	68.2 $\pm$ 12.1
CDR Global Score (%)						
0.5	7 (58)	0 (0)	3 (50)	9 (100)	11 (85)	23 (68)
1	5 (42)	6 (100)	3 (50)	0 (0)	2 (15)	11 (32)
CDR Sum of Boxes	4.1 $\pm$ 1.3	4.8 $\pm$ 0.5	4.7 $\pm$ 1.0	2.9 $\pm$ 0.6	3.3 $\pm$ 1.1	3.7 $\pm$ 1.1
Concomitant medications (%)						
Anticholinesterases	7 (58)	4 (67)	5 (83)	4 (44)	8 (62)	21 (62)
Memantine	1 (8)	2 (33)	0 (0)	3 (33)	2 (15)	7 (21)
Estrogen replacement	0 (0)	1 (17)	0 (0)	1 (11)	1 (8)	3 (9)
ApoE $\epsilon$ 4 carrier (%)	8 (67)	5 (83)	3 (50)	6 (67)	11 (85)	25 (74)
Heterozygous	6 (50)	3 (50)	3 (50)	3 (33)	8 (62)	17 (50)
Homozygous	2 (17)	2 (33)	0 (0)	3 (33)	3 (23)	8 (24)
Non-carrier	4 (33)	1 (17)	3 (50)	3 (33)	2 (15)	9 (26)
CSF t-tau (pg/mL)	387.3 $\pm$ 120.9	364.6 $\pm$ 98.1	386.4 $\pm$ 152.3	391.0 $\pm$ 111.8	443.4 $\pm$ 153.8	405.6 $\pm$ 132.7
CSF p-tau181 (pg/mL)	38.7 $\pm$ 13.0	39.1 $\pm$ 13.0	38.6 $\pm$ 16.6	39.5 $\pm$ 12.6	43.2 $\pm$ 15.9	40.7 $\pm$ 14.2
CSF t-tau/A $\beta$ 42	0.6 $\pm$ 0.2	0.6 $\pm$ 0.2	0.6 $\pm$ 0.1	0.5 $\pm$ 0.1	0.6 $\pm$ 0.2	0.6 $\pm$ 0.2

**eTable 2.** MAD baseline characteristics: Tau PET substudy participants with baseline and end-of-MAD scans

Values are presented as mean ± standard deviation. Percentages may not total 100 due to rounding.

	Placebo	BIIB080		
	Cohort D, Placebo (N=4)	Cohort C, 60mg every 4 wks (N=3)	Cohort D, 115mg every 12 wks (N=6)	BIIB080 combined (N=9)
Age (years)	67.3 ± 3.3	61.3 ± 10.6	67.2 ± 8.6	65.2 ± 9.1
Sex				
Female (%)	2 (50)	3 (100)	2 (33)	5 (56)
Male (%)	2 (50)	0 (0)	4 (67)	4 (44)
Race – white (%)	4 (100)	3 (100)	6 (100)	9 (100)
MMSE Total Score	24.5 ± 1.7	24.7 ± 3.2	23.5 ± 2.5	23.9 ± 2.6
RBANS Total Score	64.0 ± 8.3	74.0 ± 2.7	74.7 ± 12.2	74.4 ± 9.7
CDR Global Score (%)				
0.5	4 (100)	3 (100)	4 (67)	7 (78)
1	0 (100)	0 (0)	2 (33)	2 (22)
CDR Sum of Boxes	3.3 ± 0.3	2.8 ± 0.3	3.5 ± 1.3	3.3 ± 1.1
Concomitant medications (%)				
Anticholinesterases	2 (50)	1 (33)	5 (83)	6 (67)
Memantine	0 (0)	1 (33)	2 (33)	3 (33)
Estrogen replacement	0 (0)	1 (33)	1 (17)	2 (22)
ApoE ε4 carrier (%)	4 (100)	2 (66)	4 (66)	6 (66)
Heterozygous	3 (75)	1 (33)	2 (33)	3 (33)
Homozygous	1 (25)	1 (33)	2 (33)	3 (33)
Non-carrier	0 (0)	1 (33)	2 (33)	3 (33)
CSF t-tau (pg/mL)	445.0 ± 95.2	413.9 ± 167.6	465.7 ± 178.1	448.4 ± 165.9
CSF p-tau181 (pg/mL)	42.5 ± 8.9	43.3 ± 20.4	45.7 ± 18.9	44.9 ± 18.2
CSF t-tau/Aβ42	0.68 ± 0.2	0.63 ± 0.2	0.68 ± 0.3	0.67 ± 0.2
Tau PET SUVR				
Medial Temporal Composite	2.73 ± 0.47	1.97 ± 0.70	2.26 ± 0.56	2.16 ± 0.58
Temporal Composite	3.22 ± 0.74	2.17 ± 0.96	2.48 ± 0.87	2.38 ± 0.85
Frontal Composite	2.27 ± 0.75	1.64 ± 0.67	1.40 ± 0.46	1.48 ± 0.51
Parietal Composite	2.73 ± 0.65	2.10 ± 0.99	1.91 ± 0.73	1.97 ± 0.77
Occipital Composite	2.69 ± 0.85	1.85 ± 0.94	1.93 ± 0.88	1.90 ± 0.84
Cingulate Composite	2.03 ± 0.57	1.55 ± 0.53	1.25 ± 0.34	1.35 ± 0.41

**eTable 3.** MAD baseline characteristics: Tau PET substudy participants with baseline and end-of-LTE scans

Values are presented as mean ± standard deviation. Percentages may not total 100 due to rounding.

	Placebo	BIIB080		All Combined
	Cohort D (Placebo → 115mg every 12 wks) (N=2)	Cohort C (60mg every 4 wks → 60mg every 12 wks) (N=2)	Cohort D (115mg every 12 wks → 115mg every 12 wks) (N=8)	(N=12)
Age (years)	69.0 ± 2.8	60.5 ± 14.9	67.4 ± 7.7	66.5 ± 8.2
Sex				
Female (%)	0 (0)	2 (100)	3 (38)	5 (42)
Male (%)	2 (100)	0 (0)	5 (63)	7 (58)
Race – white (%)	2 (100)	2 (100)	8 (100)	12 (100)
MMSE Total Score	26.0 ± 0.0	23.5 ± 3.5	22.8 ± 2.6	23.4 ± 2.6
RBANS Total Score	71.0 ± 0.0	74.5 ± 3.5	71.1 ± 12.6	71.7 ± 10.2
CDR Global Score (%)				
0.5	2 (100)	2 (100)	6 (75)	10 (83)
1	0 (0)	0 (0)	2 (25)	2 (17)
CDR Sum of Boxes	3.0 ± 0.0	2.8 ± 0.4	3.5 ± 1.2	3.3 ± 1.0
Concomitant medications (%)				
Anticholinesterases	1 (50)	1 (50)	6 (75)	8 (67)
Memantine	0 (0)	1 (50)	2 (25)	3 (25)
Estrogen replacement	0 (0)	1 (50)	1 (13)	2 (17)
ApoE ε4 carrier (%)	2 (100)	1 (50)	6 (75)	9 (75)
Heterozygous	2 (100)	1 (50)	4 (50)	7 (58)
Homozygous	0 (0)	0 (0)	2 (25)	2 (17)
Non-carrier	0 (0)	1 (50)	2 (25)	3 (25)
CSF t-tau (pg/mL)	403.8 ± 86.1	510.4 ± 19.3	457.4 ± 163.3	457.3 ± 136.8
CSF p-tau181 (pg/mL)	39.5 ± 10.2	55.1 ± 1.4	44.7 ± 17.6	45.5 ± 15.2
CSF t-tau/Aβ42	0.56 ± 0.01	0.73 ± 0.15	0.67 ± 0.26	0.66 ± 0.22
Tau PET SUVR				
Medial Temporal Composite	2.36 ± 0.12	2.37 ± 0.17	2.39 ± 0.53	2.38 ± 0.43
Temporal Composite	2.61 ± 0.09	2.69 ± 0.48	2.61 ± 0.79	2.63 ± 0.65
Frontal Composite	1.67 ± 0.49	2.00 ± 0.33	1.50 ± 0.47	1.61 ± 0.46
Parietal Composite	2.23 ± 0.04	2.37 ± 1.25	2.30 ± 1.11	2.30 ± 0.96
Occipital Composite	2.48 ± 1.08	2.10 ± 1.18	2.31 ± 1.23	2.30 ± 1.10
Cingulate Composite	1.74 ± 0.56	1.85 ± 0.12	1.36 ± 0.39	1.51 ± 0.42

**eTable 4.** MAD baseline characteristics: LTE participants

Values are presented as mean ± standard deviation. Percentages may not total 100 due to rounding.

	Placebo → BIIB080		BIIB080 throughout				All Combined (N=33)
	Cohort A+B+C (Placebo → 60mg every 12 wks) (N=4)	Cohort D (Placebo → 115mg every 12 wks) (N=4)	Cohort A (10mg every 4 wks → 60mg every 12 wks) (N=3)	Cohort B (30mg every 4 wks → 60mg every 12 wks) (N=5)	Cohort C (60mg every 4 wks → 60mg every 12 wks) (N=7)	Cohort D (115mg every 12 wks → 115mg every 12 wks) (N=10)	
Age (years)	61.8 ± 3.1	67.3 ± 3.3	63.3 ± 7.2	63.6 ± 5.6	65.4 ± 7.7	67.8 ± 6.9	65.5 ± 6.2
Sex							
Female (%)	1 (25)	2 (50)	1 (33)	3 (60)	4 (57)	5 (50)	16 (48)
Male (%)	3 (75)	2 (50)	2 (67)	2 (40)	3 (43)	5 (50)	17 (52)
Race – white (%)	4 (100)	4 (100)	3 (100)	5 (100)	7 (100)	10 (100)	33 (100)
MMSE Total Score	23.8 ± 1.7	24.5 ± 1.7	21.3 ± 1.5	24.6 ± 1.5	24.7 ± 2.2	22.9 ± 2.3	23.7 ± 2.1
RBANS Total Score	59.8 ± 7.9	64.0 ± 8.3	55.7 ± 6.1	70.6 ± 13.0	70.7 ± 9.7	70.6 ± 14.4	67.2 ± 11.9
CDR Global Score (%)							
0.5	2 (50)	4 (100)	0 (0)	2 (40)	7 (100)	8 (80)	23 (70)
1	2 (50)	0 (0)	3 (100)	3 (60)	0 (0)	2 (20)	10 (30)
CDR Sum of Boxes	4.4 ± 1.1	3.3 ± 0.3	4.5 ± 0.5	4.9 ± 1.0	2.9 ± 0.7	3.4 ± 1.2	3.7 ± 1.1
Concomitant medications (%)							
Anticholinesterases	4 (100)	2 (50)	2 (67)	4 (80)	5 (71)	8 (80)	25 (76)
Memantine	1 (25)	0 (0)	2 (67)	3 (60)	3 (43)	3 (30)	12 (36)
Estrogen replacement	0 (0)	0 (0)	1 (33)	1 (20)	1 (14)	2 (20)	5 (15)
ApoE ε4 carrier (%)	1 (25)	4 (100)	3 (100)	3 (60)	5 (71)	8 (80)	24 (73)
Heterozygous	1 (25)	3 (75)	2 (67)	3 (60)	3 (43)	6 (60)	18 (55)
Homozygous	0 (0)	1 (25)	1 (33)	0 (0)	2 (29)	2 (20)	6 (18)
Non-carrier	3 (75)	0 (0)	0 (0)	2 (40)	2 (29)	2 (20)	9 (27)
CSF t-tau (pg/mL)	403.6 ± 128.6	445.0 ± 95.2	389.4 ± 146.5	331.8 ± 81.5	424.5 ± 99.3	443.4 ± 158.1	412.9 ± 122.4
CSF p-tau181 (pg/mL)	40.5 ± 14.3	42.5 ± 8.9	42.2 ± 19.5	32.5 ± 8.0	43.5 ± 10.7	43.5 ± 17.1	41.2 ± 13.3
CSF t-tau/Aβ42	0.53 ± 0.16	0.68 ± 0.22	0.59 ± 0.25	0.52 ± 0.08	0.56 ± 0.14	0.65 ± 0.24	0.60 ± 0.19

**eTable 5.** Number of participants in each treatment group analyzed at each timepoint for CSF t-tau and p-tau181.

Group	Study Week (N per group)												
	0	4	8	12	16	20	28	36	48	60	72	84	96
Cohort A+B+C (Placebo → 60mg every 12 wks)	7	7	7	7	5	6	3	5	4	3	2	2	2
Cohort A (10mg every 4 wks → 60mg every 12 wks)	6	6	6	6	6	5		3	3	3	2	2	3
Cohort B (30mg every 4 wks → 60mg every 12 wks)	6	6	6	6	6	5		5	5	5	5	5	4
Cohort C (60mg every 4 wks → 60mg every 12 wks)	9	9	9	9	1	7	8	7	7	7	7	7	7
Cohort D (Placebo → 115mg every 12 wks)	5	NA	NA	5	NA	4	3	4	4	2	2	2	2
Cohort D (115mg every 12 wks → 115mg every 12 wks)	13	NA	NA	12	NA	11	12	10	10	10	10	10	11



**eTable 6.** Summary statistics for % change from baseline\* of CSF t-tau

	<b>Cohort A+B+C</b> (Placebo → 60mg every 12 wks)	<b>Cohort D</b> (Placebo → 115mg every 12 wks)	<b>Cohort A</b> (10mg every 4 wks → 60mg every 12 wks)	<b>Cohort B</b> (30mg every 4 wks → 60mg every 12 wks)	<b>Cohort C</b> (60mg every 4 wks → 60mg every 12 wks)	<b>Cohort D</b> (115mg every 12 wks → 115 mg every 12 wks)
<b>Week 4</b>						
N	7	0	6	6	9	0
Mean (SD)	-1.5 (3.3)		-5.0 (3.0)	-6.3 (3.5)	-8.9 (5.5)	
Median (Q1, Q3) (Min, Max)	-2.9 (-3.9, 1.7) (-4.5, 4.1)		-5.2 (-7.8, -2.1) (-8.3, -1.5)	-6.0 (-9.7, -3.2) (-10.0, -2.8)	-9.5 (-10.8, -5.5) (-18.2, 0.6)	
<b>Week 8</b>						
N	7	0	6	6	9	0
Mean (SD)	-1.0 (2.9)		-13.2 (11.8)	-15.9 (5.0)	-20.2 (6.0)	
Median (Q1, Q3) (Min, Max)	-0.9 (-3.7, 1.8) (-4.4, 3.4)		-9.9 (-15.6, -7.7) (-35.2, -0.7)	-14.3 (-21.7, -11.7) (-22.2, -11.4)	-19.4 (-21.9, -18.9) (-32.6, -10.4)	
<b>Week 12</b>						
N	7	5	6	6	9	12
Mean (SD)	-0.4 (5.1)	-2.2 (14.8)	-15.8 (7.4)	-27.3 (6.1)	-31.9 (5.7)	-27.2 (12.2)
Median (Q1, Q3) (Min, Max)	-2.1 (-5.2, 5.0) (-5.4, 7.1)	4.8 (2.2, 4.9) (-28.7, 5.6)	-17.2 (-20.0, -8.6) (-25.5, -6.3)	-24.5 (-31.9, -23.9) (-37.6, -21.7)	-32.0 (-36.1, -27.8) (-41.8, -23.7)	-29.2 (-36.8, -20.9) (-40.6, -0.4)
<b>Week 16</b>						
N	5	0	6	6	1	0
Mean (SD)	-2.4 (4.4)		-25.6 (15.4)	-34.9 (7.2)	-50.1 ( )	
Median (Q1, Q3) (Min, Max)	-3.3 (-5.6, 0.1) (-6.8, 3.8)		-27.3 (-34.1, -12.1) (-47.9, -5.0)	-34.5 (-42.7, -27.0) (-43.5, -27.0)	-50.1 (-50.1, -50.1) (-50.1, -50.1)	
<b>Wee (P)</b>						
N	6	4	5	5	7	11
Mean (SD)	-0.6 (5.2)	-2.5 (18.5)	-29.5 (8.0)	-39.7 (5.8)	-48.8 (6.9)	-41.9 (15.4)
Median (Q1, Q3) (Min, Max)	-2.1 (-3.5, -0.2) (-5.0, 9.5)	0.9 (-15.3, 10.2) (-27.9, 15.9)	-30.5 (-35.4, -30.0) (-35.7, -16.0)	-38.1 (-41.6, -37.8) (-48.4, -32.6)	-45.9 (-51.6, -43.6) (-62.5, -43.3)	-47.6 (-50.3, -33.4) (-60.0, -5.0)
<b>Week 28</b>						
N	3	3	0	0	8	12
Mean (SD)	0.7 (13.9)	-4.4 (21.8)			-55.4 (7.3)	-49.2 (16.0)
Median (Q1, Q3) (Min, Max)	-2.8 (-11.2, 16.0) (-11.2, 16.0)	2.7 (-28.8, 13.0) (-28.8, 13.0)			-56.1 (-58.9, -51.8) (-67.1, -42.6)	-52.6 (-59.3, -42.7) (-69.4, -11.7)
<b>Week 36<sup>‡</sup> (Cohorts A &amp; B only)</b>						
N	1	0	1	1	0	0
Mean (SD)	1.1 ( )		-36.7 ( )	-47.2 ( )		
Median (Q1, Q3) (Min, Max)	1.1 (1.1, 1.1) (1.1, 1.1)		-36.7 (-36.7, -36.7) (-36.7, -36.7)	-47.2 (-47.2, -47.2) (-47.2, -47.2)		
<b>Week 36 / LTE Week 0<sup>‡</sup></b>						

N	4	4	3	5	7	10
Mean (SD)	0.5 (11.6)	-4.7 (17.0)	1.4 (41.7)	-30.9 (12.1)	-56.2 (7.7)	-50.6 (20.3)
Median (Q1, Q3) (Min, Max)	-3.1 (-7.6, 8.7) (-8.5, 16.9)	2.2 (-15.1, 5.6) (-29.8, 6.5)	-22.3 (-23.0, 49.6) (-23.0, 49.6)	-29.7 (-35.0, -22.9) (-49.2, -18.0)	-56.7 (-59.5, -50.4) (-68.9, -44.3)	-57.2 (-64.1, -31.8) (-72.2, -8.3)
Week 48 / LTE Week 12						
N	4	4	3	5	7	10
Mean (SD)	-31.1 (13.1)	-34.7 (13.8)	-12.5 (50.0)	-45.9 (8.0)	-64.0 (6.5)	-54.7 (18.5)
Median (Q1, Q3) (Min, Max)	-32.4 (-40.7, -21.5) (-45.2, -14.2)	-33.4 (-43.3, -26.0) (-52.8, -19.2)	-38.4 (-44.2, 45.1) (-44.2, 45.1)	-44.0 (-52.4, -42.5) (-55.2, -35.3)	-63.5 (-67.4, -59.7) (-74.7, -53.9)	-62.6 (-66.6, -51.9) (-74.6, -16.2)
Week 60 / LTE Week 24						
N	3	2	3	5	7	10
Mean (SD)	-44.2 (24.2)	-49.5 (3.9)	-22.0 (56.1)	-52.8 (10.0)	-65.8 (7.1)	-59.5 (18.4)
Median (Q1, Q3) (Min, Max)	-55.1 (-61.0, -16.6) (-61.0, -16.6)	-49.5 (-52.3, -46.8) (-52.3, -46.8)	-49.2 (-59.2, 42.5) (-59.2, 42.5)	-50.4 (-61.9, -48.5) (-63.6, -39.4)	-64.6 (-71.4, -60.0) (-78.5, -58.0)	-65.4 (-69.7, -59.8) (-78.5, -15.6)
Week 72 / LTE Week 36						
N	2	2	2	5	7	10
Mean (SD)	-58.5 (13.5)	-56.1 (4.4)	-43.9 (12.8)	-56.6 (5.4)	-66.6 (6.9)	-60.4 (19.3)
Median (Q1, Q3) (Min, Max)	-58.5 (-68.0, -48.9) (-68.0, -48.9)	-56.1 (-59.2, -53.0) (-59.2, -53.0)	-43.9 (-53.0, -34.8) (-53.0, -34.8)	-54.2 (-61.0, -54.2) (-63.3, -50.1)	-66.1 (-72.5, -60.2) (-78.2, -57.9)	-67.2 (-69.8, -63.6) (-79.6, -15.4)
Week 84 / LTE Week 48						
N	2	2	2	5	7	10
Mean (SD)	-58.1 (19.9)	-62.8 (1.6)	-63.1 (5.5)	-59.4 (9.3)	-67.1 (6.4)	-62.1 (17.1)
Median (Q1, Q3) (Min, Max)	-58.1 (-72.2, -44.0) (-72.2, -44.0)	-62.8 (-63.9, -61.7) (-63.9, -61.7)	-63.1 (-67.0, -59.2) (-67.0, -59.2)	-57.7 (-67.0, -55.8) (-69.9, -46.7)	-66.1 (-71.8, -62.9) (-78.9, -59.3)	-67.9 (-70.6, -63.9) (-79.8, -22.9)
Week 96 / LTE Week 60 <sup>#</sup>						
N	2	1	3	4	7	9
Mean (SD)	-65.4 (11.6)	-69.5 ( )	-29.9 (58.1)	-63.8 (6.2)	-67.6 (7.1)	-67.6 (9.6)
Median (Q1, Q3) (Min, Max)	-65.4 (-73.6, -57.2) (-73.6, -57.2)	-69.5 (-69.5, -69.5) (-69.5, -69.5)	-56.7 (-69.8, 36.8) (-69.8, 36.8)	-63.5 (-69.1, -58.6) (-70.7, -57.6)	-65.8 (-71.4, -62.4) (-80.6, -59.3)	-69.7 (-71.7, -65.8) (-79.2, -44.7)
LTE Week 64 <sup>#</sup>						
N	0	1	0	0	0	2
Mean (SD)		-63.8 ( )				-45.2 (27.9)
Median (Q1, Q3) (Min, Max)		-63.8 (-63.8, -63.8) (-63.8, -63.8)				-45.2 (-65.0, -25.5) (-65.0, -25.5)

\*Baseline was defined as the average of the screening and Day 1 pre-dose values in the MAD period.

<sup>#</sup>There was a variable gap between the end of the MAD and beginning of the LTE for Cohorts A & B. These subjects had an end-of-MAD visit at Week 36. Those who returned to enter the LTE had a start-of-LTE visit upon commencing the LTE. Subjects in Cohorts C & D moved seamlessly from the MAD to LTE and therefore have a single Week 36 / LTE Week 0 visit. These datapoints were collapsed into a single datapoint for visualization in Figure 2.

<sup>#</sup>These datapoints were collapsed into a single datapoint for visualization in Figure 2.

**eTable 7.** Summary statistics for % change from baseline\* of CSF p-tau181

	<b>Cohort A+B+C</b> (Placebo → 60mg every 12 wks)	<b>Cohort D (Placebo</b> → 115mg every 12 wks)	<b>Cohort A (10mg</b> every 4 wks → 60mg every 12 wks)	<b>Cohort B (30mg</b> every 4 wks → 60mg every 12 wks)	<b>Cohort C (60mg</b> every 4 wks → 60mg every 12 wks)	<b>Cohort D (115mg</b> every 12 wks → 115 mg every 12 wks)
<b>Week 4</b>						
N	7	0	6	6	9	0
Mean (SD)	-0.7 (2.8)		-7.7 (3.5)	-7.6 (3.5)	-10.1 (6.8)	
Median (Q1, Q3)	-1.7 (-3.1, 2.9)		-8.9 (-10.1, -3.9)	-7.8 (-9.7, -3.9)	-9.7 (-13.7, -9.3)	
(Min, Max)	(-3.4, 3.6)		(-11.3, -3.0)	(-12.5, -3.8)	(-20.5, 2.0)	
<b>Week 8</b>						
N	7	0	6	6	9	0
Mean (SD)	1.0 (4.4)		-16.6 (12.9)	-19.8 (4.6)	-24.2 (7.1)	
Median (Q1, Q3)	-0.2 (-1.4, 5.4)		-12.9 (-19.4, -6.6)	-18.2 (-24.8, -17.4)	-24.7 (-26.8, -22.3)	
(Min, Max)	(-6.2, 6.4)		(-41.0, -6.6)	(-26.0, -14.2)	(-38.2, -12.8)	
<b>Week 12</b>						
N	7	5	6	6	9	12
Mean (SD)	0.9 (5.9)	-7.3 (15.2)	-19.9 (7.7)	-31.6 (7.0)	-36.6 (6.1)	-34.2 (13.7)
Median (Q1, Q3)	1.9 (-5.3, 6.8)	-1.4 (-2.7, 0.5)	-18.8 (-27.1, -12.3)	-31.5 (-35.8, -24.5)	-36.4 (-40.7, -35.4)	-39.3 (-44.4, -25.4)
(Min, Max)	(-5.4, 7.0)	(-34.3, 1.4)	(-30.4, -12.0)	(-42.3, -23.8)	(-45.3, -27.1)	(-49.0, -7.1)
<b>Week 16</b>						
N	5	0	6	6	1	0
Mean (SD)	-3.2 (5.1)		-31.1 (16.0)	-39.6 (7.5)	-53.5 ( )	
Median (Q1, Q3)	-4.9 (-7.2, 0.4)		-31.1 (-42.9, -15.4)	-41.7 (-45.5, -31.7)	-53.5 (-53.5, -53.5)	
(Min, Max)	(-8.1, 3.6)		(-53.8, -12.5)	(-47.7, -29.2)	(-53.5, -53.5)	
<b>Week 20</b>						
N	6	4	5	5	7	11
Mean (SD)	-0.1 (5.0)	-6.7 (17.9)	-35.0 (8.1)	-43.8 (7.2)	-52.0 (7.6)	-48.5 (15.2)
Median (Q1, Q3)	-1.8 (-2.8, 5.8)	-1.2 (-18.9, 5.5)	-34.8 (-39.6, -34.0)	-46.2 (-47.7, -41.6)	-51.3 (-55.1, -45.9)	-55.2 (-57.2, -39.4)
(Min, Max)	(-6.2, 6.2)	(-32.2, 7.8)	(-44.1, -22.5)	(-51.2, -32.4)	(-66.8, -44.3)	(-67.2, -14.2)
<b>Week 28</b>						
N	3	3	0	0	8	12
Mean (SD)	1.2 (16.2)	-11.0 (19.8)			-55.0 (8.7)	-49.9 (18.1)
Median (Q1, Q3)	-2.6 (-12.8, 18.9)	-1.1 (-33.9, 1.9)			-55.6 (-59.1, -50.7)	-56.3 (-61.7, -40.7)
(Min, Max)	(-12.8, 18.9)	(-33.9, 1.9)			(-69.5, -39.9)	(-69.1, -11.6)
<b>Week 36<sup>‡</sup> (Cohorts A &amp; B only)</b>						
N	1	0	1	1	0	0
Mean (SD)	-2.8 ( )		-37.8 ( )	-48.8 ( )		
Median (Q1, Q3)	-2.8 (-2.8, -2.8)		-37.8 (-37.8, -37.8)	-48.8 (-48.8, -48.8)		
(Min, Max)	(-2.8, -2.8)		(-37.8, -37.8)	(-48.8, -48.8)		
<b>Week 36 / LTE Week 0<sup>‡</sup></b>						

N	4	4	3	5	7	10
Mean (SD)	0.4 (13.7)	2.1 (18.8)	2.7 (40.3)	-23.7 (12.0)	-56.2 (7.7)	-45.8 (20.5)
Median (Q1, Q3) (Min, Max)	-4.5 (-8.7, 9.5) (-9.6, 20.2)	10.1 (-8.2, 12.4) (-25.9, 14.0)	-18.0 (-23.0, 49.1) (-23.0, 49.1)	-25.2 (-25.7, -14.0) (-41.9, -11.6)	-54.9 (-60.1, -53.3) (-69.8, -44.3)	-52.9 (-59.3, -26.8) (-69.1, -3.3)
Week 48 / LTE Week 12						
N	4	4	3	5	7	10
Mean (SD)	-30.5 (15.1)	-42.1 (12.9)	-14.2 (45.1)	-45.3 (7.1)	-59.2 (8.2)	-53.2 (17.1)
Median (Q1, Q3) (Min, Max)	-34.7 (-39.6, -21.4) (-43.8, -8.8)	-43.4 (-51.8, -32.4) (-55.8, -25.7)	-38.0 (-42.3, 37.9) (-42.3, 37.9)	-43.0 (-50.6, -41.0) (-54.6, -37.3)	-59.3 (-63.5, -54.1) (-74.2, -48.1)	-59.9 (-63.6, -49.8) (-73.2, -17.7)
Week 60 / LTE Week 24						
N	3	2	3	5	7	10
Mean (SD)	-44.9 (20.4)	-52.9 (3.8)	-28.6 (46.1)	-52.0 (8.7)	-61.1 (9.0)	-58.5 (17.8)
Median (Q1, Q3) (Min, Max)	-54.2 (-58.9, -21.5) (-58.9, -21.5)	-52.9 (-55.6, -50.1) (-55.6, -50.1)	-53.7 (-56.6, 24.6) (-56.6, 24.6)	-49.3 (-60.5, -47.1) (-61.4, -41.6)	-58.7 (-67.8, -53.5) (-77.7, -51.7)	-62.8 (-67.9, -59.3) (-77.6, -15.9)
Week 72 / LTE Week 36						
N	2	2	2	5	7	10
Mean (SD)	-59.8 (7.8)	-58.9 (4.5)	-60.7 (2.0)	-56.7 (6.8)	-63.0 (8.3)	-60.0 (18.6)
Median (Q1, Q3) (Min, Max)	-59.8 (-65.3, -54.3) (-65.3, -54.3)	-58.9 (-62.1, -55.7) (-62.1, -55.7)	-60.7 (-62.2, -59.3) (-62.2, -59.3)	-57.8 (-62.4, -53.7) (-62.8, -46.6)	-61.7 (-71.6, -56.9) (-76.6, -53.1)	-66.2 (-68.5, -64.9) (-79.0, -18.7)
Week 84 / LTE Week 48						
N	2	2	2	5	7	10
Mean (SD)	-64.0 (6.4)	-65.7 (0.2)	-65.3 (3.0)	-60.2 (7.6)	-65.2 (6.9)	-62.1 (15.9)
Median (Q1, Q3) (Min, Max)	-64.0 (-68.5, -59.5) (-68.5, -59.5)	-65.7 (-65.9, -65.6) (-65.9, -65.6)	-65.3 (-67.5, -63.2) (-67.5, -63.2)	-56.2 (-67.1, -55.9) (-69.5, -52.1)	-62.6 (-70.3, -59.6) (-77.9, -58.4)	-67.8 (-70.1, -63.7) (-79.0, -27.1)
Week 96 / LTE Week 60 <sup>#</sup>						
N	2	1	3	4	7	9
Mean (SD)	-69.0 (4.9)	-71.9 ( )	-41.9 (43.1)	-63.2 (7.2)	-65.5 (8.4)	-66.8 (10.3)
Median (Q1, Q3) (Min, Max)	-69.0 (-72.5, -65.6) (-72.5, -65.6)	-71.9 (-71.9, -71.9) (-71.9, -71.9)	-63.5 (-69.8, 7.7) (-69.8, 7.7)	-63.5 (-69.0, -57.3) (-70.8, -54.8)	-60.6 (-71.1, -59.3) (-80.2, -57.8)	-67.7 (-69.7, -65.7) (-78.8, -42.3)
LTE Week 64 <sup>#</sup>						
N	0	1	0	0	0	2
Mean (SD)		-62.0 ( )				-47.5 (23.7)
Median (Q1, Q3) (Min, Max)		-62.0 (-62.0, -62.0) (-62.0, -62.0)				-47.5 (-64.2, -30.7) (-64.2, -30.7)

\*Baseline was defined as the average of the screening and Day 1 pre-dose values in the MAD period.

<sup>#</sup>There was a variable gap between the end of the MAD and beginning of the LTE for Cohorts A & B. These subjects had an end-of-MAD visit at Week 36. Those who returned to enter the LTE had a start-of-LTE visit upon commencing the LTE. Subjects in Cohorts C & D moved seamlessly from the MAD to LTE and therefore have a single Week 36 / LTE Week 0 visit. These datapoints were collapsed into a single datapoint for visualization in Figure 2.

<sup>#</sup>These datapoints were collapsed into a single datapoint for visualization in Figure 2.

**eTable 8.** Summary statistics for change from baseline\* of tau PET SUVR at Week 25 by composite region

	<b>Cohort D, Placebo (N=4)</b>	<b>Cohort C, 60mg every 4 wks (N=3)</b>	<b>Cohort D, 115mg every 12 wks (N=6)</b>
<b>Frontal Composite</b>			
Mean (SD)	0.096 (0.0340)	-0.029 (0.1556)	0.042 (0.0888)
Median	0.106	-0.011	0.052
Q1, Q3	0.073, 0.119	-0.193, 0.116	-0.032, 0.129
Min, Max	0.05, 0.12	-0.19, 0.12	-0.08, 0.13
<b>Cingulate Composite</b>			
Mean (SD)	0.081 (0.0603)	-0.090 (0.1003)	0.035 (0.0679)
Median	0.093	-0.044	0.015
Q1, Q3	0.038, 0.124	-0.205, -0.021	-0.014, 0.088
Min, Max	0.00, 0.14	-0.21, -0.02	-0.03, 0.14
<b>Medial Temporal Composite</b>			
Mean (SD)	-0.015 (0.1091)	-0.122 (0.2634)	-0.038 (0.2137)
Median	-0.021	-0.024	-0.028
Q1, Q3	-0.086, 0.056	-0.420, 0.079	-0.220, 0.171
Min, Max	-0.14, 0.12	-0.42, 0.08	-0.29, 0.17
<b>Temporal Composite</b>			
Mean (SD)	-0.040 (0.1224)	-0.071 (0.1589)	0.018 (0.2263)
Median	-0.056	0.009	0.028
Q1, Q3	-0.137, 0.056	-0.254, 0.032	-0.117, 0.214
Min, Max	-0.16, 0.11	-0.25, 0.03	-0.30, 0.26
<b>Parietal Composite</b>			
Mean (SD)	0.033 (0.0618)	-0.096 (0.0506)	0.039 (0.1718)
Median	0.050	-0.110	0.069
Q1, Q3	-0.006, 0.073	-0.138, -0.040	-0.037, 0.158
Min, Max	-0.06, 0.09	-0.14, -0.04	-0.25, 0.22
<b>Occipital Composite</b>			
Mean (SD)	0.034 (0.1027)	-0.080 (0.1295)	0.025 (0.1165)
Median	0.048	-0.060	0.007
Q1, Q3	-0.041, 0.109	-0.218, 0.038	-0.073, 0.098
Min, Max	-0.10, 0.14	-0.22, 0.04	-0.09, 0.21

\*Baseline was defined as the last non-missing measure prior to the first dose of study drug (BIIB080 or placebo) in the MAD period.

**eTable 9.** Summary statistics for change from baseline\* of tau PET SUVR at Week 100 by composite region

	<b>Cohort D (Placebo → 115mg every 12 wks) (N=2)</b>	<b>Cohort C (60mg every 4 wks → 60mg every 12 wks) (N=2)</b>	<b>Cohort D (115mg every 12 wks → 115mg every 12 wks) (N=8)</b>
<b>Frontal Composite</b>			
Mean (SD)	-0.244 (0.0526)	-0.342 (0.2239)	-0.102 (0.2757)
Median	-0.244	-0.342	-0.053
Q1, Q3	-0.281, -0.207	-0.500, -0.183	-0.205, 0.022
Min, Max	-0.28, -0.21	-0.50, -0.18	-0.64, 0.29
<b>Cingulate Composite</b>			
Mean (SD)	-0.396 (0.1541)	-0.447 (0.1336)	-0.196 (0.2517)
Median	-0.396	-0.447	-0.107
Q1, Q3	-0.505, -0.287	-0.541, -0.352	-0.339, -0.080
Min, Max	-0.51, -0.29	-0.54, -0.35	-0.66, 0.14
<b>Medial Temporal Composite</b>			
Mean (SD)	-0.660 (0.0548)	-0.566 (0.0318)	-0.647 (0.4444)
Median	-0.660	-0.566	-0.579
Q1, Q3	-0.699, -0.621	-0.589, -0.544	-0.960, -0.416
Min, Max	-0.70, -0.62	-0.59, -0.54	-1.35, 0.09
<b>Temporal Composite</b>			
Mean (SD)	-0.704 (0.1987)	-0.446 (0.3380)	-0.573 (0.5463)
Median	-0.704	-0.446	-0.469
Q1, Q3	-0.844, -0.563	-0.685, -0.207	-1.026, -0.319
Min, Max	-0.84, -0.56	-0.69, -0.21	-1.34, 0.38
<b>Parietal Composite</b>			
Mean (SD)	-0.456 (0.2204)	-0.404 (0.5763)	-0.385 (0.7506)
Median	-0.456	-0.404	-0.158
Q1, Q3	-0.612, -0.300	-0.812, 0.003	-0.724, 0.118
Min, Max	-0.61, -0.30	-0.81, 0.00	-1.95, 0.41
<b>Occipital Composite</b>			
Mean (SD)	-0.440 (0.5563)	-0.171 (0.3453)	-0.381 (0.6844)
Median	-0.440	-0.171	-0.070
Q1, Q3	-0.833, -0.047	-0.415, 0.073	-0.820, 0.114
Min, Max	-0.83, -0.05	-0.42, 0.07	-1.71, 0.22

\*Baseline was defined as the last non-missing measure prior to the first dose of study drug (BIIB080 or placebo) in the MAD period.

**eTable 10.** Summary statistics for change from baseline\* of partial volume-corrected tau PET SUVR at Week 25 by composite region

	<b>Cohort D, Placebo (N=4)</b>	<b>Cohort C, 60mg every 4 wks (N=3)</b>	<b>Cohort D, 115mg every 12 wks (N=6)</b>
<b>Frontal Composite</b>			
Mean (SD)	0.217 (0.0897)	-0.016 (0.1517)	0.057 (0.1702)
Median	0.205	0.000	0.097
Q1, Q3	0.147, 0.287	-0.175, 0.127	-0.008, 0.200
Min, Max	0.13, 0.33	-0.18, 0.13	-0.25, 0.20
<b>Cingulate Composite</b>			
Mean (SD)	0.187 (0.1426)	0.148 (0.2300)	0.098 (0.1395)
Median	0.207	0.097	0.096
Q1, Q3	0.088, 0.285	-0.052, 0.399	0.045, 0.138
Min, Max	0.00, 0.34	-0.05, 0.40	-0.11, 0.32
<b>Medial Temporal Composite</b>			
Mean (SD)	0.044 (0.0758)	-0.277 (0.5028)	-0.103 (0.3812)
Median	0.013	-0.024	-0.041
Q1, Q3	-0.004, 0.092	-0.856, 0.049	-0.232, 0.215
Min, Max	0.00, 0.16	-0.86, 0.05	-0.75, 0.23
<b>Temporal Composite</b>			
Mean (SD)	-0.035 (0.1603)	-0.060 (0.0964)	0.040 (0.4791)
Median	0.022	-0.058	0.117
Q1, Q3	-0.148, 0.078	-0.157, 0.035	-0.157, 0.455
Min, Max	-0.26, 0.08	-0.16, 0.04	-0.76, 0.47
<b>Parietal Composite</b>			
Mean (SD)	0.074 (0.1017)	-0.225 (0.2832)	0.039 (0.3545)
Median	0.063	-0.222	0.106
Q1, Q3	-0.008, 0.157	-0.510, 0.056	-0.041, 0.277
Min, Max	-0.03, 0.20	-0.51, 0.06	-0.60, 0.39
<b>Occipital Composite</b>			
Mean (SD)	0.051 (0.0714)	-0.076 (0.1279)	0.041 (0.2290)
Median	0.067	-0.041	-0.015
Q1, Q3	-0.002, 0.104	-0.218, 0.030	-0.098, 0.287
Min, Max	-0.05, 0.11	-0.22, 0.03	-0.24, 0.33

\*Baseline was defined as the last non-missing measure prior to the first dose of study drug (BIIB080 or placebo) in the MAD period.

**eTable 11.** Summary statistics for change from baseline\* of partial volume-corrected tau PET SUVR at Week 100 by composite region

	<b>Cohort D (Placebo → 115mg every 12 wks) (N=2)</b>	<b>Cohort C (60mg every 4 wks → 60mg every 12 wks) (N=2)</b>	<b>Cohort D (115mg every 12 wks → 115mg every 12 wks) (N=8)</b>
<b>Frontal Composite</b>			
Mean (SD)	-0.276 (0.1018)	-0.294 (0.3596)	-0.145 (0.4844)
Median	-0.276	-0.294	-0.062
Q1, Q3	-0.348, -0.204	-0.54, -0.039	-0.289, 0.088
Min, Max	-0.35, -0.20	-0.55, -0.04	-1.14, 0.51
<b>Cingulate Composite</b>			
Mean (SD)	-0.736 (0.4319)	-0.645 (0.7701)	-0.316 (0.4181)
Median	-0.736	-0.645	-0.242
Q1, Q3	-1.041, -0.430	-1.190, -0.101	-0.525, -0.055
Min, Max	-1.04, -0.43	-1.19, -0.10	-1.12, 0.23
<b>Medial Temporal Composite</b>			
Mean (SD)	-0.897 (0.0610)	-0.594 (0.0235)	-0.965 (0.6093)
Median	-0.897	-0.594	-0.974
Q1, Q3	-0.941, -0.854	-0.61, -0.577	-1.279, -0.666
Min, Max	-0.94, -0.85	-0.61, -0.58	-1.97, 0.09
<b>Temporal Composite</b>			
Mean (SD)	-1.056 (0.2744)	-0.530 (0.8888)	-0.988 (0.9872)
Median	-1.056	-0.530	-0.890
Q1, Q3	-1.250, -0.862	-1.159, 0.099	-1.711, -0.550
Min, Max	-1.25, -0.86	-1.16, 0.10	-2.41, 0.81
<b>Parietal Composite</b>			
Mean (SD)	-0.838 (0.1482)	-0.780 (0.5397)	-0.672 (1.1589)
Median	-0.838	-0.780	-0.398
Q1, Q3	-0.943, -0.734	-1.161, -0.398	-0.966, 0.008
Min, Max	-0.94, -0.73	-1.16, -0.40	-3.22, 0.55
<b>Occipital Composite</b>			
Mean (SD)	-0.527 (0.7594)	-0.138 (0.4545)	-0.630 (0.9656)
Median	-0.527	-0.138	-0.432
Q1, Q3	-1.064, 0.010	-0.459, 0.184	-1.243, 0.153
Min, Max	-1.06, 0.01	-0.46, 0.18	-2.39, 0.39

\*Baseline was defined as the last non-missing measure prior to the first dose of study drug (BIIB080 or placebo) in the MAD period.

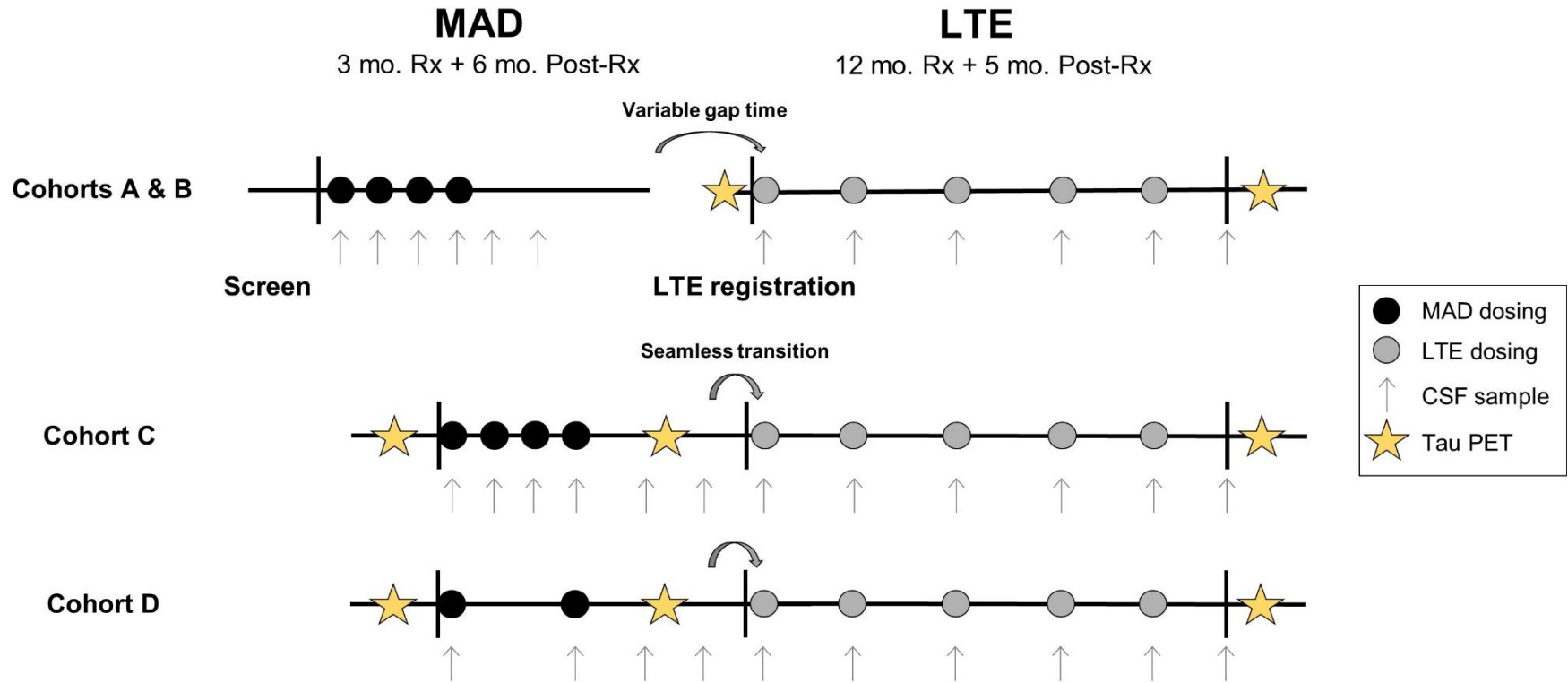


**eTable 12:** Ventricle, Hippocampus and Whole Brain Volumes. Volume measured in cm<sup>3</sup>. Values are presented as means ± standard deviation. ICV: Intracranial Volume (cm<sup>3</sup>)

Region	Cohort A+B+C (Placebo → 60mg every 12 wks)	Cohort D (Placebo → 115mg every 12 wks)	Cohort A (10mg every 4 wks → 60mg every 12 wks)	Cohort B (30mg every 4 wks → 60mg every 12 wks)	Cohort C (60mg every 4 wks → 60mg every 12 wks)	Cohort D 115mg every 12 wks → 115 mg every 12 wks)
<b>Mean Volume at Baseline (N)</b>	7	5	6	6	9	13
Total Ventricle	48.1±24.2	47.2±19.2	51.4±31.7	43.4±13.8	31.8±14.6	41.8±16.9
Total Hippocampus	4.3±0.8	4.0±0.4	3.6±0.4	4.3±0.4	4.0±0.6	3.7±0.6
Whole Brain	1117.6±179.0	1096.7±97.7	1047.5±121.9	1085.6±91.3	1158.7±78.5	1162.4±113.7
Total ICV	1566.2±193.3	1514.8±130.8	1480.7±147.9	1506.1±131.6	1557.9±145.8	1575.8±102.9
<b>Change in Volume at Day 169 (N)</b>	7	4	6	6	8	12
Total Ventricle Mean Change from Baseline	3.1±3.0 0.2±0.2	5.0±6.4 0.3±0.5	7.3±4.4 0.5±0.3	10.4±6.6 0.7±0.4	10.9±10.2 0.7±0.6	9.4±7.1 0.6±0.5
Mean Change from Baseline as % of ICV						
Hippocampus Mean Change from Baseline	0.01±0.22	0.07±0.11	-0.03±0.15	0.12±0.43	-0.19±0.17	-0.21±0.15
Mean Change from Baseline as % of ICV	0.00±0.01	0.00±0.01	-0.00±0.01	0.01±0.03	-0.01±0.01	-0.01±0.01
Whole Brain Mean Change from Baseline	-14.3±9.8	2.7±4.9	-14.2±8.1	-11.4±11.6	2.9±16.6	-11.8±9.4
Mean Change from Baseline as % of ICV	-0.9±0.6	0.2±0.3	-1.0±0.6	-0.7±0.7	0.2±1.1	-0.7±0.6
<b>Change in Volume at Day 449 (N)</b>	2	2	3	4	7	10
Total Ventricle Mean Change from Baseline	19.9±5.2	26.6±15.6	24.7±14.2	32.7±4.5	23.8±27.3	32.3±19.6
Mean Change from Baseline as % of ICV	1.3±0.1	1.6±0.9	1.7±1.0	2.1±0.3	1.5±1.6	2.1±1.4

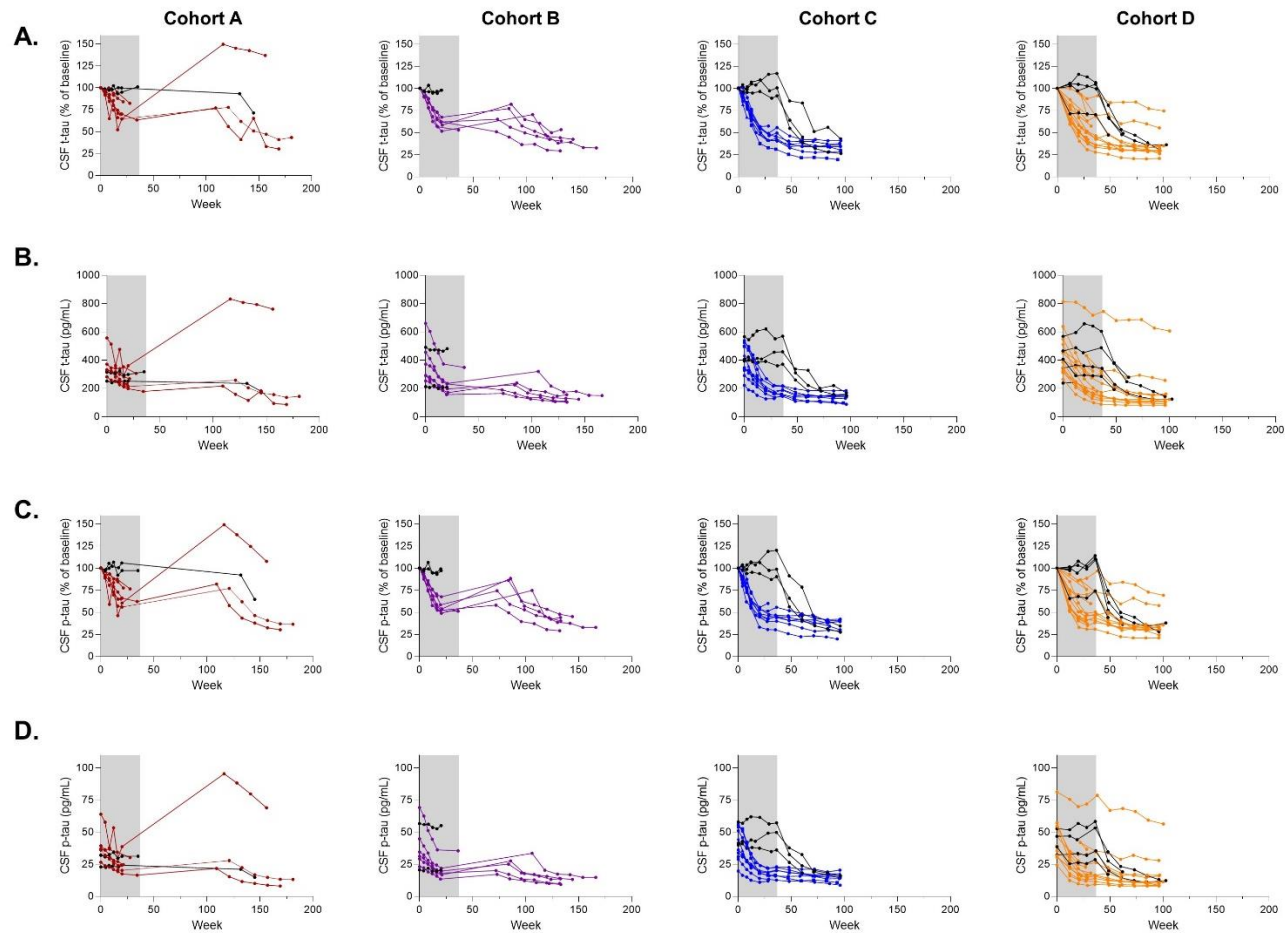
Hippocampus						
Mean Change from Baseline	-0.49±0.32	-0.52±0.08	-0.48±0.25	-0.70±0.61	-0.57±0.48	-0.48±0.19
Mean Change from Baseline as % of ICV	-0.03±0.02	-0.03±0.01	-0.03±0.01	-0.05±0.04	-0.04±0.03	-0.03±0.01
Whole Brain						
Mean Change from Baseline	-56.8±51.8	-20.3±18.7	-29.9±17.5	-47.3±10.7	-26.2±11.9	-35.2±15.4
Mean Change from Baseline as % of ICV	-3.5±2.8	-1.2±1.2	-2.0±1.0	-3.0±0.6	-1.8±1.0	-2.3±1.0

**eFigure 1.** Dosing, CSF sampling, and tau PET scan schedule for the MAD and LTE.



During the MAD, CSF samples were collected prior to study drug administration on Days 1, 29, 57, and 85 in Cohorts A, B, and C, and on Days 1 and 85 in Cohort D. CSF samples were also collected in the post-treatment period of the MAD on Days 113 and 141 in Cohorts A and B, and on Days 141 and 197 in Cohorts C and D. During the LTE, CSF samples were collected prior to study drug administration on LTE Day 1, 85, 169, 253, 337, and 421 and in the post-treatment period on LTE Day 449. Tau PET scans were collected at LTE registration and LTE Day 449 (Week 100) in Cohorts A and B, and at MAD Day 1, MAD Day 169 (Week 25), and LTE Day 449 (Week 100) in Cohorts C and D.

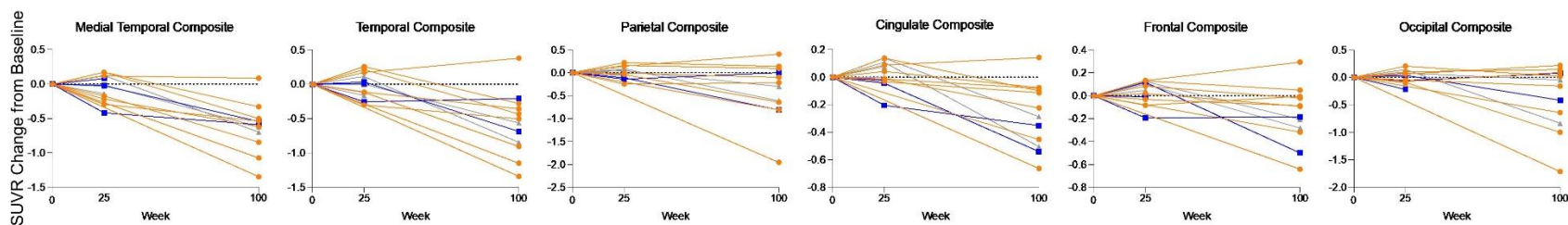
**eFigure 2.** Change from baseline on CSF t-tau and p-tau181 in the MAD and LTE



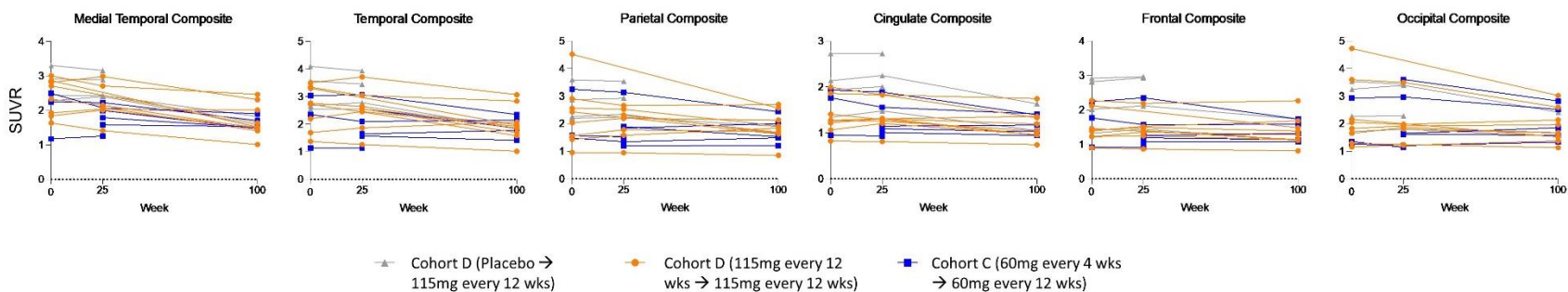
Change from baseline on levels of t-tau (A and B) and p-tau181 (C and D) in the CSF are plotted both as a percent of baseline values and as raw concentration values. The period corresponding to the MAD study is shaded in grey. Data are presented based on actual collection dates to clearly demonstrate the gap period between the end of the MAD and beginning of the LTE for Cohorts A & B. Participants treated with placebo during the MAD are shown in black, while participants treated with BIIB080 during the MAD are shown in color.

**eFigure 3.** Longitudinal tau PET for individual participants

**A. Tau PET SUVR Change from Baseline**



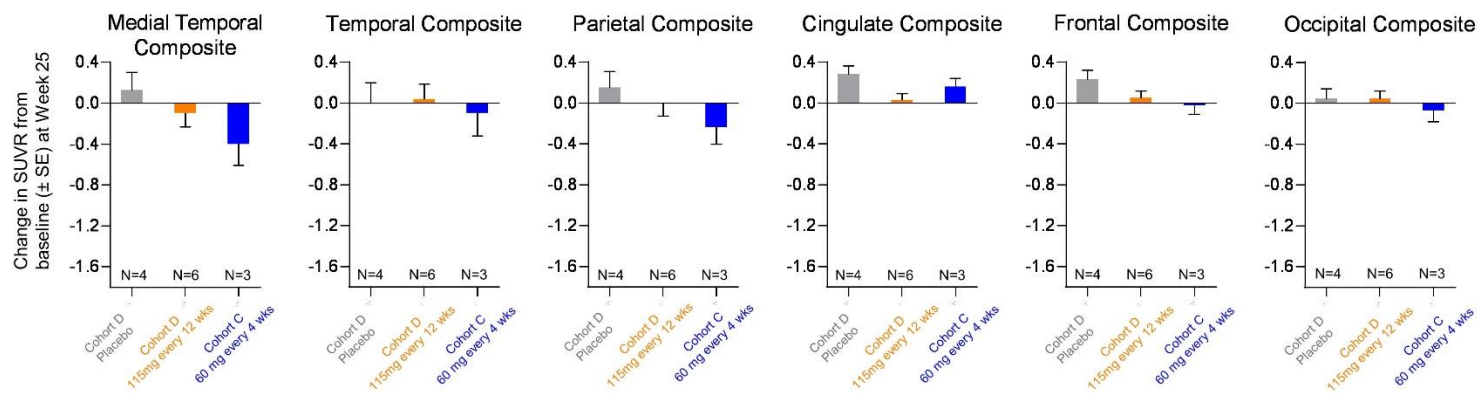
**B. Tau PET SUVR**



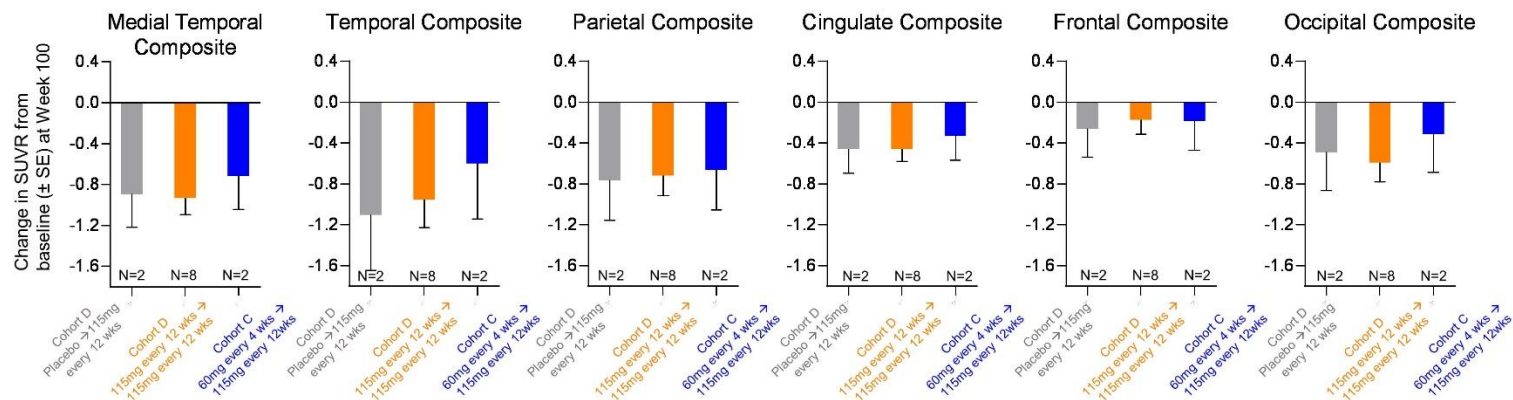
Change from baseline in tau PET SUVR is shown for each participant with available longitudinal tau PET data at weeks 25 and 100 in the top graphs (A). Tau PET SUVR is shown for each participant with available longitudinal tau PET data at screening (week 0), weeks 25, and week 100 in the bottom graphs (B).

**eFigure 4.** Change from baseline on partial volume corrected tau PET in the MAD and LTE

**A. MAD Partial Volume Corrected Tau PET**

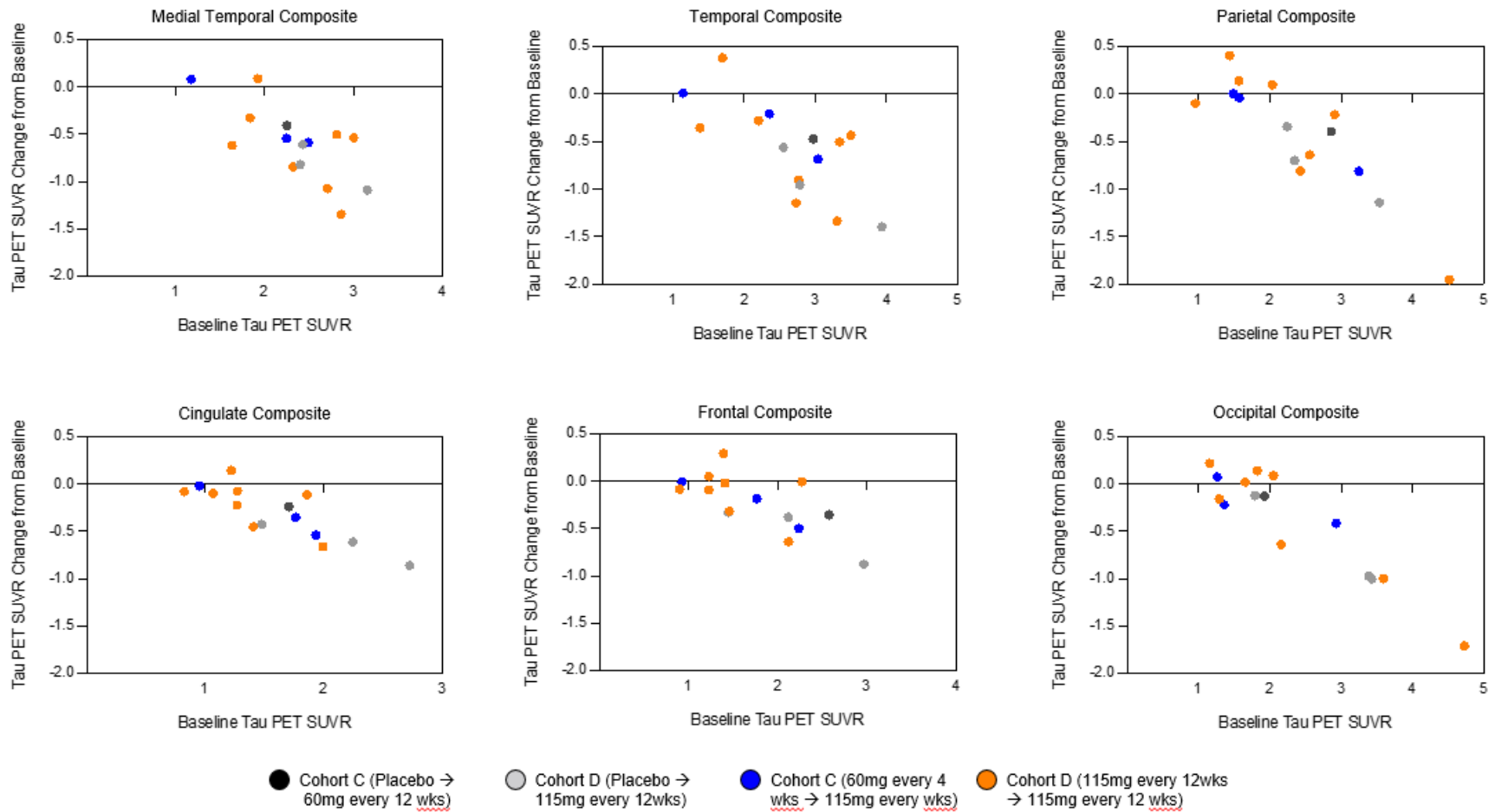


**B. MAD+LTE Partial Volume Corrected Tau PET**



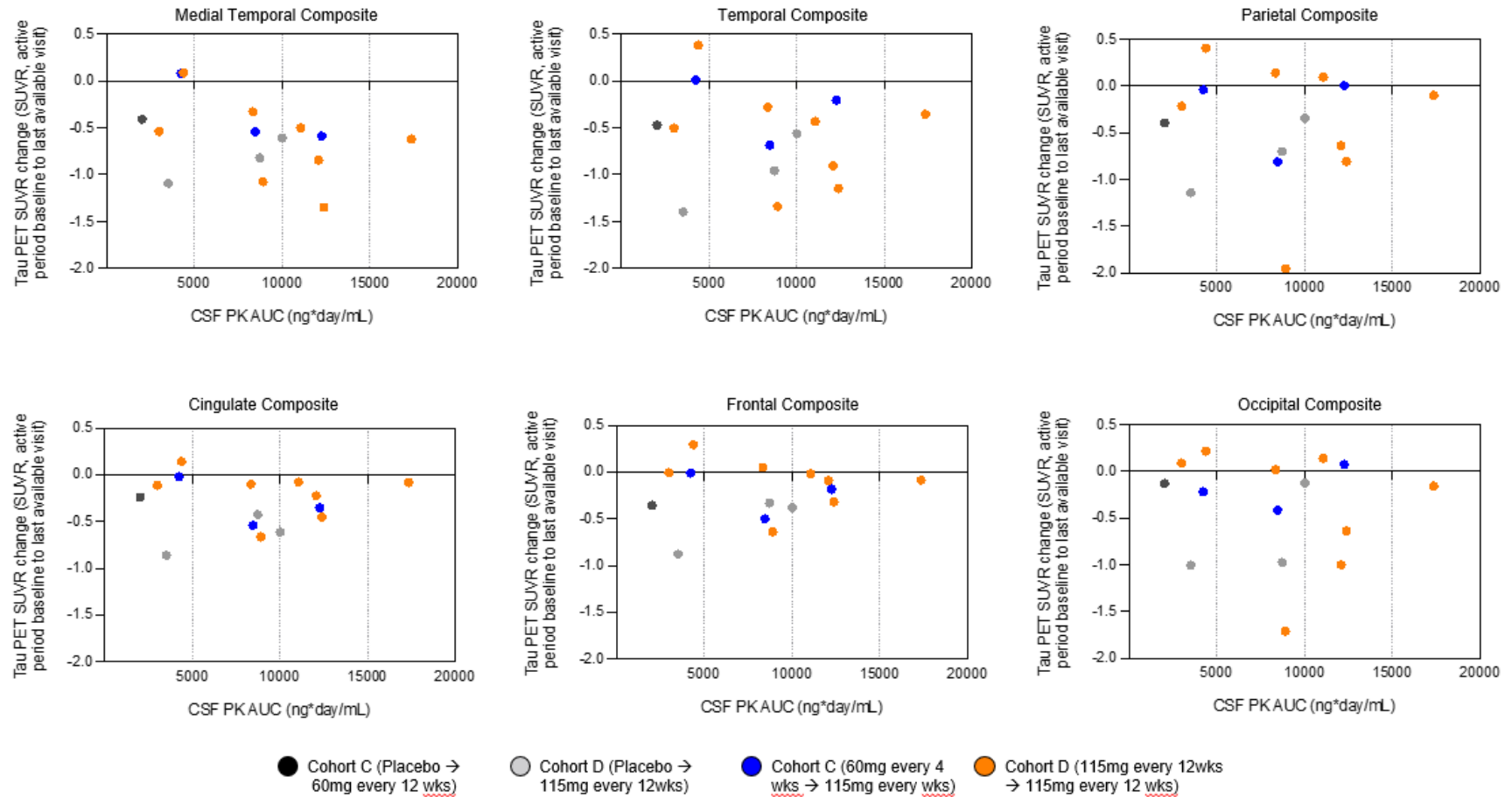
Adjusted mean change from baseline on partial volume corrected tau PET SUVR at Week 25 in the MAD (A) and Week 100 in the LTE (B). The adjusted mean SUVR change was estimated using an ANCOVA model with fixed effects of treatment group and baseline SUVR value. Error bars represent standard error.

**eFigure 5.** Baseline tau PET vs change from baseline tau PET



Scatterplots show baseline tau PET SUVR (x-axis) and tau PET SUVR change from baseline across the six ROIs.

**eFigure 6.** Relationship between model-predicted CSF PK and tau PET change from baseline



Scatterplots show the model-predicted CSF PK and tau PET SUVR change from baseline, unadjusted for baseline SUVR, across the six ROIs.



## eReferences

<sup>1</sup>Greve, DN, Svarer, C, Fisher, PM, et al. Cortical surface-based analysis reduces bias and variance in kinetic modeling of brain PET data. *Neuroimage*. 2014; 92: 225-236. doi:

10.1016/j.neuroimage.2013.12.021.

<sup>2</sup>Thomas, BA, Erlandsson, K, Modat, M, et al. The importance of appropriate partial volume correction for PET quantification in Alzheimer's disease. *Eur J Nucl Med Mol Imaging*. 2011; 38(6), 1104–1119.

doi: 10.1007/s00259-011-1745-9.

<sup>3</sup>Dadar, M, Camicioli, R, Duchesne, S. Multi sequence average templates for aging and neurodegenerative disease populations. *Sci Data*. 2022; 9(1), 238. doi: 10.1038/s41597-022-01341-2.

<sup>4</sup>Hammers A, Allom R, Koepp MJ, et al. Three-dimensional maximum probability atlas of the human brain, with particular reference to the temporal lobe. *Hum Brain Mapp*. 2003;19(4):224-47. Doi:

10.1002/hbm.10123.

<sup>5</sup>Budd Haeberlein S, Aisen PS, Barkhof F, et al. Two Randomized Phase 3 Studies of Aducanumab in Early Alzheimer's Disease. *JPAD*. 2022; 9(2): 197-210. doi:10.14283/jpad.2022.30.