



Reply: Unblinding in the lecanemab trial in Alzheimer's disease

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Dr Van Gool suggests¹ functional unblinding together with a placebo effect may underlie the statistically positive reported effects of lecanemab as an Alzheimer drug.² He further suggests that the reported 27% slowing of progression is not clinically meaningful. On the first point, he suggests separate analysis of those individuals with infusion reactions (both drug and placebo infused): this is a clear suggestion which can be requested both for this trial and also for the recently announced, apparently successful, donanemab trial.³ We noted, however, in our article,⁴ that the effectiveness of therapies closely followed their effectiveness in achieving amyloid removal and (as one example) gantenerumab, whose trial would have been predicted to suffer from the same systematic bias, was not efficient in removing amyloid and did not reach its clinical end points. We think the more parsimonious interpretation of all the trial data is that drugs that remove amyloid are effective and those that do not, are not: a view that seems to have been overwhelming taken by other observers.

On the second point, he suggests that the statistical significance of the results do not amount to clinical significance. This, no doubt, is an argument that will run and run and the question as to who makes this judgement is clearly important: the patient, the prospective caregiver, the clinician or the payer. However, this criticism misses two points: the first is to assume that these are the best improvements which can be achieved by these drugs (and here there is tantalizing evidence from the donanemab trial that giving the drugs earlier may lead to better outcomes) and second, as we noted in our original article: these drugs teach us what we need to do to achieve a therapy. We think, two swallows, in this case, do presage a spring.

Responding to Dr Van Gool gives us the opportunity to also respond to his implicit suggestion, explicit in his reference list, that pursuing amyloid therapies has led to misuse of research efforts in this direction. We reject this suggestion as it implies a zero sum game. We recognize that public health measures, largely aimed at better heart health,⁵ appear to have reduced dementia incidence, and that preventative measures need to be more precisely understood and built on in dementia. Indeed, current preventative trials integrate public health and medical interventions such as

exercise or statins. We expect a multi-pronged approach to Alzheimer's disease and other dementias is what should be supported and not internecine bickering about research efforts.⁶

Data availability

Data sharing is not applicable to this article as no new data were created or analysed in this article

Competing interests

J.H. has consulted for Eisai, Roche and Eli Lilly on their Alzheimer programmes. C.M. holds a grant from Biogen for the use of ultrafast MRI in trials, has an educational travel award from Roche, has received honoraria for presentations from Biogen, Roche and IONIS and has consulted on Advisory Boards for Biogen, Roche, IONIS, Lilly, WAVE and Alnylam.

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