ABSOLUTE BIOAVAILABILITY OF A SINGLE, FIXED SUBCUTANEOUS DOSE OF LECANEMAB IN HEALTHY SUBJECTS

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Introduction

- Lecanemab is a humanized IgG1 monoclonal antibody that preferentially targets soluble aggregated Aβ species (protofibrils) with activity at insoluble fibrils[1-5]
- A large, 18-month phase 2 proof of concept study (BAN2401-G000-201, NCT01767311) using Bayesian adaptive design was recently conducted in 856 patients with early Alzheimer's disease (AD): mild cognitive impairment (MCI) due to AD or mild AD dementia[6-7]
- A subcutaneous (SC) formulation is in development as an alternative to body weight-based intravenous (IV) infusion
- The present study evaluated the absolute bioavailability (BA), pharmacokinetics (PK), safety and immunogenicity of lecanemab following a single fixed 700 mg SC dose

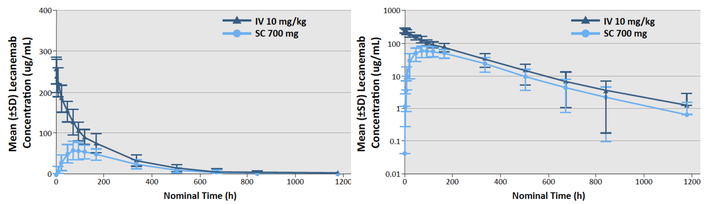
Methods

- This was an open-label, parallel-group study conducted in healthy subjects that were randomized into IV or SC dose group; 5 Japanese subjects were randomized to the SC dose group
- Serum samples for determination of lecanemab PK parameters were collected after single dose of 10 mg/kg IV infused over approximately 1 hour or fixed 700 mg SC injection in the abdomen
- The absolute BA was determined by the ratio of dose normalized area under the curve from zero to infinity ($AUC_{(0\text{-}inf)}$) for SC versus IV dosing

Results

- The PK Analysis set included 30 subjects in the intravenous dose group who received 10 mg/kg IV lecanemab and 29 subjects in the subcutaneous dose group who received 700 mg SC lecanemab
- After subcutaneous dosing, the maximum lecanemab concentration (C_{max}) was observed 72 hours post dose and was 4-fold lower compared to intravenous infusion, which reflects the relatively long absorption phase following subcutaneous dose administration compared with 1-hour intravenous infusion (**Figure 1**)

Figure 1. Mean Serum Lecanemab Concentration-Time Profiles after 10 mg/kg IV Lecanemab Infusion and 700 mg SC Lecanemab Injection on Linear and Semi-Logarithmic Scales



10 mg/kg intravenous (IV) lecanemab infusion over approximately 1 hour: n=30. Fixed 700 mg SC lecanemab injection administered in the abdomen: n=29.

- The AUC was approximately 2-fold lower for subcutaneous administration compared with intravenous infusion (Table 1)
- Lecanemab half-life (~ 7 days) was similar following subcutaneous and intravenous administration (**Table 1**)

Results

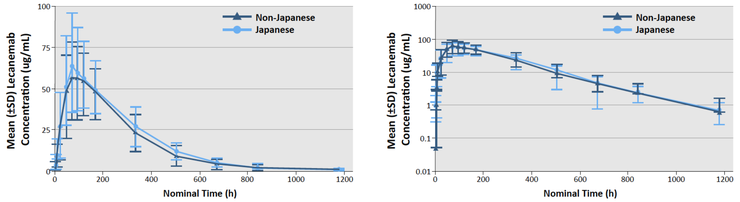
Table 1. Pharmacokinetic Parameters of Lecanemab in Serum after 10 mg/kg IV Lecanemab Infusion or 700 mg SC Lecanemab Injection

	t_{max} (h)	C_{max} (µg/mL)	$AUC_{(0\text{-}inf)}$ (h*µg/mL)	$t_{1/2}$ (h)
Intravenous Dose - 10 mg/kg				
n	30	30	30	30
Geometric Mean (CV%)	2.05 (44.6)	262 (16.4)	36,300 (24.8)	160 (29.2)
Subcutaneous Dose - 700 mg				
n[a]	29	29	27	27
Geometric Mean (CV%)	86.9 (35.7)	59.8 (36.5)	16,700 (37.4)	150 (25.3)

a: The 5 Japanese subjects were included in the total of 29 subjects in Treatment B.

- After subcutaneous dosing, C_{max} was achieved approximately 81 hours post dose in Japanese subjects (**Figure 2**)

Figure 2. Mean (±SD) Serum Lecanemab Concentration-Time Profiles after 700 mg SC Lecanemab Injection (Treatment B) to Japanese and Non-Japanese Subjects on Linear and Semi-Logarithmic Scale



Treatment B: Fixed 700 mg SC lecanemab injection administered in the abdomen. Japanese, (n=5); Non-Japanese, (n=24).

- Mean, C_{max}, $AUC_{(0\text{-}inf)}$, and half-life of lecanemab after subcutaneous administration in Japanese subjects were similar to those in non-Japanese subjects (**Table 2**)

Table 2. Pharmacokinetic Parameters of Lecanemab in Serum after 700 mg SC Lecanemab Injection to Japanese and Non-Japanese Subjects

	t_{max} (h)	C_{max} (µg/mL)	$AUC_{(0\text{-}inf)}$ (h*µg/mL)	$t_{1/2}$ (h)
Japanese				
n	5	5	5	5
Geometric Mean (CV%)	79.2 (23.5)	58.9 (51.1)	18,200 (53.1)	167 (18.1)
Non-Japanese				
n	24	24	22	22
Geometric Mean (CV%)	88.6 (37.9)	59.9 (34.4)	16,300 (34.5)	146 (26.3)

- The absolute bioavailability following a single SC 700 mg dose of lecanemab was 49.7% (90% CI: 43.5 – 56.8) (**Table 3**)

Table 3. Statistical Analysis of the Dose-Normalized, Natural Log-Transformed AUC Values of Lecanemab Comparing 700 mg Lecanemab SC Injection to 10 mg/kg Lecanemab IV Infusion

	N SC	N IV	GeoMean[a] SC	GeoMean[a] IV	Ratio (%)[b] (SC/IV)	90%CI [c]
$AUC_{(0\text{-}t)}$/Dose (µg/mL/mg)	29	30	24.1	46.9	51.4	45.0, 58.8
$AUC_{(0\text{-}inf)}$/Dose (h*µg/mL/mg)	27	30	23.6	47.5	49.7	43.5, 56.8

$AUC_{0\text{-}t}$ = Area under the concentration-time curve from time zero to time of last quantifiable concentration, or SC administration, $AUC_{0\text{-}inf}$ = Area under the concentration-time curve from time zero to time extrapolated to infinity, GeoMean = Geometric Mean, CI = Confidence Interval. The actual dose in mg for each subject form the IV group was used in the dose-normalization. a: Geometric Mean based on Least Squares Mean. b: Ratio (%) = Geometric Mean (SC)/Geometric Mean (IV). c: 90% Confidence Interval.

Safety

- The incidence of adverse events was similar between Intravenous (40.0%) and subcutaneous dose groups (34.5%; **Table 4**)
- Mild to moderate injection site reactions were experienced by 6 (20.7%) subjects in the subcutaneous dose group. Grade 1 and 2 infusion related reactions were experienced by 10 (33.3%) subjects in the intravenous dose group
- No deaths and no serious adverse events were reported
- None of the changes from baseline laboratory data or abnormal electrocardiogram data were considered to be clinically significant
- There were 4 anti-drug antibodies (ADA) positive subjects. Three out of 4 subjects (1 intravenous; 2 subcutaneous), had confirmed positive ADA, with low titers ranging from 16 to 32. One subject in the intravenous dose group was confirmed positive at predose, the subject was not on any prior immunotherapy, None of the 4 ADA positive subjects tested positive for neutralizing antibodies (NAb)

Table 4. Adverse Events

	Intravenous Dose (N=30) N (%)	Subcutaneous Dose(N=29) N (%)
Number of Subjects with Adverse Events	12 (40.0)	10 (34.5)
Adverse Events that Occurred in > 10% in Either Group		
Any Infusion Related Reaction	10 (33.3)	0
Any Injection Site Reaction	0	6 (20.7)
Headache	5 (16.7)	2 (6.9)
Chills	4 (13.3)	0
Procedural headache	3 (10.0)	0

MedDRA Version 24.1.

Conclusions

- The absolute bioavailability of lecanemab following a single subcutaneous injection was 49.7%
- Lecanemab half-life (~ 7 days) was similar following subcutaneous and intravenous administrations
- Lecanemab was well tolerated and had low immunogenicity following both subcutaneous and intravenous administrations.
- Lecanemab PK following a single subcutaneous dose administration was similar between Japanese and non-Japanese subjects

Acknowledgments

We thank the subjects and the sites who participated in these studies. 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.

Presented at the 2022 Alzheimer's Association International Conference (AAIC) Annual Meeting. Poster # 69438

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