Safety and Amyloid Plaque Reduction Effects of Remternetug in Patients with Alzheimer's Disease: Interim Analysis from a Phase 1 Study

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Disclosure

- Yan Jin is an employee and shareholder of Eli Lilly and Company
- J1G-MC-LAKB (NCT04451408) was sponsored by Eli Lilly and Company
- Amyvid® (Florbetapir F 18) was developed at Avid Radiopharmaceuticals and is marketed by Eli Lilly and Company as a radioactive diagnostic agent for Positron Emission Tomography (PET) imaging of the brain to estimate β-amyloid neuritic plaque density; safety and effectiveness of Amyvid has not been established for predicting development of dementia or other neurologic conditions and monitoring responses to therapies

Background

- Remternetug (LY3372993) is an IgG1 monoclonal antibody directed at the pyroglutamate modification of the third amino acid of amyloid-beta peptide that is present only in brain amyloid plaques

- Preclinical pharmacology studies of remternetug showed dose-dependent amyloid plaque removal in PDAPP mice

Abbreviations: PDAPP=platelet-derived growth factor–driven human amyloid precursor protein

Study Overview

- J1G-MC-LAKB (NCT04451408) is a phase 1 multi-center, investigator and participant double-blind, randomized multiple ascending dose study

Primary Objective:
Safety and tolerability of remternetug in participants with AD

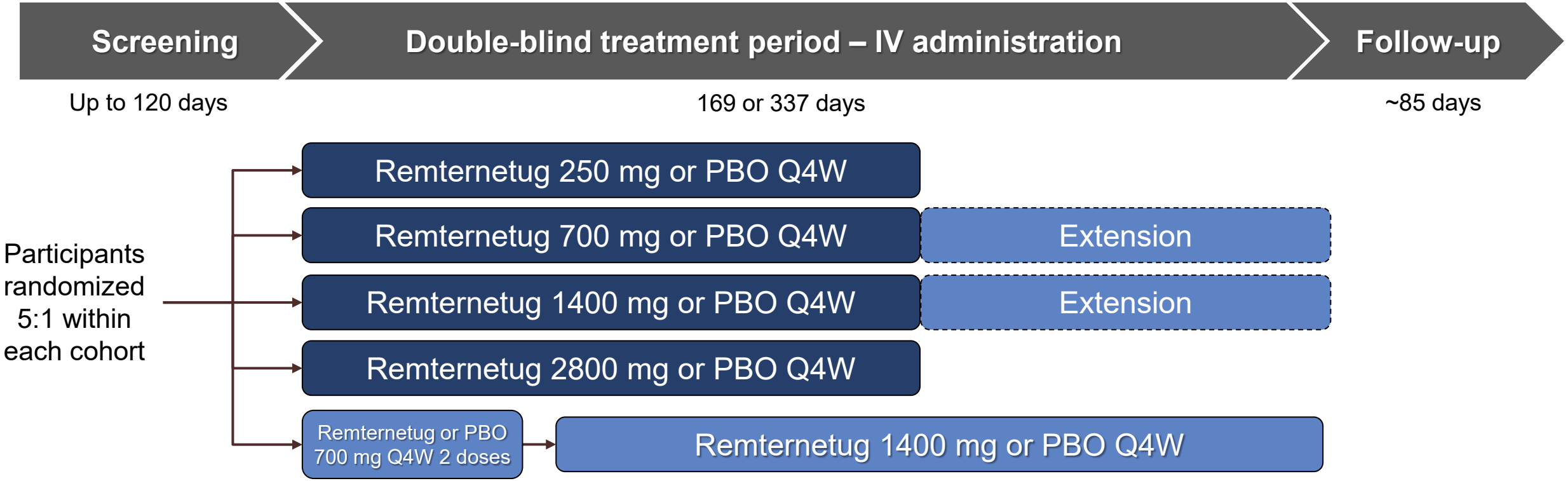
Key Secondary Objective:
Effect of remternetug on brain amyloid plaque level in participants with AD

Study Population:
Participants with MCI due to AD or mild to moderate dementia due to AD

- Age: 55-85 inclusive
- Meet florbetapir PET entry criteria based on a central read (≥ 37 CL*)
- MMSE ≥ 16
- MRI: no evidence of ARIA-E, ≤ 4 microhemorrhage, ≤ 1 superficial siderosis, or any evidence of macrohemorrhage

*Patients with amyloid SUVR ≥ 1.17, equivalent to 37 centiloids
Abbreviations: AD=Alzheimer's disease; ARIA-E= amyloid-related imaging abnormality-edema/effusions; CL=centiloid; MCI=mild cognitive impairment; MAD=multiple ascending dose**;** MMSE=Mini-Mental State Examination; MRI=magnetic resonance imaging; PET=positron emission tomography; SUVR=standardized uptake ratio value

Study Design



Abbreviations: IV=intravenous; PBO=placebo; PET=positron emission tomography; Q4W=every 4 weeks; MRI=magnetic resonance imaging

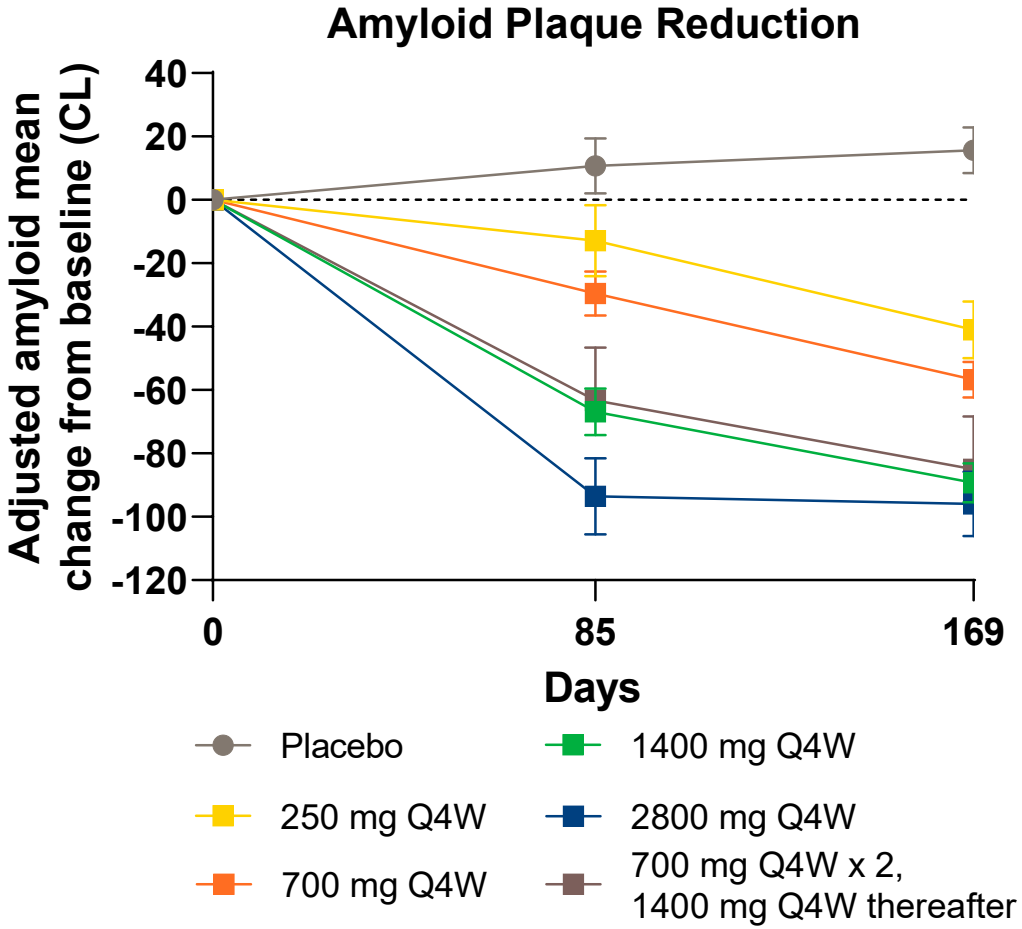
Baseline Characteristics

This interim analysis included 41 participants who received at least a single dose of placebo or remternetug:

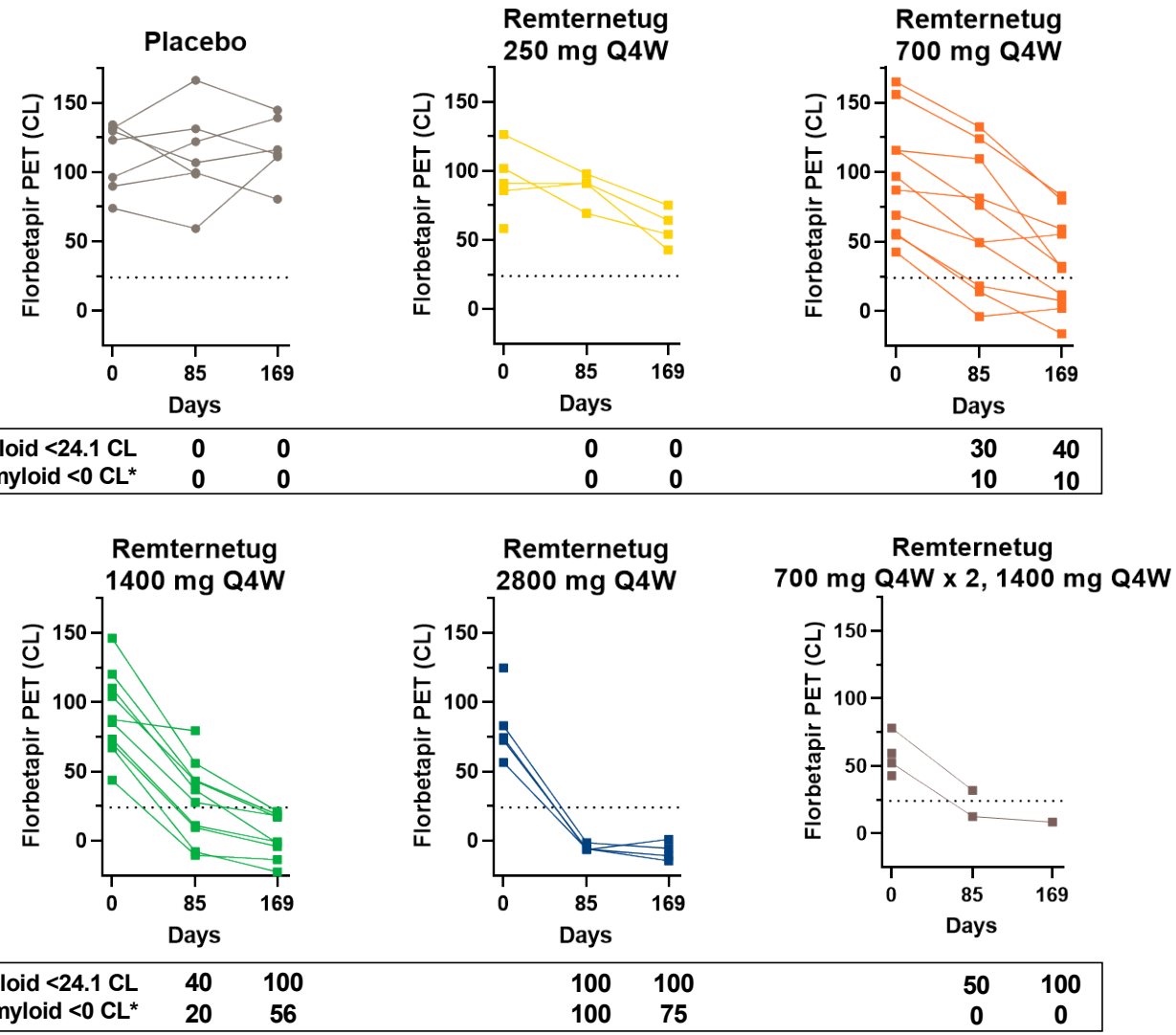
Characteristic	Placebo (N=7)	Remternetug Q4W 250 mg (N=5)	Remternetug Q4W 700 mg (N=10)	Remternetug Q4W 1400 mg (N=10)	Remternetug Q4W 2800 mg (N=5)	Remternetug Q4W 700-1400 mg (N=4)
Age (years), mean ± SD	79.3 ± 4.03	67.4 ± 7.83	72.6 ± 6.36	74.7 ± 5.03	76.6 ± 6.39	73.0 ± 5.72
Gender, n (%) women	5 (71.4%)	3 (60.0%)	4 (40.0%)	5 (50.0%)	3 (60.0%)	3 (75.0%)
Race, n (%) White	7 (100.0%)	5 (100%)	10 (100%)	9 (90.0%)	5 (100%)	4 (100%)
MMSE, mean ± SD	24.9 ± 4.63	23.0 ± 4.80	25.0 ± 4.14	24.6 ± 4.72	24.0 ± 4.18	23.5 ± 5.45
APOE ε4 carrier, n (%)	**3 (42.9%)**	**3 (60.0%)**	**5 (50.0%)**	**8 (80.0%)**	**5 (100.0%)**	**3 (75.0%)**
Amyloid level (CL), mean ± SD	**111.27 ± 24.14**	**92.6 ± 24.70**	**95.84 ± 42.27**	**90.78 ± 29.87**	**82.22 ± 25.59**	**58.04 ± 14.98**

Abbreviations: CL=centiloid; MMSE=Mini-Mental State Examination; N=number of participants; Q4W=once every 4 weeks; SD=standard deviation.

Dose-Dependent Amyloid Plaque Lowering With Remternetug



p<0.001 versus placebo for all except remternetug 250 mg at day 85 via mixed model repeated measures



% Amyloid <24.1 CL	0	0	0	0	30	40
% Amyloid <0 CL*	0	0	0	0	10	10
% Amyloid <24.1 CL	40	100	100	100	50	100
% Amyloid <0 CL*	20	56	100	75	0	0

Dotted line = 24.1 CL to indicate the amyloid clearance level[1,2]

**Threshold of 0 CL is an average value in "high certainty" amyloid negative subjects i.e., young (≤45 years) controls[3]*

Abbreviations: CL=centiloid; PET=positron emission tomography; Q4W=once every 4 weeks

References: [1]Mintun et al *NEJM* 2021; [2]Navitsky et al *Alzheimers Dement.* 2018; [3]Klunk et al 2015 *Alzheimers Dement*

Blinded Safety Profile

Number of participants with safety events or who discontinued early

Participants, n (%)	250 mg Remternetug or PBO (N=6)	700 mg Remternetug or PBO (N=12)	1400 mg Remternetug or PBO (N=12)	2800 mg Remternetug or PBO (N=6)	700-1400 mg Remternetug or PBO (N=5)	Total (N=41)
Deaths	0	0	1 (8.3)*	0	0	1 (2.4)
Serious AE						
ARIA-E, ARIA-H, and suicidal attempt	0	0	0	0	1 (20.0)	1 (2.4)
COVID-19 pneumonia*	0	0	1 (8.3)	0	0	1 (2.4)
Pleural effusion*	0	0	1 (8.3)	0	0	1 (2.4)
Chest pain*	0	1 (8.3)	0	0	0	1 (2.4)
Early discontinuation						
AEs	0	0	0	0	1 (20.0)	1 (2.4)
Withdrawal by participant	1 (16.7%)	1 (8.3)	5 (41.7)**	1 (16.7)	0	8 (19.5)

Blinded safety data by dosing cohorts as of May 31, 2022.
*considered not related to study treatment by the investigator (death reported due to COVID-19 pneumonia); ** 4 participants declined to complete the extended treatment duration.
Abbreviations: AE=adverse event; ARIA = amyloid-related imaging; ARIA-E = ARIA-edema/effusion; ARIA-H = ARIA-microhemorrhages and haemosiderin deposits; IV=intravenous; N=number of participants who received at least 1 dose of remternetug or PBO; n=number of participants with at least 1 AE per event type; PBO=placebo

Treatment-Emergent Adverse Events

Treatment-emergent adverse events of all causality (≥2 participants)

Preferred Term	250 mg Remternetug or PBO N=6 n (%)	700 mg Remternetug or PBO N=12 n (%)	1400 mg Remternetug or PBO N=12 n (%)	2800 mg Remternetug or PBO N=6 n (%)	700-1400 mg Remternetug or PBO N=5 n (%)	Total N=41 n (%)
Participants with ≥1 TEAE, n (%)	0	5 (41.7)	7 (58.3)	4 (66.7)	4 (80.0)	20 (48.8)
ARIA-E	0	1 (8.3)	3 (25.0)	3 (50.0)	3 (60.0)	10 (24.4)
ARIA-H	0	1 (8.3)	3 (25.0)	1 (16.7)	2 (40.0)	7 (17.1)
Diarrhea	0	1 (8.3)	0	0	1 (20.0)	2 (4.9)
Infusion site reaction*	0	1 (8.3)	0	0	1 (20.0)	2 (4.9)

*Infusion site reaction included a case of local reaction at infusion site and a case of infusion site phlebitis.

- No treatment-emergent antidrug antibodies were detected, and no systemic infusion-related reactions occurred following single or multiple administrations of remternetug

Abbreviations: ARIA-E = amyloid-related imaging abnormality-edema/effusion; ARIA-H = amyloid-related imaging abnormality-microhemorrhages and haemosiderin deposits; N = number of participants who received at least 1 dose of remternetug or PBO; n = number of participants with event; PBO = placebo; TEAE = treatment-emergent adverse event.

Amyloid-Related Imaging Abnormalities

Incidence of ARIA-E, microhemorrhage, and superficial siderosis based on MRI

Participants, n (%)	250 mg Remternetug or PBO (N=6)	700 mg Remternetug or PBO (N=12)	1400 mg Remternetug or PBO (N=12)	2800 mg Remternetug or PBO (N=6)	700-1400 mg Remternetug or PBO (N=5)	Total (N=41)
ARIA-E	0	1 (8.3)	3 (25.0)	3 (50.0)	3 (60.0)	10 (24.4)
Microhemorrhage	0	1 (8.3)	4 (33.3)	2 (33.3)	2 (40.0)	9 (22.0)
Superficial siderosis	0	0	2 (16.7)	1 (16.7)	1 (20.0)	4 (9.8)

- One participant experienced an SAE of ARIA-E and ARIA-H (microhemorrhage) in the 700-1400 mg titration cohort
  - Symptoms reported: aphasia, imbalance, and visual field defect
  - Symptoms resolved after discontinuation of study drug, and oral steroids
- Remaining participants with ARIA were asymptomatic
- All participants who experienced ARIA were APOE ε4 carriers
- No macrohemorrhages were observed

Abbreviations: APOE=apolipoprotein E; ARIA-E= amyloid-related imaging abnormality-edema/effusions; ARIA-H=amyloid-related imaging abnormality-hemorrhage; N=number of participants with AD who received at least 1 dose of remternetug or PBO; n=number of participants with ARIA; PBO=placebo; SAE=serious adverse event

Conclusions

- Remternetug demonstrated rapid and robust amyloid plaque reduction in participants with AD

- The safety, tolerability, and pharmacokinetic/pharmacodynamic data support the ongoing phase 3 trial (NCT05463731)

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