SUBCUTANEOUS DOSE SELECTION OF LECANEMAB FOR TREATMENT OF SUBJECTS WITH EARLY ALZHEIMER'S DISEASE

Seiichi Hayato[1], Sumit Rawal[2], Osamu Takenaka[1], Ishani Landry[2], Peter Boyd[3], Jagadeesh Aluri[2], Brian Willis[2], Chad J Swanson[2], Sanae Yasuda[2], Ziad Hussein[3], and Larisa Reyderman[2]

1. Eisai Co., Ltd., Tokyo, Japan, 2. Eisai Inc, Nutley, NJ, USA, 3. Eisai Ltd., Hatfield, United Kingdom.

Introduction

- Lecanemab (BAN2401), a humanized IgG1 monoclonal antibody, preferentially targets soluble aggregated Aβ species (protofibrils) with activity at insoluble fibrils[1-5]
- An 18-month phase 2 proof-of-concept study (BAN2401-G000-201, NCT01767311) using Bayesian adaptive design was conducted in 856 patients with early Alzheimer's disease (EAD): mild cognitive impairment (MCI) due to AD or mild AD dementia[6-7]
- Lecanemab 10 mg/kg intravenous (IV) biweekly dose is being evaluated in the Clarity AD Phase 3 study in EAD
- A phase 1 study was conducted to assess the absolute bioavailability (BA) of subcutaneous (SC) administration relative to IV infusion[8]
  - After SC dosing, the maximum concentration (C_{max}) was observed 72 hours post dose and was 4-fold lower compared to IV infusion
  - This reflects the relatively long absorption phase following SC dose administration compared with 1-hour IV infusion
- In this analysis, modeling and simulation was conducted to compare a fixed weekly SC dose to body weight-based 10 mg/kg IV bi-weekly dose with regard to lecanemab exposure, safety, and efficacy

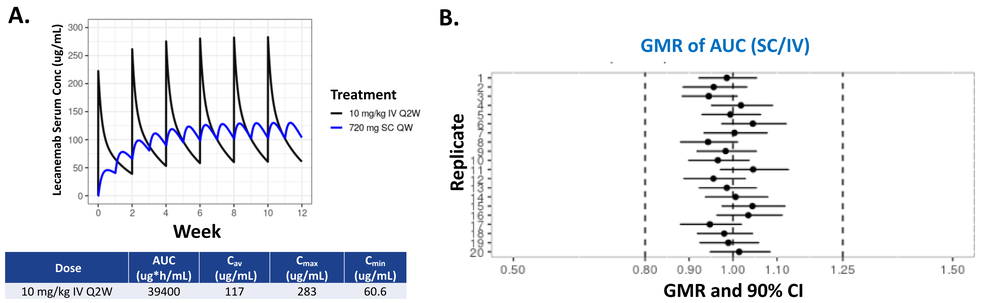
Methods

- Based on estimates of BA (49.7%) and absorption rate constant (0.0146/h) from phase 1 and the population pharmacokinetic (PK) model for EAD patients describing lecanemab PK after IV infusion,[9] estimates of the area under the concentration-time curve (AUC) and $C_{max,ss}$ at steady-state were generated for the proposed fixed SC dose and 10 mg/kg IV bi-weekly
- Simulations were conducted to compare positron emission tomography (PET) standard uptake ratio (SUVr) as a measure of pharmacodynamic effect, and incidence of amyloid related imaging abnormality-E (ARIA-E) as a measure of safety between SC and IV doses, based on the exposure-response models for EAD patients developed from phase 2 data after IV infusion[9, 10]
- The impact of body weight on the lecanemab exposure, reduction in amyloid PET SUVr and ARIA-E risk when administered as a fixed SC dose and body weight-based IV dose were explored

Results

- Phase 1 data support a proposed fixed lecanemab SC dose of 720 mg administered weekly (720W); PK simulations demonstrate that both AUC and average concentration (C_{av}) at steady state of SC 720W are predicted to be similar to 10 mg/kg IV bi-weekly, whereas $C_{max,ss}$ is predicted to be lower following SC administration (Figure 1A)
  - AUC_{ss} ratio is higher than 1.25 for subjects with low body weight (5th percentile) and slightly lower than 0.8 for subjects with high body weight (95th percentile; Figure 2B)

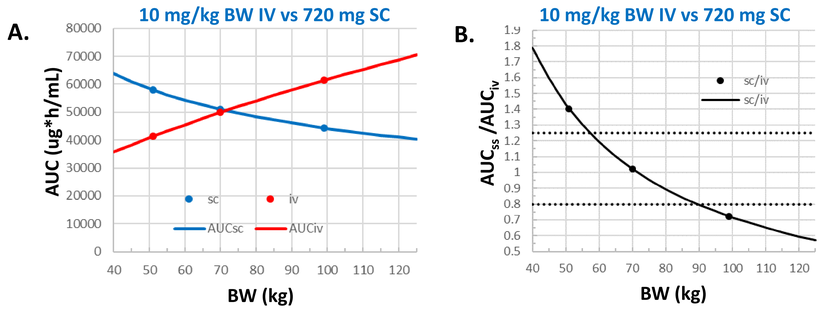
Figure 1. Comparability. (A) PK comparability of SC dose (mg) to IV dose (mg/kg) Following Multiple Dose Administration and (B) Geometric Mean Ratios (GMR) of Simulated AUC at Steady State



Dose	AUC (ug*h/mL)	C_{av} (ug/mL)	C_{max} (ug/mL)	C_{min} (ug/mL)
10 mg/kg IV Q2W	39400	117	283	60.6
720 mg SC QW (2 x 1.8mL)	40300	120	130	103
Ratio SC/IV	1.02	1.02	0.460	1.70

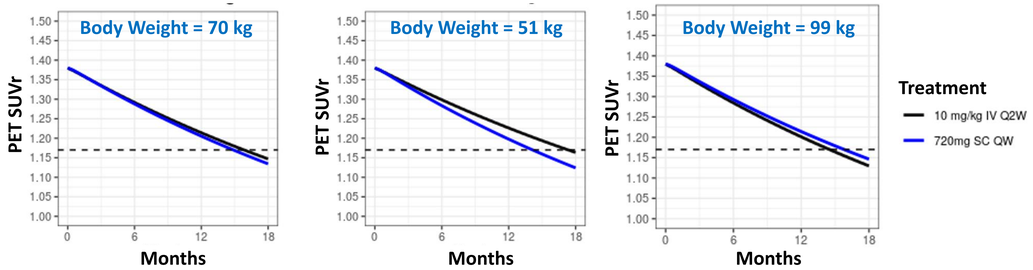
- Lecanemab exposure differences between a fixed 720 mg SC dose and body weight-based IV dose were observed at the extremes of body weight (Figure 2)
- For majority of subjects (57-90kg) exposures are comparable as demonstrated by AUC ratio (SC/IV) within 0.8-1.25.

Figure 2. Effect of Body Weight on Model-Predicted Lecanemab Exposure ([A] AUC and [B] AUC_{ss}/AUC_{iv}) Following Fixed SC Dose (720mg Weekly) and Body-Weight Based IV Dose (10mg/kg Bi-Weekly)



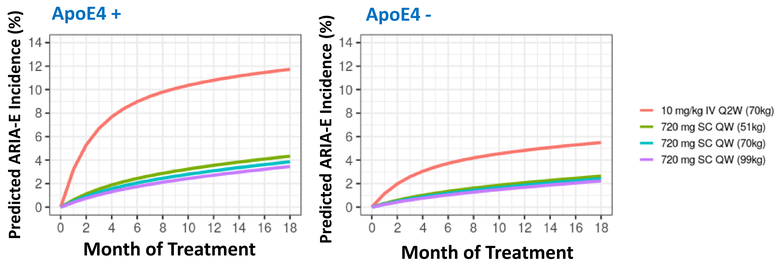
- Simulations using an established PK/PD model for PET SUVr demonstrated comparable reduction in SUVr following a SC 720 mg weekly dose and 10 mg/kg IV BW dose for a typical 70 kg subject (Figure 3)
- Small differences observed at high (95th percentile) or low (5th percentile) body weight would not have a meaningful effect on lecanemab efficacy as defined by PET SUVr

Figure 3. Model-Predicted Effect of Body Weight on PET SUVr Reduction Following Fixed SC Dose (720 mg weekly) and Body-Weight Based IV Dose (10 mg/kg Bi-Weekly)



- Probability of experiencing ARIA-E following SC weekly administration is predicted to be lower than following IV biweekly administration and minimally affected by body weight (Figure 4).
- Exposure-Response model is based on the established correlation between ARIA-E and C_{max}.[10] At steady-state a lower C_{max} following SC 720 mg QW is expected to be associated with a lower risk of ARIA-E compared to lecanemab 10 mg/kg IV bi-weekly

Figure 4. Model-Predicted Probability of ARIA-E Incidence Following Fixed SC Dose (720 mg weekly) and Body-Weight Based IV Dose (10 mg/kg Bi-Weekly) in Subjects with EAD by APOE4 Status and Body Weight



Conclusions

- This analysis demonstrates that fixed lecanemab SC dose of 720 mg administered weekly results in comparable exposure (AUC) and efficacy as measured by reduction in amyloid PET SUVr to 10mg/kg IV dose administered bi-weekly
- SC lecanemab dose is predicted to have a lower incidence of ARIA-E compared to IV lecanemab due to lower C_{max} following SC administration

Acknowledgments

We thank the subjects and the sites who participated in this study. Editorial support, funded by Eisai Inc, was provided by Mayville Medical Communications. Funding for the studies and analyses was provided by Eisai Inc. and Biogen Inc.

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. Rawal et al. Presented at the 2022 AAIC Annual Meeting. July 31-Aug 4, 2022. Poster #69438. 9. Hayato et al. Presented at Population Approach Group Europe (PAGE 2022), June 28 – July 1, 2022. 10. Hussein et al. Presented at the 2019 ADPD Annual Meeting. March 26-31, 2019.

If you have any questions about this poster, please email or call Eisai Medical Information at ESI_Medinfo@eisai.com or 888-274-2378