Baseline characteristics from CELIA: a Phase 2 study to evaluate BIIB080 in participants with early Alzheimer's disease

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Objective

- To describe the baseline characteristics of the Phase 2 CELIA trial (NCT05399888)[1], which is designed to evaluate the efficacy, safety, and tolerability of BIIB080 compared with placebo in patients with mild cognitive impairment (MCI) due to Alzheimer's disease (AD) or mild AD dementia.

Conclusions

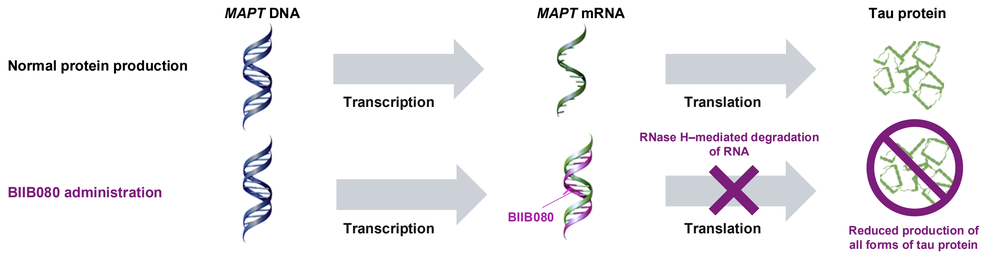
- CELIA baseline characteristics are consistent with early AD (MCI due to AD and mild AD dementia) and largely overlap with contemporaneous trials in a similar study population.

Introduction

Therapeutic hypothesis

- Amyloid plaques can be detectable within the brain many years before symptoms manifest[2]; whereas clinicopathologic studies have established that the density and distribution of tau neurofibrillary tangles are more closely associated with the severity of clinical impairment[3].
- BIIB080 is an antisense oligonucleotide that inhibits translation of microtubule-associated protein tau (*MAPT)* mRNAs into tau protein and is under investigation for the treatment of early AD (**Figure 1**).
- Lowering the production of all tau species may reduce post-translationally modified forms of tau, including aggregates, and is hypothesized to slow or halt disease progression.

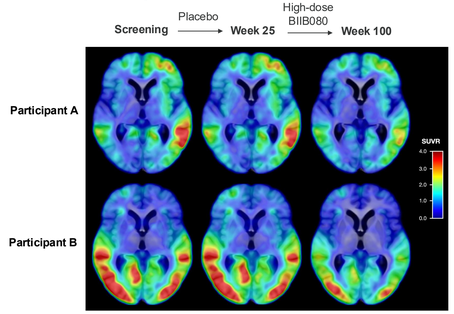
Figure 1. BIIB080 mechanism of action[a]



BIIB080 Phase 1b study

- The first part of the Phase 1b study, ISIS 814907-CS1 (NCT03186989)[4,5], was a randomized, double-blind, placebo-controlled, multiple ascending dose (MAD) period, with the primary goal to evaluate safety and tolerability of BIIB080 in patients with mild AD (N=46). The MAD treatment period was 13 weeks, followed by a 23-week follow-up period. The second part of the Phase 1b study consisted of a subsequent open-label, long-term extension (LTE) study (up to Week 100). Biomarkers and clinical outcomes were exploratory.
- BIIB080 was generally well tolerated in the MAD and LTE periods of the Phase 1b study[5].
- In the BIIB080 Phase 1b study, exploratory analyses revealed that:
  - Dose-dependent and sustained reduction in cerebrospinal fluid (CSF) total and phosphorylated tau 181 levels showed target engagement[6].
  - Reduction of parenchymal tau pathology measured by tau positron emission tomography (PET) was observed in high-dose groups across all brain regions assessed (data not shown).
  - Participants who initially received placebo showed reduced tau burden following BIIB080 administration in the LTE (**Figure 2**)[6].
  - Clinical outcomes showed a consistent trend of slowed decline on cognitive, functional, and global measures favoring BIIB080 high-dose groups at the end of both the MAD and LTE periods (see **Figure 3** for Clinical Dementia Rating [CDR] Box scores at Week 100)[7].
  - Phase 1b clinical outcome analyses should be considered exploratory given the small sample sizes and use of external controls in the LTE[7].
- Further details of the BIIB080 Phase 1b study can be found in references 5 and 6.

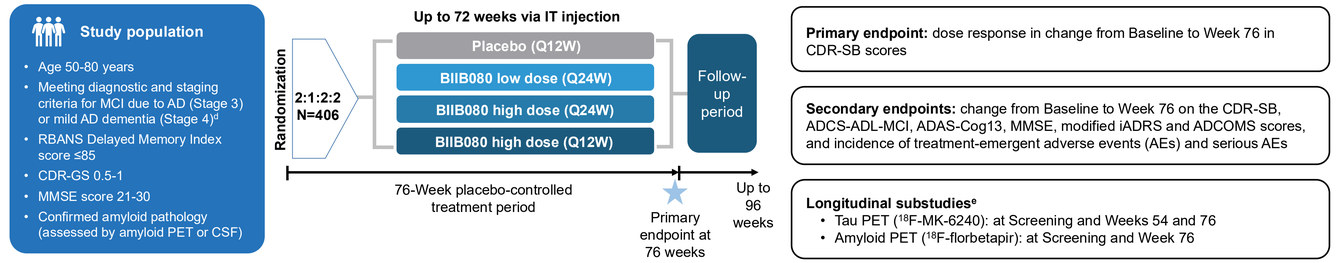
Figure 2. Tau PET SUVR from MAD Baseline to Week 100 in the Phase 1b study[6,b]



Methods

- The ongoing Phase 2 CELIA trial (Study 247AD201; NCT05399888)[1] aims to evaluate the efficacy, safety, and tolerability of BIIB080 in patients with MCI due to AD or mild AD dementia (**Figure 4**).

Figure 4. CELIA study design



Results

- A total of 416 participants were randomized in CELIA, and 406 participants were dosed; baseline demographic and clinical characteristics are shown in **Table 1**.
- Exploratory standardized uptake value ratio (SUVR) thresholds (defined as >2 SD from the mean)[f] were derived from an external ^{18}F-MK-6240 sample of elderly, cognitively unimpaired, amyloid-negative adults in Braak composite regions of interest (**Table 2**).
- All baseline CELIA tau PET scans aligned with Braak staging, which posits a sequential spread of tau through Braak regions.
- Only 9% of participants were tau negative, with a majority of participants having tau pathology that had spread to Braak stage V/VI.
- Baseline tau and amyloid PET distributions from CELIA are presented in **Figures 5** and **6** and are consistent with contemporaneous trials in early AD[10,11].

Table 1. CELIA baseline demographic and clinical characteristics

	Total (N=406)
Age, mean years ± SD	68.3 ± 7.3
Female, n (%)	208 (51.2)
***APOE4* carrier, n (%)**	278 (68.5)
MCI and mild AD, n (%)	**244/162 (=60/40)**
CDR-GS, n (%)	
0.5	347 (85.5)
1	59 (14.5)
CDR-SB, mean ± SD	**3.12 ± 1.5**
CDR Memory Box, n (%)	
0.5	186 (45.8)
1	208 (51.2)
2	12 (3.0)
ADCS-ADL-MCI, mean ± SD	41.5 ± 6.1
ADAS-Cog13, mean ± SD	25.0 ± 7.2
RBANS Delayed Memory, mean ± SD	56.8 ± 13.5
MMSE, mean ± SD	24.7 ± 3.0

Table 2. Tau PET Braak staging in CELIA using quantitative thresholds

Tau PET stage	Brain regional positivity: Braak I/II composite	Braak III/IV composite	Braak V/VI composite	N (%)
Tau negative	Negative	Negative	Negative	**11 (9)**
Braak stage I/II	Positive	Negative	Negative	**15 (12)**
Braak stage III/IV	Positive	Positive	Negative	**32 (25)**
Braak stage V/VI	Positive	Positive	Positive	**69 (54)**

Figure 3. Exploratory clinical outcomes: CDR Box scores of high→high dose groups versus matched external controls at Week 100 in the Phase 1b study[c]

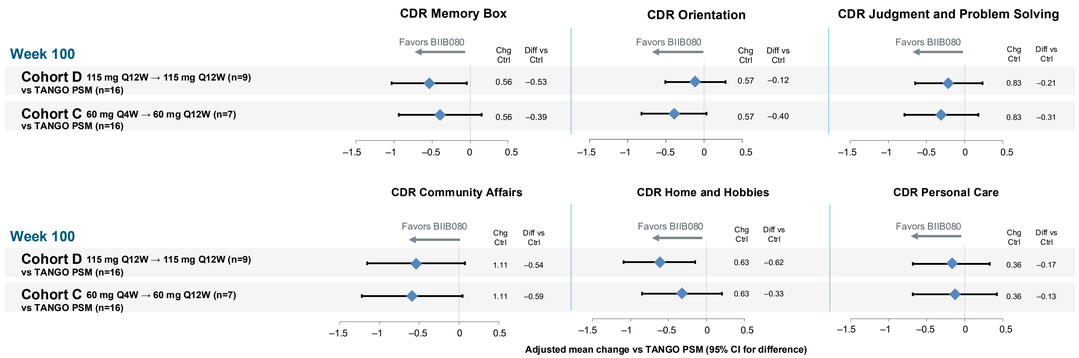


Figure 5. CELIA baseline tau PET distributions in whole-brain grey matter and Braak composite regions

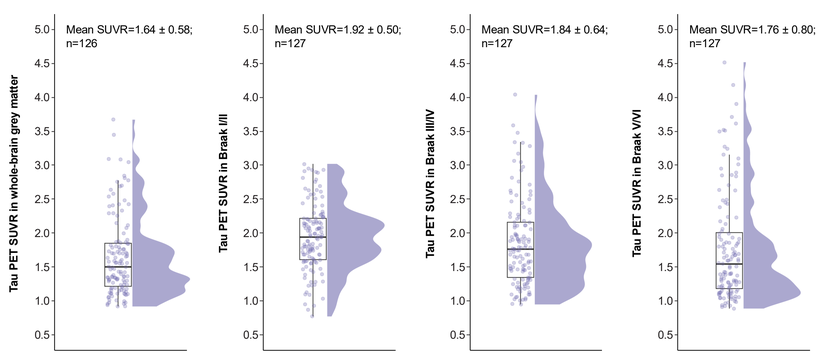
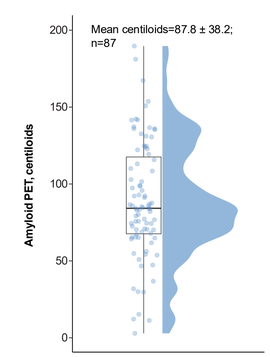


Figure 6. CELIA baseline amyloid PET distributions



Abbreviations AD, Alzheimer's disease; ADAS-Cog13, AD Assessment Scale Cognitive Subscale; ADCOMS, AD Composite Score; ADCS-ADL-MCI, AD Cooperative Study–Activities of Daily Living Scale for use in Mild Cognitive Impairment; AE, adverse event; APOE, apolipoprotein E; CDR-GS; Clinical Dementia Rating global score; CDR-SB, CDR Scale Sum of Boxes; Chg, change; CSF, cerebrospinal fluid; Ctrl, control; Diff, difference; iADRS, Integrated AD Rating Scale; IT, intrathecal; LTE, long-term extension; MAD, multiple ascending dose; MAPT, microtubule associated protein tau gene; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; mRNA, messenger RNA; PET, positron emission tomography; PSM, propensity score matching; Q4W, once every 4 weeks; Q12W, once every 12 weeks; Q24W, once every 24 weeks; RBANS, Repeatable Battery for the Assessment of Neuropsychological Status; RNase H, ribonuclease H; SD, standard deviation; SUVR, standardized uptake value ratio. [a] Figure adapted from Goldberg A, et al., *J Clin Lipidol*. 2010;4:350-356. [b] High-dose BIIB080 indicates a 115-mg dose given to participants Q12W (or a 60-mg dose given Q4W; data not shown). There were only 2 participants in the placebo group who then received a 115-mg dose of BIIB080 Q12W to Week 100. [c] Participants in the high→high groups in the Phase 1b study received high-dose BIIB080 throughout the MAD and the LTE periods and had evaluable clinical data at both MAD Baseline and Week 100. TANGO, a Phase 2 anti–N-terminal tau monoclonal antibody clinical trial, was selected as a contemporaneous study with similar population characteristics as the BIIB080 Phase 1b study. BIIB080-treated groups were compared with TANGO participants who were selected with PSM. [d] According to the NIA-AA[2,3] The tau PET substudy is being conducted in a subset of participants and is mandatory for study sites that can be supplied with ^{18}F-MK-6240 PET radioligand and have the capability to perform ^{18}F-MK-6240 PET scans. Tau PET scans are performed in participants who meet all eligibility criteria and have provided full informed consent. The baseline tau PET scan occurred after confirmation of amyloid positivity but prior to the first IT injection of study treatment. The tau PET substudy was conducted in Japan, the US, Canada, Switzerland, Australia and the UK. The amyloid PET substudy was conducted in Japan and the US. [e] Braak I/II SUVR composite cutoff: >1.29, Braak III/IV SUVR composite cutoff: >1.40, Braak V/VI SUVR composite cutoff: >1.40. [f] Exploratory standardized uptake value ratio (SUVR) thresholds (defined as >2 SD from the mean) were derived from an external ^{18}F-MK-6240 sample of elderly, cognitively unimpaired, amyloid-negative adults in Braak composite regions of interest (Table 2).

References 1. ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT05399888. Accessed April 17, 2025. 2. Selkoe DJ, Hardy J. *EMBO Mol Med*. 2016;8(6):595-608. 3. Bejanin A, et al. *Brain*. 2017;140(12):3286-3300. 4. ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT03186989. Accessed April 17, 2025. 5. Mummery CJ, et al. *Nat Med*. 2023;29(6):1437-1447. 6. Edwards AL, et al. *JAMA Neurol*. 2023;80(12):1344-1352. 7. Dogan N, et al. Data presented at CTAD 2023. 8. Jack Jr CR, et al. *Alzheimers Dement*. 2018;14:535-562. 9. US Food and Drug Administration. https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM596728.pdf. Accessed April 17, 2025. 10. Sims JR, et al. *JAMA*. 2023;330(6):512-527. 11. Chanil A, et al. Data presented at AD/PD 2024.

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