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Vincent Planche[1,2], MD, PhD and Nicolas Villain[3,4*], MD, PhD.

1. Univ. Bordeaux, CNRS, IMN, UMR 5293, F-33000 Bordeaux, France.

2. Centre Mémoire Ressources Recherches, Pôle de Neurosciences Cliniques, CHU de Bordeaux, F-33000 Bordeaux, France

3. AP-HP Sorbonne Université, Hôpital Pitié-Salpêtrière, Department of Neurology, Institute of Memory and Alzheimer's Disease, Paris, France

4. Institut du Cerveau - ICM, Sorbonne Université, INSERM U1127, CNRS 7225, Paris, France

* Corresponding author:

Institut de la Mémoire et de la Maladie d'Alzheimer

Département de Neurologie

Groupe Hospitalier Pitié-Salpêtrière

47-83 boulevard de l'Hôpital

75651 PARIS Cedex 13, France

nicolas.villain@aphp.fr

tel: 33 1 42 16 18 37

On June 7th 2021, the American Food and Drug Administration (FDA) publicly announced that it would grant accelerated approval for aducanumab in Alzheimer's disease (AD) based on the "evidence that Aduhelm™ reduces amyloid-beta plaques in the brain and that the reduction in these plaques is reasonably likely to predict important benefits to patients". For the first time in the field of AD, a governmental agency has used a surrogate endpoint for drug approval, *i.e.* an endpoint "that is thought to predict clinical benefit but is not itself a measure of clinical benefit". The FDA considered reduction of amyloid load, as measured with amyloid positron emission tomography (PET), to be a valid surrogate endpoint of clinical benefit in AD. This position is unprecedented and raises numerous controversies.

What is a surrogate endpoint? In the late 1980's, methodologists defined operational criteria for using surrogate endpoints in clinical trials[1]. The definition of surrogacy implies a causal relationship: the surrogate marker must mediate the treatment effect on the "true" clinical outcome. In the case of AD, the application of these operational criteria to establish amyloid-load measured with PET as a surrogate endpoint would require that: *(1)* the treatment has an effect on cognitive decline; *(2)* the treatment effect on slowing cognitive decline is captured by amyloid load; *(3)* the treatment has an effect on amyloid load; and *(4)* amyloid load is associated with cognitive decline (Figure 1). In neurology, this approach accelerated for instance the development of disease-modifying therapies in relapsing-remitting multiple sclerosis. New T2-lesions on brain MRI were first validated as surrogates of clinical relapses using seminal clinical trials of beta-interferons and glatiramer-acetate (positive on clinical outcomes), and then these MRI surrogate markers were successfully implemented in subsequent phase II trials to develop second-generation drugs. With this definition of surrogacy in mind, what do we know about the relationships between anti-amyloid therapies, amyloid load, and potential clinical outcomes in AD?

First, in order to use amyloid load as a surrogate endpoint, there needs to be a preceding clinical trial that demonstrates that anti-amyloid therapies reduce cognitive decline. This is a pre-requisite to

being able to assess a surrogate marker within the framework of this positive trial, which can then be used as an endpoint in a subsequent, separate trial. Otherwise, how can we expect that a treatment may have an effect on cognitive decline when we are relying on surrogate endpoints? However, to date, no phase III clinical trial using an anti-amyloid therapy has yet proven to be positive without controversies. One could argue that the recent positive donanemab[2] and lecanemab[3] phase II trials, combined to the aducanumab's EMERGE trial, could be used to fulfill this criterion but this would ignore the negative aducanumab's ENGAGE trial and the other negative anti-amyloid clinical trials (which could arguably be the consequence of lower pharmacodynamic potential, the use of lower doses or the wrong target population).

Second, even under the hypothesis that the donanemab, lecanemab and aducanumab EMERGE trials provide evidence for a positive effect of the treatment on cognitive decline, amyloid load should be mediating the treatment effect on cognitive decline. In other words, anti-amyloid therapies should reduce cognitive decline by reducing an individual's amyloid load and not by reducing another, more causal and direct, surrogate marker[1]. This can be tested statistically (mediation analyses), but, to the best of our knowledge, Biogen did not provide this information with the aducanumab trials (and the publicly available FDA statistician's report suggests the opposite at the individual level). While there is currently a lack of data regarding the mediation effect of amyloid load reduction between the treatment effect and cognitive decline, some examples from previous anti-amyloid clinical trials underline that there might not be such a direct mediation effect. On the one hand, previous results from active and passive immunotherapies have failed to demonstrate a clinical effect despite a significant reduction of amyloid load[4,5]. On the other hand, anti-amyloid immunotherapies targeting specifically soluble ABeta species may also have an impact on cognition, that would not be mediated by amyloid plaques removal (amongst the published phase III studies, the results from the solanezumab EXPEDITION3 trial were actually the closest to be significant on clinical outcomes, without any effect on amyloid load)[6].

Third and fourth, while aducanumab has convincingly demonstrated a reduction of amyloid load in every trial, observational studies have previously shown that amyloid load is poorly directly associated with cognition. Furthermore, longitudinal cohorts have also shown that cognitively unimpaired individuals above 60 years old with in vivo evidence of amyloid pathology have a lifetime risk of progression to symptomatic AD below 50%, and show no or only minimal acceleration of tau-PET tracer uptake in the following 1 or 2 years[7]. Using multi-modal imaging and mediation statistical analyses, amyloid load has proven to be only indirectly related to cognitive decline[8].

The methodological points discussed here lead to an obvious conclusion: to date, there is no valid surrogate marker of clinical outcome in AD therapeutic trials. In addition, the decision to use a surrogate endpoint should be decided a priori, before the beginning of the study. But the FDA decision raises a good question: what could be a good surrogate endpoint for future clinical trials in AD? In this regard, measurements of neurodegeneration or tau pathology are known to be more direct correlates of cognitive decline than amyloid load[8]. Small subgroup analyses from aducanumab, lecanemab and donanemab trials suggest through heterogeneous findings that these drugs have an impact on tau pathology (measured with PET or CSF phospho-tau) and on neurodegeneration (measured with CSF total tau or neurofilament light chain - NfL)[2,3]. Thus, the potential surrogacy of all these promising biomarkers should now be properly investigated in the ongoing aducanumab, lecanemab, and donanemab trials with larger samples so that they could be used in future trials as valid surrogate endpoints. Indeed, after the learning curve the field has undergone in anti-amyloid therapies, the development of surrogate endpoints, based on a strict methodology, is of utmost importance to speed up the development of disease-modifying therapies in AD, as it did in the past speed up the development and management of disease-modifying therapies in multiple sclerosis.

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Figure legends

Figure 1. Graphical representation of the criteria demonstrating surrogacy (known as Prentice criteria). *(1)* the treatment must have an effect on the clinical outcome; *(2)* the treatment effect on the clinical outcome is captured by the surrogate (demonstration of the lack of statistical relationship between the treatment and the clinical outcome when taking into account the surrogate); *(3)* the treatment must have an effect on the potential surrogate marker; and *(4)* the surrogate is associated with the clinical outcome. Currently, only the third criterion is unarguably fulfilled to support amyloid load has a valid surrogate endpoint for anti-amyloid clinical trials in AD.