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Unblinded by the light: amyloid-related imaging abnormalities in Alzheimer's clinical trials

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Title: Unblinded by the light: ARIA in Alzheimer's clinical trials

Running title: Unblinding by ARIA in Alzheimer's trials

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A disease modifying therapy for Alzheimer's disease is one of the highest priorities in medicine. Dozens of amyloid-modifying trials have failed to meet primary endpoints. Aducanumab, a monoclonal anti-amyloid antibody, lowers plaque burden. Early findings suggested a slowing of cognitive deterioration(1). However, phase 3 trials of aducanumab were ceased in March 2019 based on a futility analysis. A new analysis of a larger dataset from these trials, released in October 2019, showed a statistically significant benefit in the high dose arm on the primary endpoint, the Clinical Dementia Rating Scale Sum of Boxes (CDR-SB), and two secondary endpoints, the Alzheimer's Disease Cooperative Study-Activity of Daily Living Inventory (ADCS-ADL-MCI) and the Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog13), for one of the phase 3 studies (EMERGE) but not the other (ENGAGE)(2). In July 2020, Biogen submitted a FDA registration application.

It is important to alert the community to a potential major confounder related to unblinding by amyloid-related imaging abnormalities (ARIA).

ARIA, including edema (ARIA-E; hyperintense on FLAIR MRI) and haemorrhage (ARIA-H; hypointense on T2*/GRE), are a complication of anti-amyloid- β monoclonal antibody therapeutics. Whether ARIA are harmful, clinically insignificant, or a sign of amyloid clearance, remains uncertain. As a precaution, ARIA protocols are enacted in A β -antibody trials that prescribe MRI monitoring and suspension of treatment, allowing for lesion resolution(1, 3).

The most common adverse event in the EMERGE and ENGAGE trials was ARIA-E, seen in 35% of patients on treatment(2). ARIA incidence is dose-dependent for aducanumab(1), and other anti-A β monoclonals, albeit with less frequency than aducanumab(4). Therefore, the highest dose group in the EMERGE study, which was reported as cognitively protected, was also the group with the highest incidence of ARIA (>35%).

In the phase 1b trial of aducanumab, subjects who developed ARIA required management with a contingent protocol (including repeated MRI)(1). A contingent protocol for management of ARIA was also adopted for the ENGAGE and EMERGE studies (including dose suspension)(5). These protocols may disclose treatment-arm allocation to subjects, caregivers, and investigators. Such unblinding can impact outcome assessments, especially the ADCS-ADL-MCI and CDR-SB that rely heavily on caregiver report. Thus, unblinding

due to ARIA may have confounded the outcomes of these studies. This effect would be less likely to impact results for other compounds due to less frequent ARIA(4).

Future amyloid-modifying clinical trials should be designed to reduce the risk of ARIA-related unblinding. ARIA could be rated by a blinded radiologist, and subjects in whom doses are to be withheld could receive placebo without the knowledge of site staff. A remedy for unblinding caused by multiple MRIs needed during the discontinuation period might be more difficult to achieve. To address this, the study could be designed such that whenever a patient on drug is prescribed an 'ARIA protocol' (including repeated MRI scans) a matched patient on placebo will be assigned an identical protocol. In this way both patients on drug and placebo will undergo ARIA protocols in equal proportion, and this change in protocol will not provide insight into who is on drug.

Conflict of interest

Dr. Bush is a shareholder in Prana Biotechnology Pty Ltd., Cogstate Pty Ltd, Eucalyptus Pty Ltd., Mesoblast Pty Ltd., Brighton Biotech LLC, Nextvet Ltd, Grunbiotics Pty Ltd, Collaborative Medicinal Development LLC, and a paid consultant for Collaborative Medicinal Development.

Drs Gleason and Ayton have no financial, personal, or other potential conflicts to declare.

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