The phase-3 CLARITY-AD clinical trial of lecanemab, an amyloid-targeting antibody showed a small clinical benefit in Alzheimer’s disease (AD). However, several questions remain to be answered to assess whether lecanemab is a clinically meaningful, safe and potentially accessible treatment for patients with AD.

Lecanemab trial brings hope but requires greater clarity

Demonstration of a potential clinical benefit in Alzheimer disease with lecanemab, a monoclonal antibody against beta-amyloid protofibrils is a scientific *tour de force*. Thorough appraisal of the data is important to guid evidence-based decision-making by regulators, physicians and payors to determine if this drug represents a truly meaningful advance for patients with Alzheimer's disease.

Statistically significant differences favoring lecanemab over placebo were observed on the primary outcome, Clinical Dementia Rating–Sum of Boxes (CDR-SB) and secondary outcomes including the cognitive subscale of the Alzheimer's Disease Assessment Scale (ADAS-cog14), Alzheimer's Disease Composite Score (ADCOMS) and the Alzheimer's Disease Cooperative Study–Activities of Daily Living Scale for Mild Cognitive Impairment (ADCS-MCI-ADL). Convergence of results across multiple clinical endpoints, together with demonstration that the drug robustly reduced brain amyloid levels suggest target engagement with the disease process. However, results are not inconsistent with prior negative trials, where uncertainty estimates have included the potential for small clinical benefits[16]. Could such small, but statistically significant differences reflect biases from loss to follow-up or functional unblinding, as these effects may be accentuated in a trial with a large (n=1800) sample size? The overall participant dropout rate was 17.2%. Patients randomized to active treatment were more likely to discontinue the trial agent due to an adverse event than those on placebo (62 patients; 6.9% versus 26 patients; 2.9% respectively). The researchers report that sensitivity analyses were performed using imputation of missing data with mean values from the placebo group at each visit. The primary outcome of differences on the CDR-SB at 18 months in this sensitivity analysis is attenuated compared to the primary analysis (-0.39 versus -0.45 points) but still statistically significant, favoring drug over placebo ($p<0.001$, table S2).

A prespecified exploratory analysis tested whether the drug slowed disease progression, defined as an increase in the global CDR (indicating clinical worsening) score of at least 0.5 points on two consecutive visits (fig S6). The results "numerically favored lecanemab over placebo." However, this analysis does not include 95% confidence intervals for the reported hazard ratio of 0.69 favouring lecanemab.

A key source of bias that may influence results of amyloid-targeting immunotherapy trials is a common treatment-related adverse event, amyloid-related imaging abnormalities (ARIA). ARIA necessitate additional MRI surveillance and may require dose suspensions until resolution of symptoms. The reported incidence of ARIA in lecanemab versus placebo groups were ARIA-E; 12.6% and 1.7% and ARIA-H; 17.3% and 9.0% respectively. Additionally, 26.4% lecanemab participants experienced infusion related reactions compared to 7.4% in the placebo group.

In sensitivity analyses to address the risk of functional unblinding, the primary MMRM analysis for group differences on CDR-SB was repeated after censoring data subsequent to the occurrence of ARIA-E. Results were generally consistent with the primary analysis. However, as with data from aducanumab, the FDA's statistical reviewer noted that such analyses of censored data have significant limitations, as they break the randomization and/or imbalance the treatment and placebo groups' distributions of follow-up. This is

especially true of sensitivity analyses in “post-randomization event-defined subgroups", where the adverse events (i.e., ARIA and/or infusion related reactions) are strongly associated with drug exposure [19]. Further, the sensitivity analyses in the lecanemab trial did not account for potential unblinding due to infusion related reactions or ARIA-H.

The trial protocol specified that ARIA and infusion-related reactions were monitored by an independent medical team so that clinical assessment raters were unaware of safety assessments and trial-group assignments. While these precautions are important, they do not mitigate the risks of unblinding on patient and caregiver responses to questions assessing their subjective impression of changes in functional abilities. These subjective reports are key components of both primary (CDR-SB) and secondary trial outcome scores, including the ADCOMS and ADCS-ADL-MCI.

The treatment benefit of 0.45 points on the 18-point CDR-SB is well below the minimal clinically important difference (MCID) in AD clinical trials. In a retrospective analysis of the National Alzheimer’s Coordinating Center Uniform Data Set, researchers from Eli Lilly proposed that the MCID on the CDR-SB is 0.98 for patients with MCI due to AD and 1.63 for those with mild AD (the range of disease severity represented in CLARITY-AD). Similarly, using data from a 3-year, phase-3 multicenter study in patients with MCI, researchers from Roche recently estimated MCIDs of 1–2.5 points in the CDR-SB and 2–5 points on the ADAS-cog over one year.

In the small number of participants with symptomic ARIA-E (2.8% in the treatment group), the most common were headache, visual disturbance, and confusion. Macrohemorrhages (measuring more than 10 mm) occurred more commonly in the lecanemab group (5 patients; 0.6%) compared to placebo (1 patient; 0.1%). Although no deaths were attributable to lecanemab during the trial, at least two deaths during open label extension have been reported and may have occurred in patients receiving concomitant therapy with anticoagulants and thrombolytic treatment.

Accelerated brain atrophy following amyloid immunotherapies has been largely ignored. Given that increase in ventricular volume is an established imaging biomarker of AD progression and is associated with both severity of cognitive impairment as well as AD pathology at death, it is incumbent upon drugmakers to show that these changes are not indicative of worsening neurodegeneration after treatment. It is disappointing that results of MRI volumetric analyses or associations of brain volume changes with cognitive outcomes have not been reported from CLARITY-ADt.

CLARITY-AD trial made significant progress towards recruiting participants from a diverse group of patients in North America, Europe, and Asia with enrolment of more than 20% non-White patients. In the United States, 4.5% and 22.5% of randomized patients were Black and Hispanic, respectively. The generalizability of findings from carefully controlled clinical trials to real-world clinical practice however remains to be confirmed.

Finally, it is important to consider the ability of healthcare systems to provide the infrastructure and capability to screen patients through brain amyloid PET imaging or

CSF assays, obtain baseline and follow-up MRI scans and administer intravenous infusions for an undetermined treatment period.

In summary, while the trial brings hope to millions of people with Alzheimer’s disease, there is an urgent need for greater clarity to determine whether this promise is fulfilled and represents a meaningful advance in our efforts to address the global public health challenge of dementia.