PLASMA Aβ42/40 RATIO TRACKS WITH CHANGES IN BRAIN AMYLOID PET SUVR IN THE CORE AND OPEN LABEL EXTENSION OF THE PHASE 2 PROOF-OF-CONCEPT STUDY BAN2401-G000-201 FOLLOWING TREATMENT WITH LECANEMAB IN SUBJECTS WITH EARLY ALZHEIMER'S DISEASE

Chad J. Swanson,[1] Michio Kanekiyo,[1] June Kaplow,[1] Shobha Dhadda,[1] Michael Irizarry,[1] Akihiko Koyama,[1] David Li,[1] David Verbel,[1] Robert Gordon,[2] Helena Heanue-Travers,[2] Mark Hodgkinson,[2] and Lynn D. Kramer[1]

1. Eisai Inc., Woodcliff Lake, NJ, USA. 2. Eisai Ltd., Hatfield, United Kingdom

Introduction

- Lecanemab (BAN2401) is a humanized IgG1 monoclonal antibody that preferentially targets soluble aggregated Aβ species (oligomers, protofibrils) and insoluble fibrils[1-5]
- Lecanemab reduced the amyloid PET standard uptake value ratio (SUVr) and slowed clinical decline in an 18-month phase 2 proof-of-concept study in early Alzheimer's disease[6-7]
- An open label extension (OLE) with 10 mg/kg IV bi-weekly lecanemab dosing was implemented after analysis of the Core Study, with an intervening Gap Period off-treatment ranging from 9-59 months (mean 24 months)
- The present study aimed to evaluate longitudinal plasma Aβ42/40 ratio (C2N PrecivityAD assay) and the relationship to longitudinal amyloid PET in the Core Study, Gap Period, and OLE, focusing on:
  - Correlations between amyloid PET SUVr, clinical cognition endpoints, and fluid biomarkers (Aβ42/40 ratio) from C2N Precivity assay following treatment with lecanemab
  - Additional evidence that continued dosing is advantageous to maintaining effects of lecanemab treatment

Methods

- The methods and results from the Core Study have been previously published[6-7]
- Briefly, the Core Study was an 18-month multinational, multicenter, double-blind, placebo-controlled study, using a Bayesian design with response adaptive randomization (RAR) across placebo or 5 active arms of lecanemab to explore the dose response of lecanemab at 12 months using ADCOMS
- The OLE was initiated following the Core Study to allow subjects to receive open-label lecanemab 10mg/kg bi-weekly for up to 60 months (5 years)
- Any subject who completed Core Study treatment and fulfilled the OLE inclusion and exclusion criteria had the option to participate
- Subjects who discontinued the Core Study were also eligible to participate in the OLE, provided they met the inclusion and exclusion criteria for the OLE
- The amyloid PET sub-study assessed baseline, 12 and 18 months SUVr with florbetapir, and participants in the OLE amyloid PET sub-study were imaged at baseline, 3 or 6 months, and 12 months
- Plasma samples were collected at the same timepoints and analyzed as described previously[8] and plasma Aβ42/40 were determined by C2N Precivity assay
- Mean changes from Core or OLE baseline were calculated. Pearson correlation coefficients were calculated at the group and individual levels for amyloid PET SUVr and plasma Aβ42/40 ratio, accounting for repeated measures
- These analyses include only subjects that enrolled in the OLE who reached OLE 12 months and had a minimum of core baseline assessments

Results

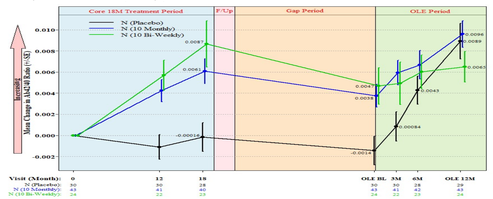
Table 1. Subjects

	Core Placebo	Core 10 mg/kg monthly	Core 10 mg/kg bi-weekly	Total
Plasma biomarker analysis set*	30	43	24	97
Plasma biomarker analysis set (excluding severe subjects**) – Used in analyses with clinical endpoints	25	31	18	74
PET sub study with plasma biomarker	8	13	5	26
PET sub study (excluding severe subjects) – Used in analyses with clinical endpoints	9	10	4	23

*Plasma Biomarker Analysis Set: Defined as the group of subjects with plasma Aβ42/40 ratio at core baseline and at least 1 post core baseline assessment
**Severe subjects are subjects with global CDR>1 at OLE baseline

- A summary of subjects included in the analysis are included in **Table 1**
- The mean changes in Aβ42/40 ratio by core treatment group for the Core, Gap Period, and OLE are shown in **Figure 1**
  - In the Core, plasma Aβ42/40 ratio increases in 10 mg/kg bi-weekly and 10 mg/kg monthly during Core Study with no change in placebo
  - In the Gap Period, plasma Aβ42/40 ratio slightly decreases in all three groups
  - In the OLE, plasma Aβ42/40 ratio increases in all three groups during OLE, who receive 10 mg/kg bi-weekly in the OLE

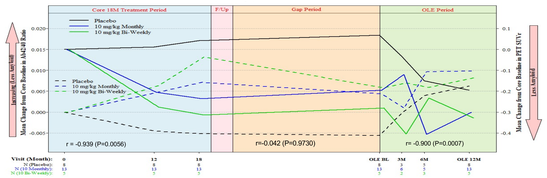
Figure 1. Observed Mean Change in Aβ42/40 Ratio by Core Treatment Group in the Core, Gap, and OLE



Analysis population: All subjects with plasma Aβ42/40 ratio at Core baseline and at least one post-baseline visit

- Longitudinal changes in amyloid assessed by PET SUVr are mirrored by (inverse) changes in Aβ42/40 ratio for all three Core treatment groups (placebo, 10 monthly, 10 bi-weekly) across Core, Gap, and OLE (**Figure 2**)
- Aβ42/40 ratio correlates with PET SUVr and clinical outcomes during lecanemab treatment phases in Core & OLE while losing correlation in untreated GAP period

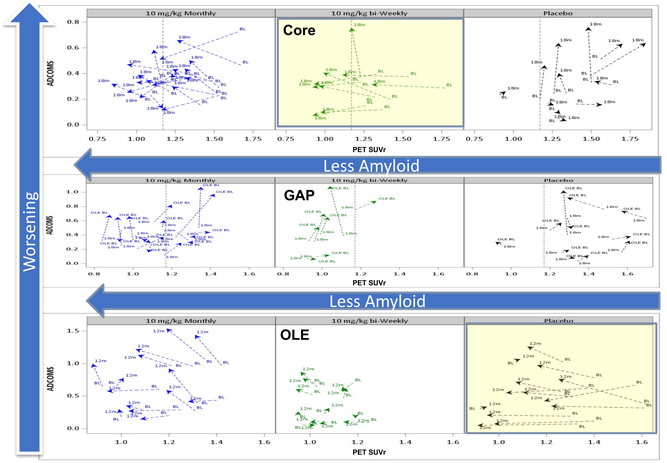
Figure 2. Observed Mean Change in Aβ42/40 Ratio PET SUVr by Core Treatment Group in the Core, Gap, and OLE



Analysis population: All subjects with both plasma Aβ 42/40 ratio and PET SUVr (by Florbetapir) in Core and OLE
r is population level Pearson correlation coefficient

- Change in PET SUVr correlation at a group level with change in ADCOMS during Core is r=0.790 (p=0.0614). The correlation is not significant during Gap (r=0.663, p=0.5385) & OLE (r = -0.154, p=0.7706), during which all groups are receiving no treatment (Gap) or 10 mg/kg IV (OLE)
- Change in PET SUVr correlation at a group level with change in CDR-SB during Core is r=0.936, (p=0.0060). The correlation is not significant during Gap (r=0.435, p=0.7137) & OLE (r = -0.195, p=0.7114).
- Change in PET SUVr correlation at a group level with change in ADAS-Cog during Core is r=0.590 (p=0.2177). The correlation is not significant during Gap (r=0.958, p=0.1843) & OLE (r = 0.118, p=0.8237)
- The pattern of individual patient level changes with 10 mg/kg biweekly treatment in the Core is similar to that of subjects newly started on 10 mg/kg biweekly in the OLE (Figure 3): generally greater reductions of PET SUVr with slower progression on ADCOMS

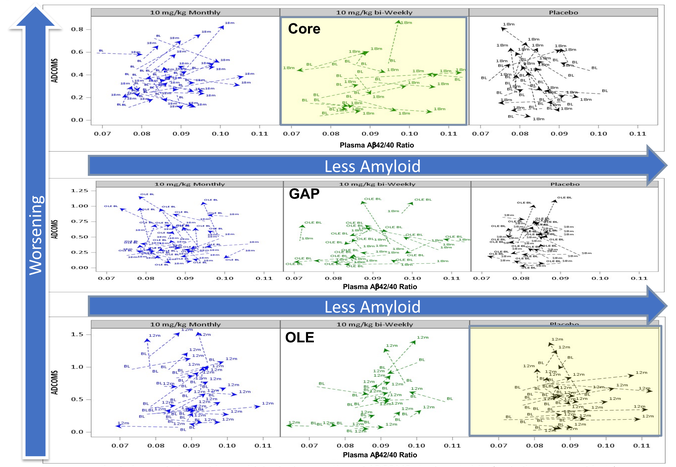
Figure 3. Data Correlation of PET SUVr with ADCOMS During Core, Gap, & OLE



Analysis population: subjects with both PET SUVr (by Florbetapir) and ADCOMS at relevant visits (excluding severe subjects)

- Change in plasma Aβ42/40 ratio inverse correlation at a group level with change in ADCOMS during Core is r= -0.672 (p=0.1435). The correlation is not significant during Gap (r=0.054, p=0.9654) & OLE (r=-0.005, p=0.9919)
- Change in plasma Aβ42/40 ratio inverse correlation at a group level with change in CDR-SB during Core is r = -0.745 (p=0.0894). The correlation between them is not significant during Gap (r=-0.190, p=0.8782) & OLE (r=0.174, p=0.7420)
- Change in plasma Aβ42/40 ratio inverse correlation at a group level with change in ADAS-cog during Core is r = -0.482 (p=0.3330). The correlation between them is not significant during Gap (r=0.558, p=0.6232) & OLE (r=0.243, p=0.6432)
- The pattern of individual patient level changes with 10 mg/kg biweekly treatment in the Core is similar to that of subjects newly started on 10 mg/kg biweekly in the OLE (Figure 4): generally greater increases of Aβ42/40 ratio with slower progression on ADCOMS

Figure 4. Data Correlation of Aβ42/40 Ratio with ADCOMS During Core, Gap, & OLE



Analysis population: subjects with both plasma ratio and ADCOMS at relevant visits (excluding severe subjects)

Conclusions

- **Plasma Aβ42/40 ratio shows dose-dependent increase in Core over 18 months of lecanemab treatment. Plasma Aβ42/40 ratio demonstrates relationship to lecanemab treatment**
- **Plasma Aβ42/40 ratio and PET SUVr changes track for all doses across Core, Gap, and OLE, at both group and individual levels. Longitudinal changes in amyloid assessed by PET SUVr are mirrored by (inverse) changes in Aβ42/40 ratio for all three Core treatment groups across Core, Gap, and OLE**
- **These data show correlations between amyloid PET SUVr, clinical cognition endpoints, and fluid biomarkers (Aβ42/40 ratio) following treatment with lecanemab**
- **These data provide evidence that continued dosing is advantageous to maintaining effects of lecanemab treatment**
- **These results suggest potential to use plasma Aβ42/40 ratio to monitor for drug effects in individual subjects/patients and will be verified in lecanemab pivotal studies, Clarity AD & AHEAD 3-45**

See Related Presentation: Swanson et al. 2021 AAIC
Hybrid Oral Session #57780 (4-HO-10)
Thursday, July 29, 2021: 1:00 PM – 2:15 PM

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References
1.Tucker S, et al. J Alzheimers Dis. 2015;43(2):575-88. 2. Lord A, et al. *Neurobiol Dis*. 2009;36:425–34. 3. Sehlin D, et al. *PLoS One*. 2012;7:e32014. 4. Sehlin D, et al. *Neurodegener Dis*. 2011;8:117–23. 5. Logovinsky V, et al. *Alzheimer's Research & Therapy*. 2016;8:14. 6. Satlin A, et al. *Alzheimers Dement (N Y)*. 2016;1:1-12. 7. Swanson CJ, et al. Alzheimers Res Ther. 2021 Apr 17;13(1):80. 8. West et al, Mol Neurodegen 2021.

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