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Editorial

From trial population to treated population: why EU-eligible subgroup analyses matter for anti-amyloid immunotherapy

The approval of donanemab and lecanemab in the European Union came with a narrower label than the pivotal trials that supported it. Both agents are restricted to patients with early symptomatic Alzheimer's disease (AD) who are apolipoprotein E (APOE) ε4 non-carriers or heterozygotes, and both carry additional EU-specific contraindications beyond genotype - anticoagulant use is excluded under both labels, and donanemab is further restricted by superficial siderosis and uncontrolled hypertension [1,4]. As discussed below, however, only the analysis by Jessen et al. in this issue explicitly incorporates the full set of these additional exclusions into its efficacy and safety analysis. This is a sensible regulatory response to the well-documented, genotype-dependent risk of amyloid-related imaging abnormalities (ARIA) with these therapies, but it leaves clinicians with an obvious question: does the efficacy demonstrated in the full trial population still hold once the label's restrictions are applied to a real clinic population? The post-hoc analysis by Jessen and colleagues, together with a parallel analysis of lecanemab published earlier this year, gives a reassuringly consistent answer.

Jessen et al. re-analysed the 76-week placebo-controlled period of TRAILBLAZER-ALZ 2 restricted to the EU-eligible population - APOE ε4 non-carriers and heterozygotes without siderosis, anticoagulation, or uncontrolled hypertension, roughly 87% of the non-homozygous trial cohort. Using the conservative hybrid imputation method requested by the European Medicines Agency (EMA), donanemab still produced an 18–28% slowing of decline across five independent clinical scales (iADRS, CDR-SB, ADAS-Cog13, ADCS-iADL, MMSE), a 40.3% reduction in the risk of progressing to the next disease stage, and a 47.2% reduction in the risk of progressing to moderate dementia, translating into roughly five additional months before reaching a given level of decline on the CDR-SB [2]. Safety in this narrower population was not merely similar to the full trial but somewhat better: any ARIA occurred in 32.0% versus 36.8% of donanemab-treated participants overall, the great majority of ARIA-E was mild-to-moderate and asymptomatic, and no ARIA-related deaths occurred in the EU-eligible group [2].

Among these results, the reduction in risk of progressing to the next CDR-Global stage deserves particular emphasis, and arguably more attention than it typically receives relative to the mean change-from-baseline endpoints. Unlike a group-level mean difference on a continuous scale, progression to a discrete clinical stage is a threshold event that a patient, a caregiver, and a treating physician can recognise and agree upon without ambiguity - the transition from mild cognitive impairment to mild dementia, or from mild to moderate dementia, is a lived experience, not a statistical abstraction. In oncology, progression-free survival has become one of the most consequential endpoints by which therapies are judged and by which patients understand what a treatment offers them, precisely because it captures a discrete, meaningful transition rather than an average difference in tumour size. A 40.3% lower risk of progressing to the next CDR-Global stage, and a 47.2% lower risk of progressing to moderate dementia, are conceptually the same kind of endpoint applied to a neurodegenerative disease: they describe how much longer a patient remains at a stage of disease compatible with retained autonomy, driving, employment, or living independently. There is a reasonable case that this endpoint carries at least as much clinical weight in AD as progression-free survival does in oncology, since the 'stage' being delayed here is not a radiological measurement but a directly experienced level of function and independence for the patient and their family - and it is precisely this endpoint that remained robust once the EU-eligibility restrictions were applied.

For clinicians in daily practice, the distinction between the trial population and the population that actually meets the label is not academic. Patients who qualify for treatment under the EU indication are, by construction, a lower-risk subgroup than the randomised trial as a whole. Knowing that both the magnitude of clinical benefit - including the stage-progression findings discussed above - and the safety profile hold up, and if anything improve slightly, in this specific subgroup is what allows a clinician to translate trial-level statistics into a credible, individualised conversation with a patient and their family about what several additional months of preserved function and independence might realistically mean for them, weighed against a quantifiable infusion and monitoring burden.

This is where the comparison with lecanemab becomes valuable, not just as a footnote but as corroborating evidence - though the two analyses are not methodologically identical and the difference is worth stating explicitly. Perry et al. isolated the 1521 of 1795 Clarity AD participants (85%) who were APOE ε4 non-carriers or heterozygotes, stratifying by genotype alone [3]. Jessen et al. go a step further: beyond genotype, they additionally exclude participants with superficial siderosis, anticoagulant use, or uncontrolled hypertension - the full set of contraindications relevant to anti-amyloid antibody treatment under the EU label, not genotype alone. The donanemab EU-eligible analysis therefore approximates the population actually treated in European practice more closely than a genotype-only subgroup, and the lecanemab findings are best read as a genotype-based sensitivity analysis pending an equivalent full-eligibility re-analysis. That caveat aside, the direction of both results is strikingly consistent: clinical benefit on CDR-SB and secondary endpoints was preserved in the lecanemab genotype subgroup, and ARIA incidence was roughly halved relative to the overall Clarity AD population. Two independently developed antibodies, assessed in separate trials by different sponsors, point the same

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direction once genotype is accounted for: restricting treatment by APOE ε4 status does not erode efficacy, and improves the benefit-risk balance.

None of this removes the usual caveats attached to post-hoc subgroup work. Both analyses are exploratory and unadjusted for multiplicity, so p-values and confidence intervals should be read as descriptive rather than confirmatory. In the donanemab long-term extension, the absence of a randomised placebo comparator means efficacy is inferred against an external, propensity-weighted ADNI cohort rather than a concurrent internal control - a materially weaker design however carefully the weighting is performed. Neither dataset can yet tell us how these figures translate once the more gradual titration regimens now used in practice are applied at scale, or how outcomes look once comorbidities and adherence vary as they do outside a trial.

What clinicians in the EU need next is prospective, registry-based follow-up of patients actually treated under the approved label - ideally using the same full-eligibility definition across donanemab and lecanemab, and continuing to track stage-progression endpoints alongside continuous scales. Until that evidence matures, the analyses discussed here give European clinicians a reasonably precise, eligibility-matched estimate of what to expect for the patients who will actually receive these medicines.

Taken as a whole, the evidence supports a clearly favourable risk-benefit ratio for anti-amyloid immunotherapy in appropriately selected, EU-eligible patients. Judged by effect size, the disease-modification achieved here compares well with many antibody therapies now standard of care in other chronic diseases. In cardiovascular medicine, for instance, the monoclonal antibody evolocumab reduced the risk of the primary composite cardiovascular endpoint by 15% and of the key secondary endpoint - cardiovascular death, myocardial infarction, or stroke - by 20% versus placebo in the FOURIER trial [5], a relative risk reduction of essentially the same order as the 40.3% lower risk of progressing to the next CDR-Global stage and the 18–28% slowing of decline reported here for donanemab. Evolocumab is now embedded in international guidelines and widely regarded as practice-changing for secondary cardiovascular prevention, which puts the magnitude of benefit seen with anti-amyloid antibodies in AD in useful perspective: comparable relative risk reductions are routinely accepted elsewhere in medicine as clinically meaningful, not as a modest or borderline result. Preserving brain health and delaying the transition to more advanced, dependent stages of dementia is arguably one of the most consequential goals in contemporary healthcare, given the scale of the personal and societal burden of AD - and the data reviewed here suggest that goal is now realistically within reach for the patients Europe has chosen to treat.

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TG contributed to

- the conception and design of the study and interpretation of data.
- Drafting the article.
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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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