Exploratory clinical outcomes from the BIIB080 Phase 1b multiple ascending dose and long-term extension study in mild Alzheimer's disease

Nick Ziogas,[1a] Shuang Wu,[1] Yumeng Li,[1] Lin Lin,[1] Amanda Edwards,[1] Jessica Collins,[1] Irene Tien,[1] Catherine Mummery,[2] Roger Lane,[3] Candice Junge,[3] John Beaver,[1a] Ying Tian,[1a] Jaren Landen,[1] Diana Gallagher,[1] Melanie Shulman[1]

[1]Biogen, Cambridge, MA, US; [2]Dementia Research Centre, National Hospital for Neurology and Neurosurgery, University College London, London, UK; [3]Ionis Pharmaceuticals, Carlsbad, CA, USA

[a]Denotes an author who was an employee of Biogen at the time of this study

Disclosures

- This study was sponsored by Ionis and Biogen
- Editorial support was provided by Meditech Media and funded by Biogen
- SW, YL, LL, AE, JC, IT, JL, DG, and MS are employees of Biogen and may hold stock
- NZ, JB, and YT are former employees of Biogen and may hold stock
- CJ and RL are employees of Ionis Pharmaceuticals and may hold stock
- CM is a BIIB080 trial site Investigator and is supported by the NIHR Biomedical Research Centre at UCLH and has acted as a consultant to Biogen, Roche, Eli Lilly, Prevail, Alnylam, Alector, Eisai, WAVE, PeerView, and Ionis.

BIIB080 is a *MAPT*-targeting ASO designed to reduce production of all forms of tau

Mechanism of action

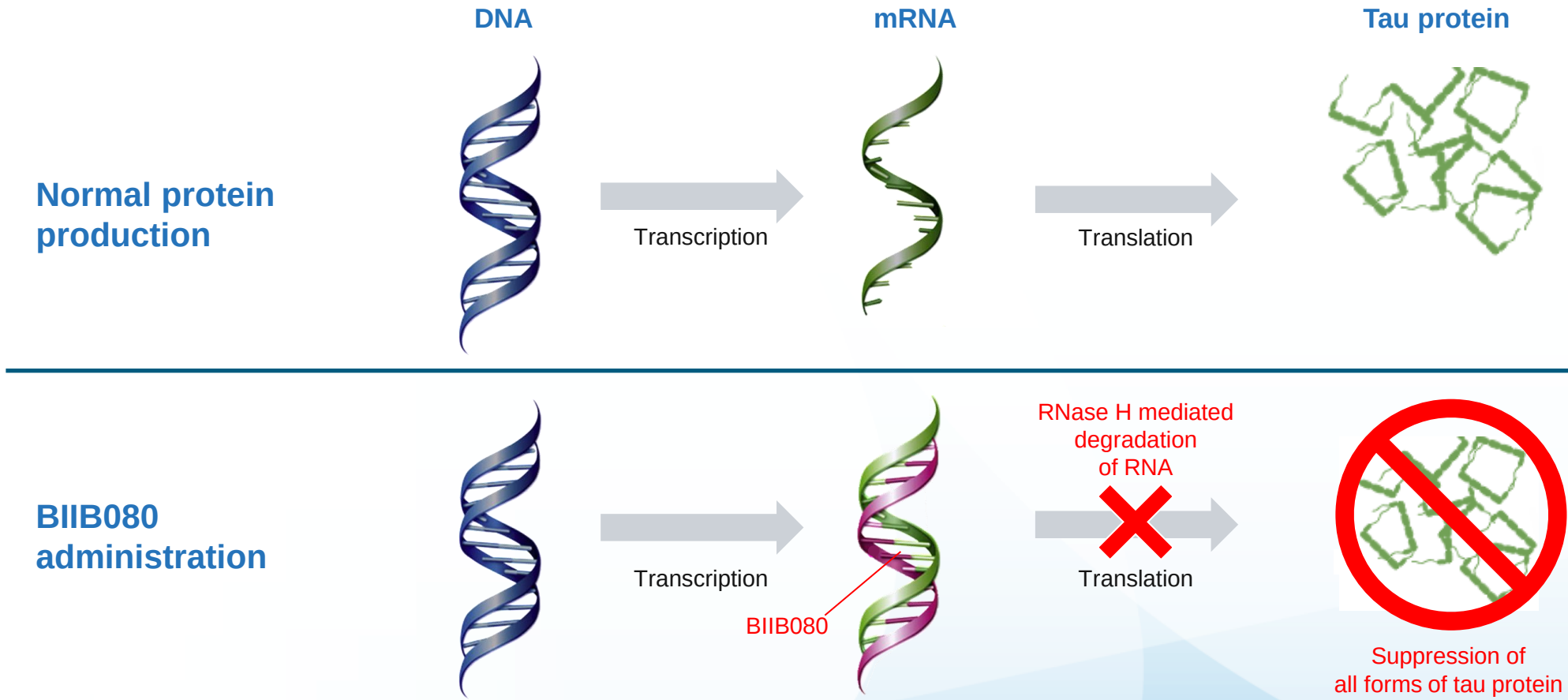
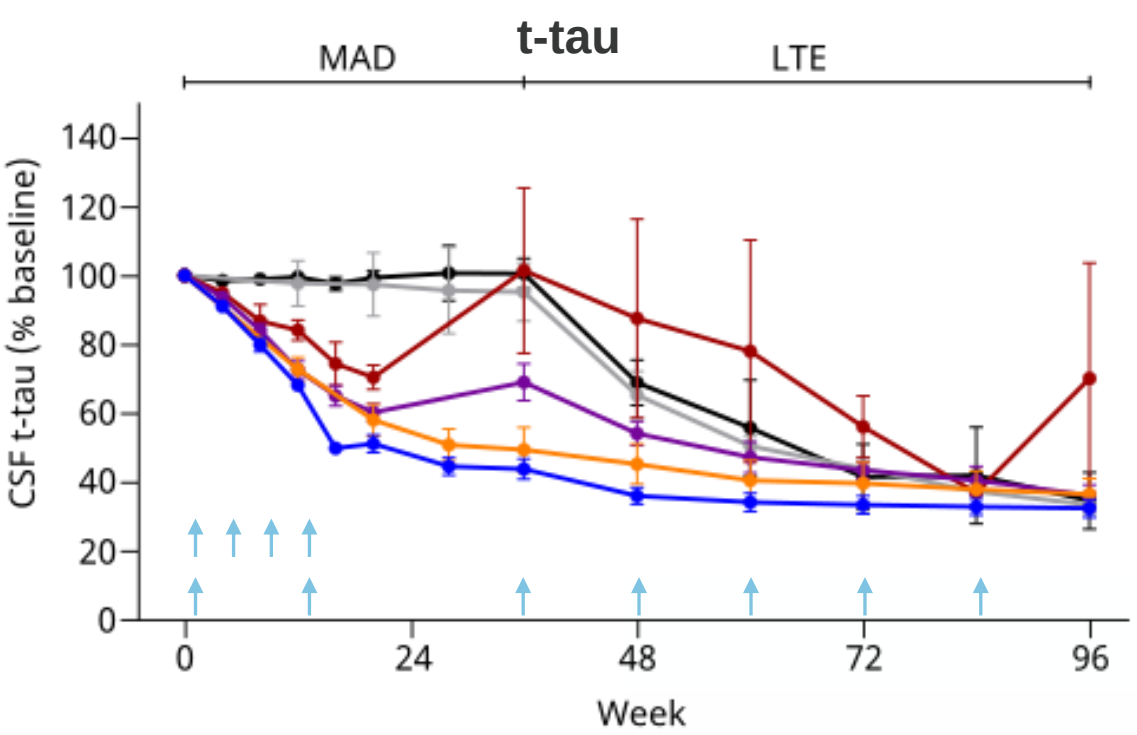
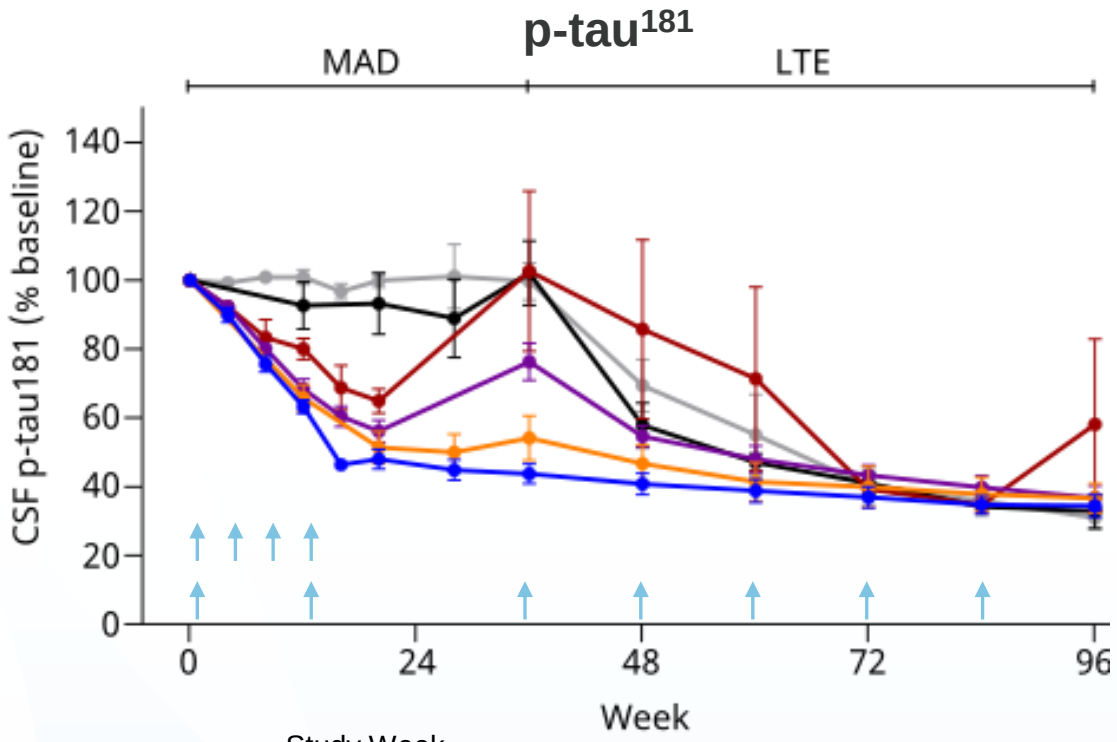


Figure adapted from Goldberg A, et al., *J Clin Lipidol*. 2010;4:350-6.
ASO, antisense oligonucleotide; *MAPT*, microtubule-associated protein tau; mRNA, messenger RNA; RNase H, Ribonuclease H.

Data shared at AD/PD 2023: BIIB080 Phase 1b showed robust dose-dependent and sustained CSF t-tau and p-tau^{181} reduction



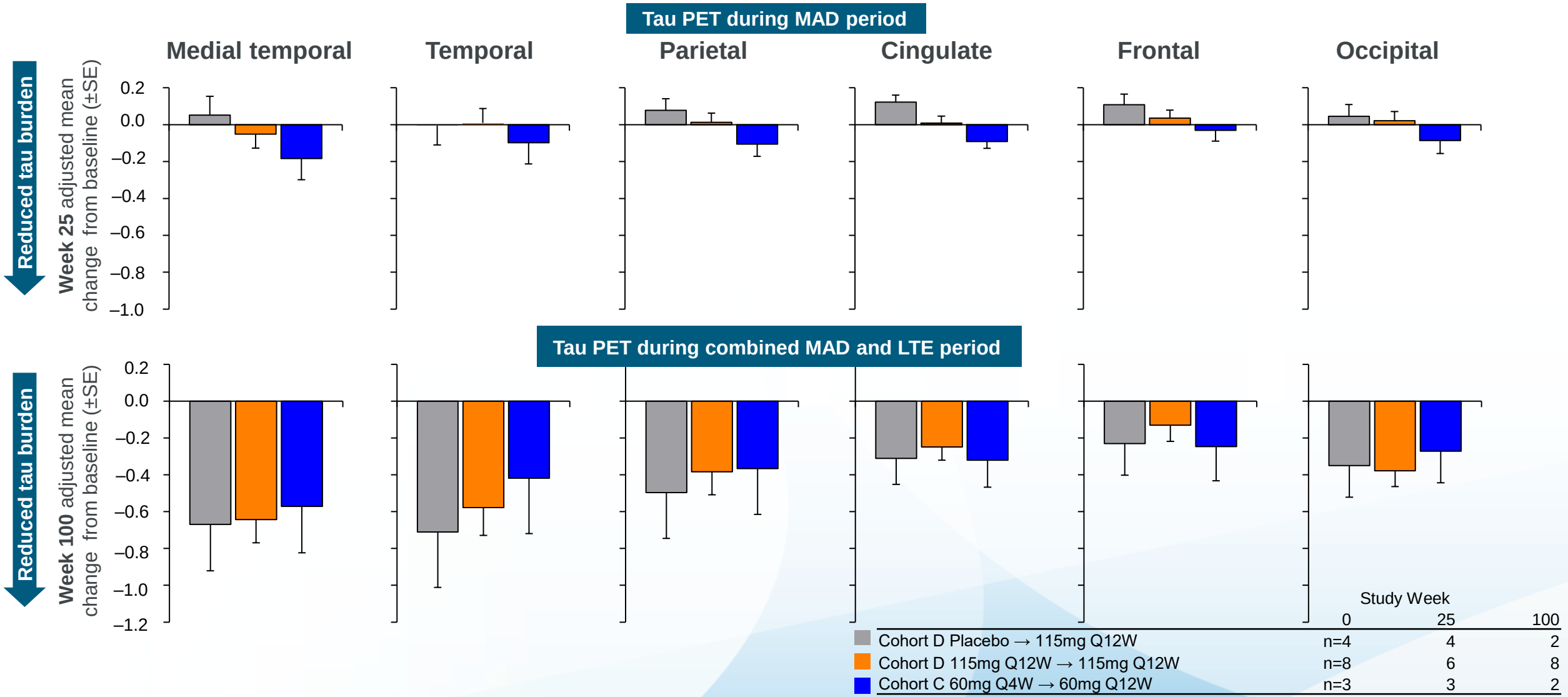


	Study Week		
	0	36	96
Cohort A 10mg Q4W → 60mg Q12W	n=6	3	3
Cohort B 30mg Q4W → 60mg Q12W	n=6	5	4
Cohort C 60mg Q4W → 60mg Q12W	n=9	7	7
Cohort D 115mg Q12W → 115mg Q12W	n=13	10	11
Cohort A+B+C Placebo → 60mg Q12W	n=7	5	2
Cohort D Placebo → 115mg Q12W	n=5	4	2

Dosing visit

CSF t-tau and p-tau^{181} were assessed using the Roche Elecsys® platform; error bars reflect standard error of the mean. Note that start of the LTE for Cohorts A & B is 5-19 mos after end of the MAD.
Collins J, et al. Oral presentation at: AD/PD; March 28th- April 1st, 2023; Gothenburg, Sweden. Abstract 2506.
CSF, cerebrospinal fluid; LTE, long term extension; MAD, multiple ascending dose; p-tau, phosphorylated tau; t-tau, total tau.

Data shared at AD/PD 2023: BIIB080 slowed tau accumulation as early as 25 weeks and reduced tau burden from baseline at the end of the LTE



[18F]-MK6240 SUVRs were calculated with inferior cerebellum as the reference region. Adjusted mean change from baseline based on ANCOVA model adjusting for categorical treatment and baseline tau PET SUVR. Error bars reflect standard error of the mean.

Collins J, et al. Oral presentation at: AD/PD; March 28th- April 1st, 2023; Gothenburg, Sweden. Abstract 2506.

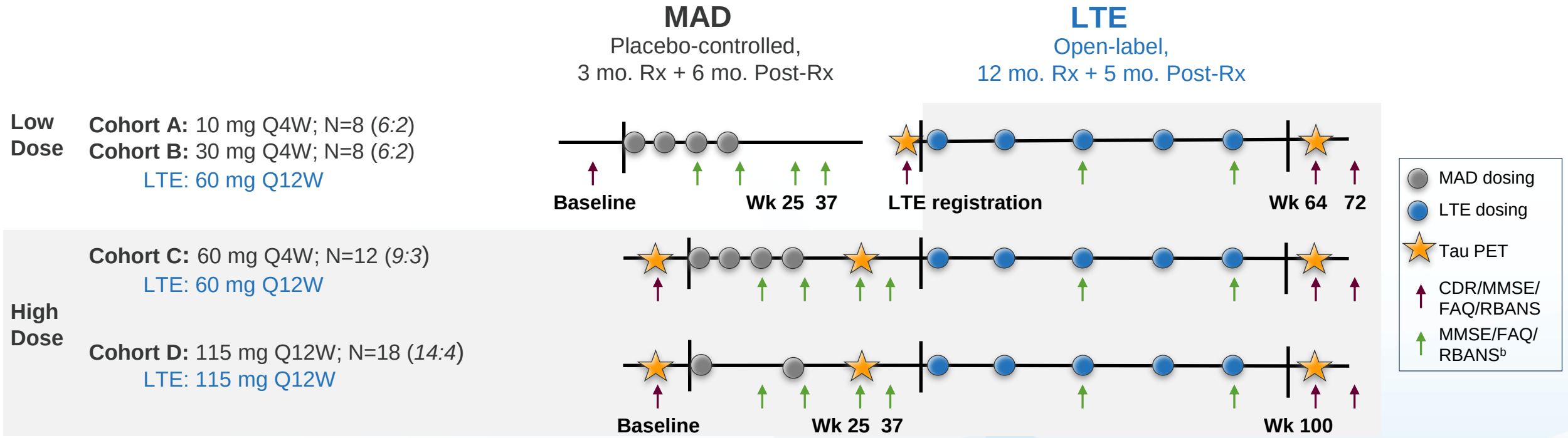
LTE, long term extension; PET, positron emission tomography; SUVRs, standard uptake value ratios.

BIIB080 phase 1b MAD + LTE

Evaluate safety, tolerability, and optimal dosing of intrathecally-administered ASO

Exploratory clinical measures: MMSE, FAQ, RBANS, and CDR

Study population: 46 patients with mild Alzheimer's disease and confirmed amyloid positivity,[a] age 50−74, CDR Global Score: 0.5 or 1 (0.5 added during Cohort B)



(drug:placebo)

N reflects cohort sizes at the beginning of MAD

Cohorts A and B had gap (5–19 months) between MAD & LTE; Cohorts C and D had seamless transition between MAD and LTE

[a]Amyloid positivity confirmed using CSF Aβ42/ptau181 ratio (high concordance with amyloid PET). [b]FAQ not collected at Week 9.

Aβ, amyloid beta; CDR, Clinical Dementia Rating scale; CSF, cerebrospinal fluid; FAQ, Functional Activities Questionnaire; LTE, long term extension; MAD, multiple ascending dose; MMSE, Mini Mental State Examination; NFT, neurofibrillary tangles; PET, positron emission tomography; PK, pharmacokinetic; RBANS, Repeatable Battery for the Assessment of Neuropsychological Status.

Characteristics of patients at MAD baseline

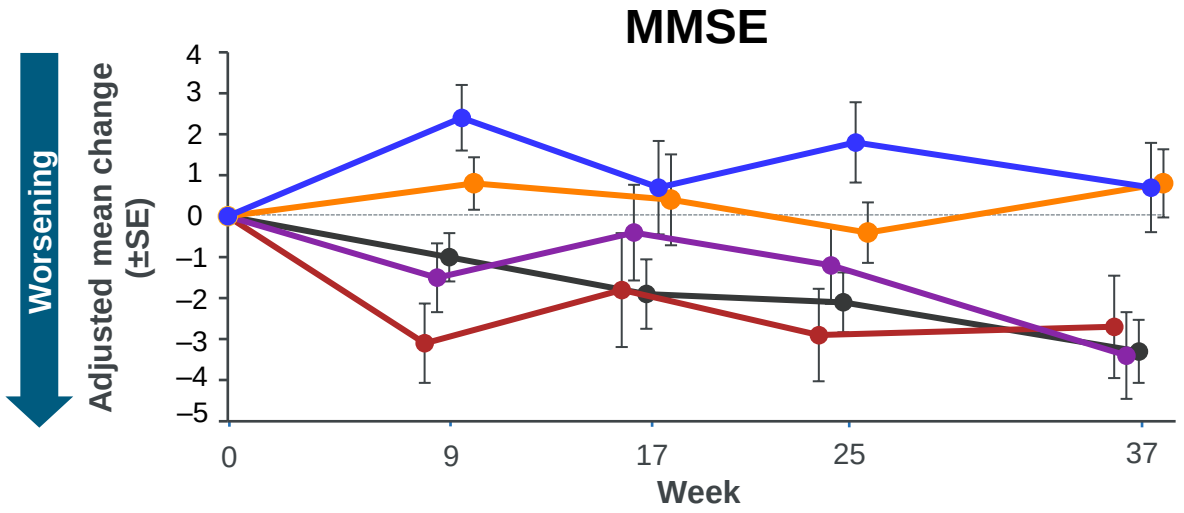
Differences seen in disease severity across dose groups

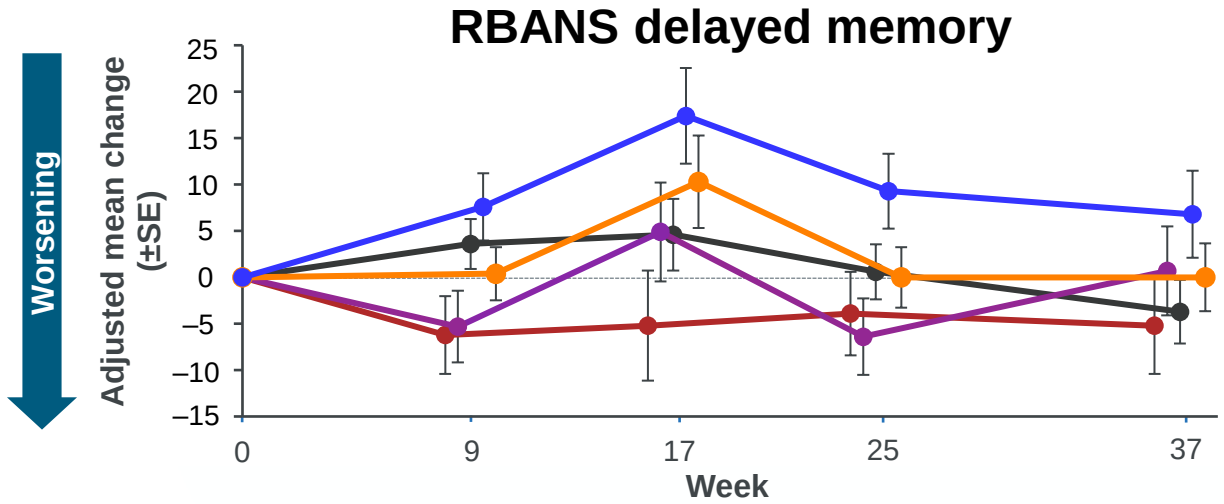
		Low dose		High dose	
	Pooled placebo (n=12)	**Cohort A 10 mg Q4W (n=6)**	**Cohort B 30 mg Q4W (n=6)**	**Cohort D 115 mg Q12W (n=13)**	**Cohort C 60 mg Q4W (n=9)**
Age, mean years ± SD	66 ± 4.6	64 ± 5.2	65 ± 6.1	67 ± 6.3	66 ± 6.8
Female, n, (%)	6 (50)	2 (33)	4 (67)	6 (46)	5 (56)
APOE4 carrier, n, (%)	8 (67)	5 (83)	3 (50)	11 (85)	6 (67)
CDR Global Score, n, (%)					
0.5	7 (58)	0 (0)	3 (50)	11 (85)	9 (100)
1	5 (42)	6 (100)	3 (50)	2 (15)	0 (0)
CDR Sum of Boxes, mean ± SD	**4.08 ± 1.28**	**4.75 ± 0.52**	**4.67 ± 1.03**	**3.35 ± 1.07**	**2.94 ± 0.58**
CDR Memory Box, n, (%)					
0.5	1 (8)	1 (17)	1 (17)	0 (0)	0 (0)
1	10 (83)	4 (67)	5 (83)	13 (100)	9 (100)
2	1 (8)	1 (17)	0 (0)	0 (0)	0 (0)
MMSE, mean ± SD	24.2 ± 1.7	21.5 ± 1.6	24.5 ± 1.4	23.2 ± 2.5	24.6 ± 2.5
FAQ, mean ± SD	8.3 ± 7.2	6.3 ± 3.5	14.5 ± 4.4	9.3 ± 5.1	5.6 ± 2.8
RBANS Delayed Memory, mean ± SD	54 ± 14.5	51.3 ± 16.7	63.5 ± 25.8	52.2 ± 14.2	51.1 ± 9.5

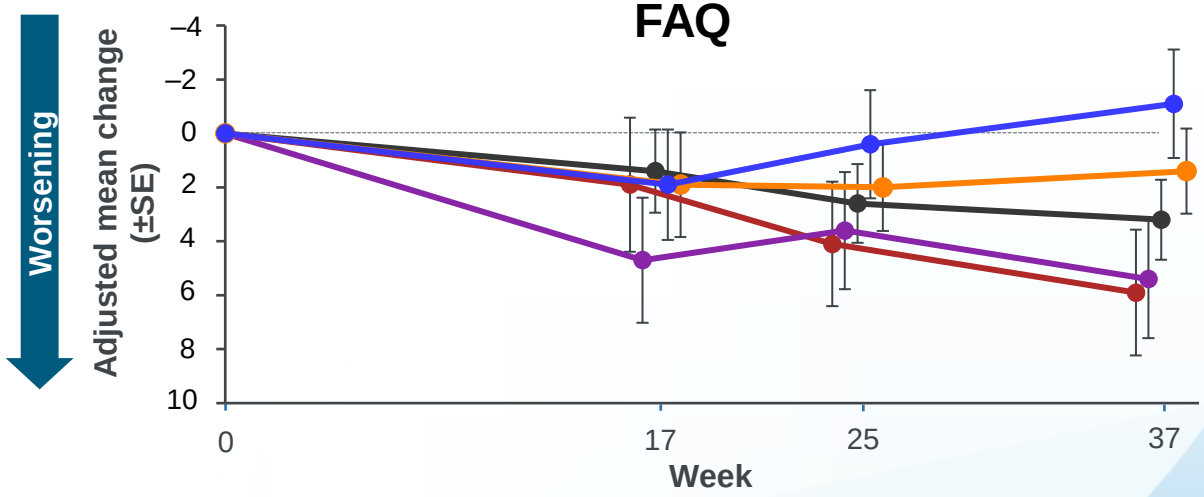
APOE4, apolipoprotein E4; CDR, Clinical Dementia Rating scale; FAQ, Functional Activities Questionnaire; MMSE, Mini Mental State Examination; RBANS, Repeatable Battery for the Assessment of Neuropsychological Status.

Longitudinal change in clinical outcomes from baseline in MAD

Mixed trends observed by dose groups







	Number of participants by study Week[a]				
Cohort	Week 0	Week 9	Week 17	Week 25	Week 37
Cohort A+B+C+D Placebo	12	12	11	10	11
Cohort A 10mg Q4W	6	6	6	6	6
Cohort B 30mg Q4W	6	6	6	6	6
Cohort C 60mg Q4W	9	9	9	8	8
Cohort D 115mg Q12W	13	13	8	12	12

Results at each visit were based on an ANCOVA model, fitted with change from baseline as dependent variable, and with treatment group, baseline value and baseline CDR global score as independent variables.
Error bars reflect standard error of the mean.
[a] Number of participants by study week based on MMSE. Small differences in N seen for RBANS. FAQ not collected at Week 9.

LTE analyses

Differential considerations for the High → High Groups and Low → High Switchers

	High → High Groups (Cohorts C & D)	Low → High Switchers (Cohorts A & B)
N	16	6
Dose regimen	High dose in MAD and LTE	Low dose in MAD, high dose in LTE
Gap between MAD and LTE	No gap	5–19 months
Analysis target	Change from **MAD baseline** to **Week 100**	Change from **LTE baseline** to **Week 64/72**
Baseline scores	**MAD baseline** for CDR-SB: 3.13	**LTE baseline** for CDR-SB: 4.92
External control comparator	**TANGO** (Gosuranemab Phase 2 study) was the optimal choice for external control • Contemporaneous study as BIIB080 Phase 1b thus similar diagnosis method and standard of care expected • Similar inclusion criteria as BIIB080 Phase 1b (amyloid positivity, age, CDR global score, MMSE) • Rigorous and extensive data collection in clinical trial setting **Propensity score matching (PSM)** was utilized to select matched external controls with similar characteristics as the High → High Group and Low → High Switcher, respectively	

High->High Groups include Cohort C 60mg Q4W->60mg Q12W & Cohort D 115mg Q12W->115mg Q12W; Low->High Switchers include Cohort A 10mg Q4W->60mg Q12W & Cohort B 30mg Q4W->60mg Q12W
Out of 33 participants who enrolled in LTE, 11 were not included in the analyses: 7 participants received placebo in MAD and switched to BIIB080 in LTE but did not have LTE baseline due to seamless transition; 4 participants did not have any clinical assessments collected at the end of LTE.
Week 64 analogous to Week 100. Week 72 was safety follow-up. Week 108 safety follow-up was not analyzed for High → High Groups due to only N of 1 from Cohort C and N of 2 from Cohort D available.

Baseline characteristics of High → High Groups vs TANGO PSM

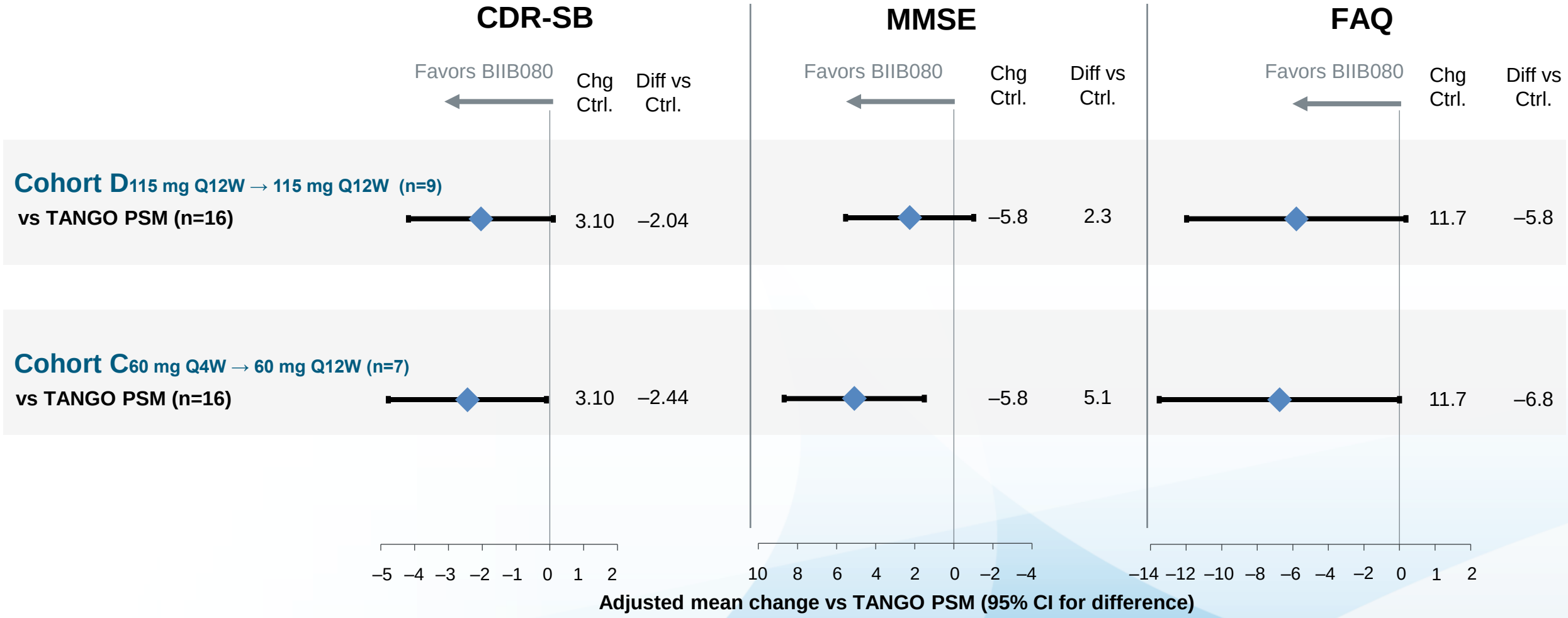
Well-matched between groups

	TANGO PSM[a]	High → High Groups (Cohorts C & D)
N	16	16
Age, years ± SD	65.4 ± 8.38	66.9 ± 7.34
Female, n, (%)	8 (50)	8 (50)
APOE4 carrier, n, (%)	12 (75)	12 (75)
CDR Global Score, n, (%)		
0.5	14 (87.5)	14 (87.5)
1	2 (12.5)	2 (12.5)
CDR-SB, mean ± SD	3.03 ± 1.19	3.13 ± 1.04
CDR Memory Box, n, (%)		
0.5	5 (31)	0 (0)
1	11 (69)	16 (100)
MMSE, mean ± SD	23.9 ± 2.5	23.9 ± 2.3
FAQ, mean ± SD	7.3 ± 6.3	6.9 ± 4.6

[a]TANGO PSM used 1:1 match and adjusted for 7 covariates: CDR-GS (exact match), CDR-SB, MMSE, FAQ, APOE, age, and sex.
APOE4, apolipoprotein E4; CDR, Clinical Dementia Rating scale; FAQ, Functional Activities Questionnaire; MMSE, Mini Mental State Examination; PSM, propensity score matching; RBANS, Repeatable Battery for the Assessment of Neuropsychological Status.

High → High Groups vs TANGO PSM at Week 100

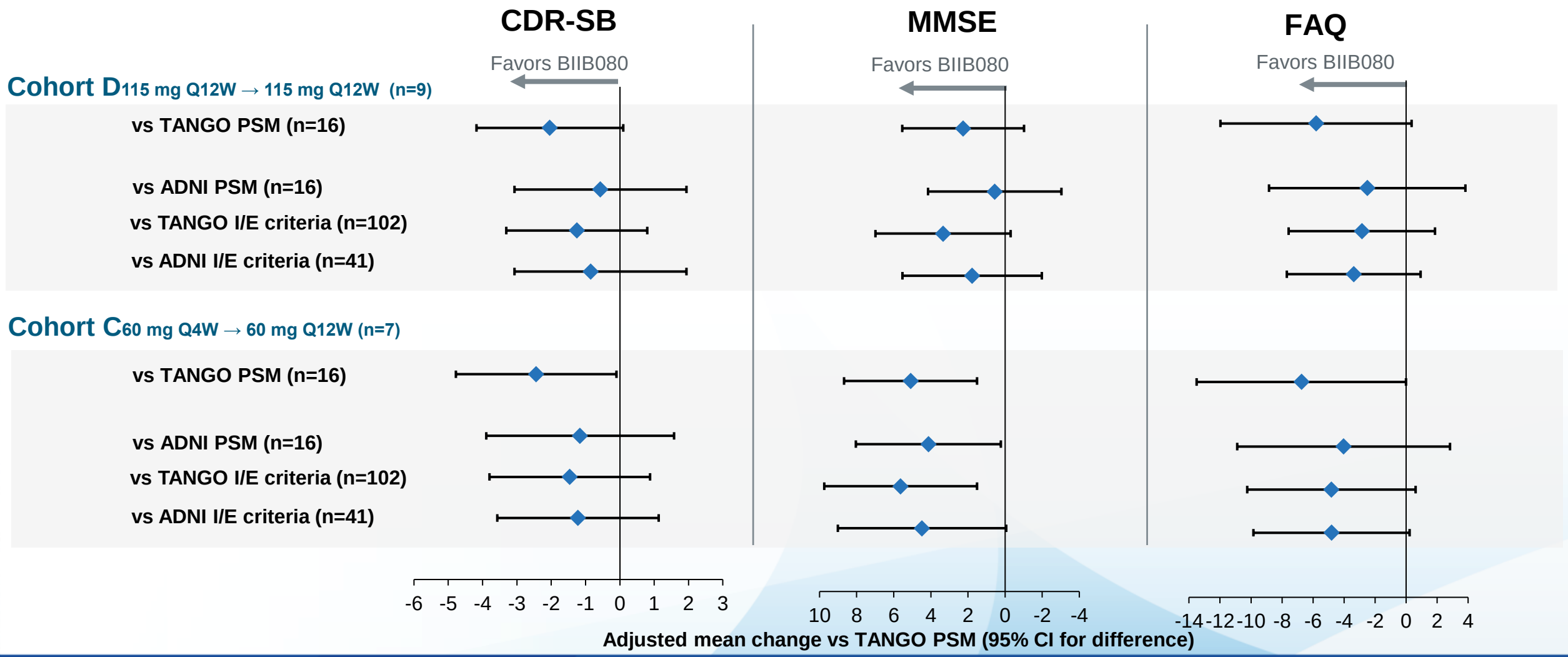
Group difference consistently trended in favor of BIIB080 for all clinical scales



TANGO PSM used 1:1 match and adjusted for 7 covariates: CDR-GS (exact match), CDR-SB, MMSE, FAQ, APOE, age, and sex. Results were based on an ANCOVA model, with treatment group, baseline value and baseline CDR global score as independent variables.
CI, confidence interval; PSM, propensity score matching.

Supplementary analyses of High → High Groups vs external controls at Week 100

Consistent trend in favor of BIIB080 across all analyses for all clinical scales



TANGO PSM used 1:1 match and adjusted for 7 covariates: CDR-GS (exact match), CDR-SB, MMSE, FAQ, APOE, age, and sex. ADNI PSM used 1:1 match and adjusted for 5 covariates: CDR-GS (exact match), CDR-SB, MMSE, FAQ, APOE. I/E criteria method selected participants by key inclusion criteria of BIIB080 Phase 1b study.
Results were based on an ANCOVA model, with treatment group, baseline value and baseline CDR global score as independent variables.
CI, confidence interval; PSM, propensity score matching.

LTE baseline characteristics of Low → High Switchers vs TANGO PSM

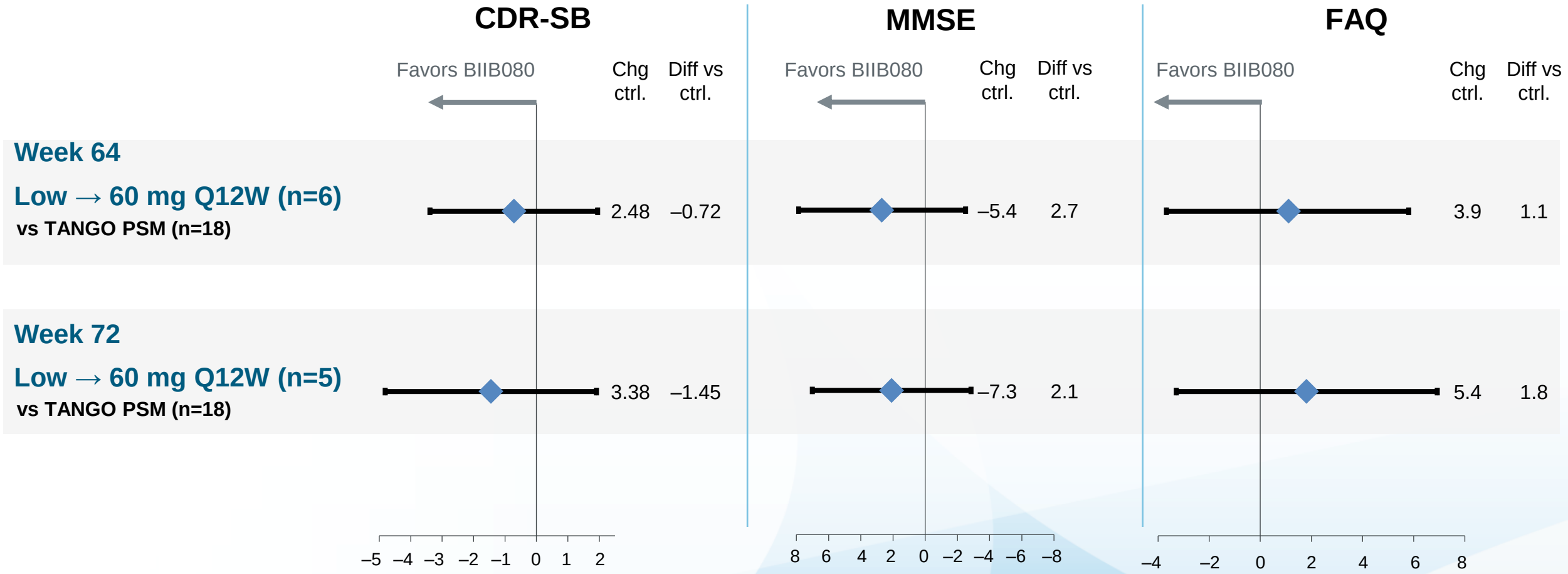
Less well-matched for age and clinical scales

	TANGO PSM[a]	Low → 60 mg Q12W (Cohorts A & B)
N	18	6
Age, years ± SD	70.8 ± 7.44	63.5 ± 5.82
Female, n, (%)	11 (61.1)	3 (50)
APOE4 Carrier, n, (%)	9 (50)	4 (66.7)
CDR Global Score, n, (%)		
0.5	3 (16.7)	1 (16.7)
1	15 (83.3)	5 (83.3)
CDR-SB, mean ± SD	4.86 ± 1.42	4.92 ± 0.97
CDR Memory Box, no. (%)		
0.5	1 (6)	1 (17)
1	16 (89)	4 (67)
2	1 (6)	1 (17)
MMSE, mean ± SD	22.3 ± 0.7	20.3 ± 2.7
FAQ, mean ± SD	14.1 ± 7.9	16.7 ± 4.3

[a]TANGO PSM used a 1:3 match and adjusted for 4 covariates: CDR-GS (exact match), CDR-SB, MMSE, and APOE.
PSM, propensity score matching.

Low → High Switchers vs TANGO PSM at Week 64/72 post-LTE baseline

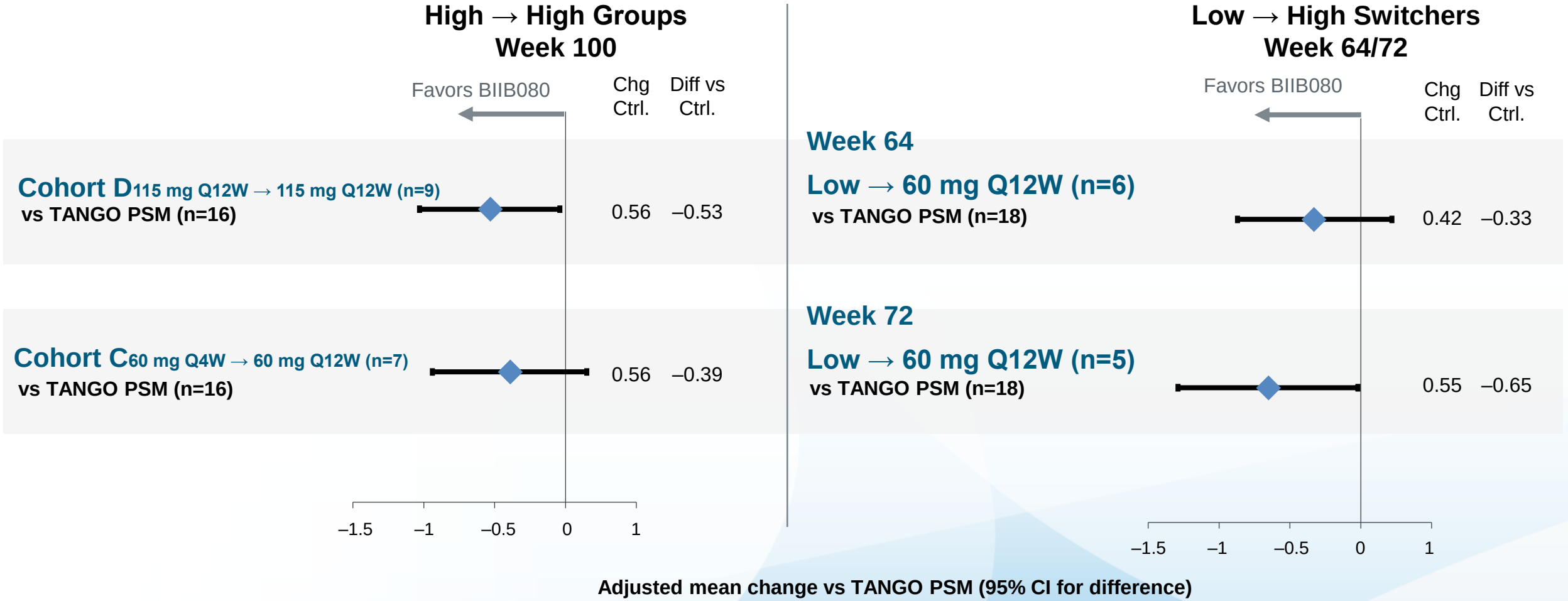
Mixed trend in group difference across clinical scales



TANGO PSM used a 1:3 match and adjusted for 4 covariates: CDR-GS (exact match), CDR-SB, MMSE and APOE. Results were based on an ANCOVA model, with treatment group, baseline value, and baseline CDR global score as independent variables.
PSM, propensity score matching. CI, confidence interval.

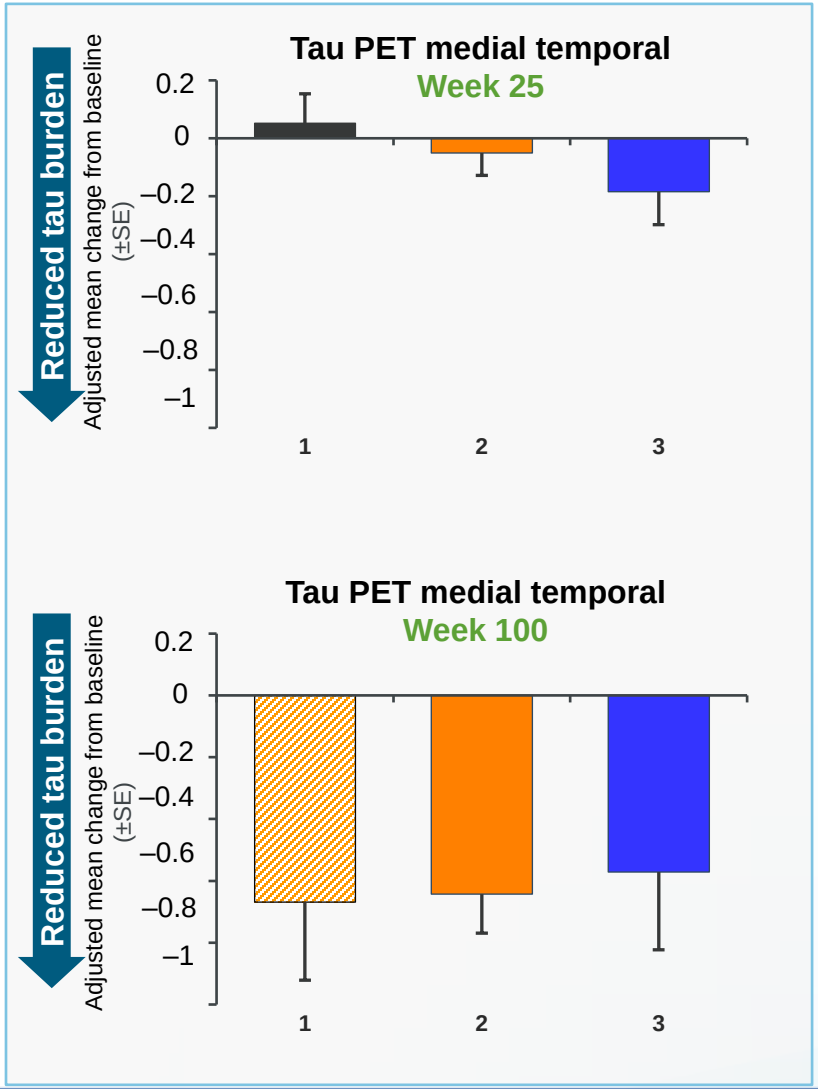
CDR Memory Box in LTE for High → High Groups and Low → High Switchers

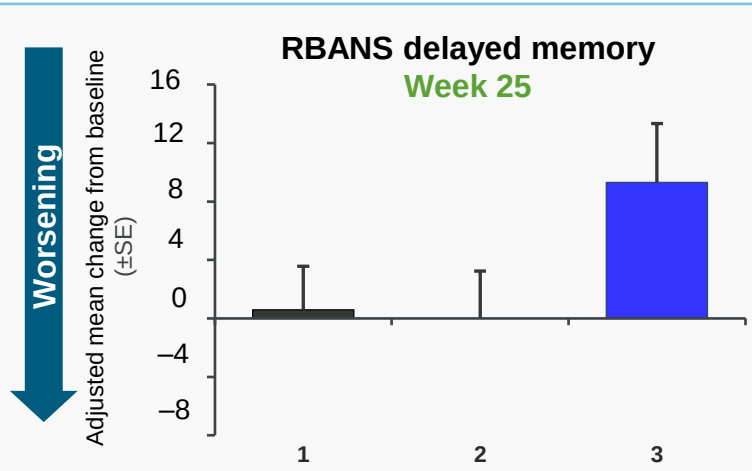
Consistent benefit across high-dose treated groups on CDR memory box

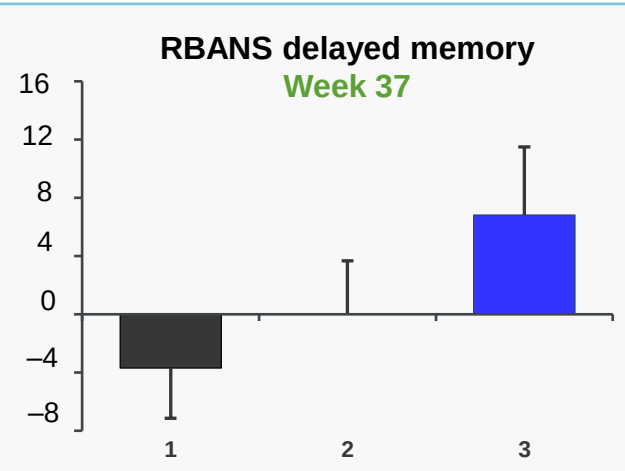


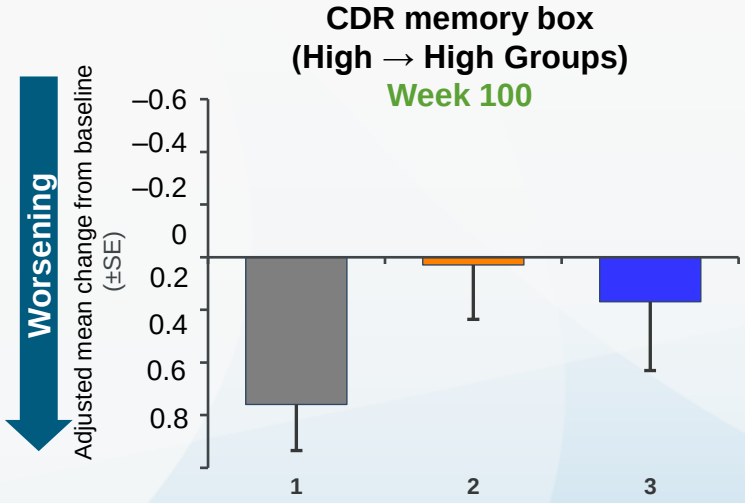
For High → High Groups, TANGO PSM used 1:1 match and adjusted for 7 covariates: CDR-GS (exact match), CDR-SB, MMSE, FAQ, APOE, age, and sex. For Low → High Switchers, TANGO PSM used 1:3 match and both adjusted for 4 covariates: CDR-GS (exact match), CDR-SB, MMSE, and APOE. Results were based on an ANCOVA model, with treatment group, baseline value, and baseline CDR global score as independent variables.
CI, confidence interval; PSM, propensity score matching.

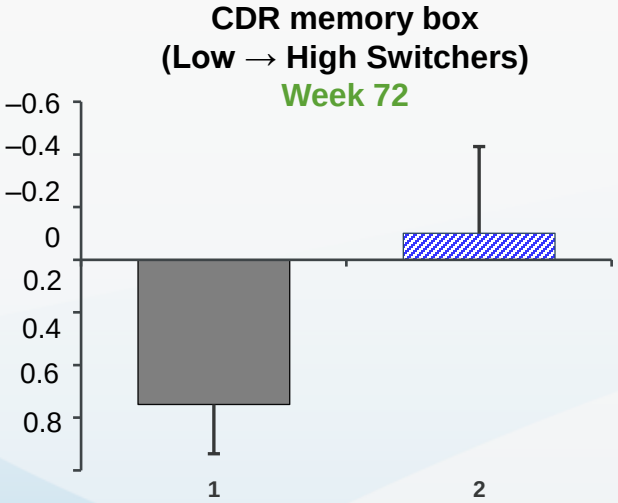
Favorable performance in memory scales mirrors changes in tau PET suggestive of a clinical-pathological link











Error bars reflect standard error of the mean.
PSM, Propensity score matching.

BIIB080 was generally well-tolerated by participants in the Phase 1b study in both MAD and LTE

- Adverse Events (AEs) occurred in 40 (95%) participants treated with BIIB080 and 9 (75%) participants treated with placebo
- Eight serious AEs were reported; none were assessed by the investigator to be related to study treatment or study procedure. No deaths were reported
- All treatment-emergent adverse events (TEAE) were reported as mild to moderate in severity, except 1 event of severe pain in lower extremity
- The most common TEAEs included headache, back pain, pain in extremity, post-lumbar puncture syndrome, and procedural pain
- TEAEs assessed as potentially related to lumbar puncture occurred in 32 (69.6%) participants in the MAD and 24 (72.7%) participants in the LTE

AE, adverse event; MAD, multiple ascending dose; LTE, long-term extension; TEAE, treatment-emergent adverse event.

Conclusions

- In phase 1b, BIIB080 was generally well-tolerated during both MAD and LTE
- Dose-dependent and sustained reduction in total and phosphorylated tau showed target engagement
- Reduction of parenchymal tau pathology as measured by PET was observed across all brain regions assessed
- Now we report a numerical difference favoring BIIB080 for high-dosed groups on multiple cognitive and functional scales at completion of the MAD and LTE
- Analyses should be considered as exploratory given the small sample sizes and use of external controls in LTE
- These data continue to support further investigation of the clinical efficacy and safety of BIIB080 in patients with MCI due to AD/mild AD in the CELIA Phase 2 trial

CSF, cerebrospinal fluid; MAD, multiple ascending dose; LTE, long-term extension; PET, positron emission tomography.