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Comparative Analysis of Trontinemab and Lecanemab in Early Alzheimer Disease

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Abstract. Alzheimer's disease (AD) is the leading cause of dementia, affecting about 55 million people today and projected to reach 140 million by 2050. Two monoclonal antibodies against amyloid-β (Aβ), lecanemab and trontinemab, are at different stages of clinical development. This review compares their mechanisms, trial results, and safety profiles. Lecanemab is a humanized IgG1 antibody that binds soluble Aβ protofibrils. In CLARITY AD (n = 1,795), 10 mg/kg every two weeks reduced CDR-Sum of Boxes progression by 27% at 18 months and cut amyloid PET signal by 55.5 Centiloids (placebo: +3.6). ARIA-E appeared in 12.6% of treated participants versus 1.7% on placebo, reaching roughly 35% in APOE ε4 homozygotes. Trontinemab uses Roche's Brainshuttle™ module, an extra Fab arm against transferrin receptor 1 that drives the antibody across the BBB by receptor-mediated transcytosis. In TRONTIER 1, the drug reduced amyloid PET by about 65 Centiloids at 28 weeks at 0.3–3.0 mg/kg every four weeks, with lower ARIA rates than lecanemab. Cognitive endpoint data from TRONTIER 3 are expected in 2027. If TRONTIER 3 confirms these biomarker effects, brain-penetrating antibody designs will set a new benchmark for AD immunotherapy.

Keywords: Alzheimer's disease, trontinemab, lecanemab, blood-brain barrier

1. Introduction

Alzheimer's disease (AD) is the leading cause of dementia worldwide, and the patient count, around 55 million today, could reach 140 million by 2050 as populations age [1]. Patients lose memory, executive function, and the ability to live independently, and the costs fall on families, on health systems, and on the wider economy, with global dementia costs already above USD 1 trillion per year [1]. The two pathological hallmarks are extracellular amyloid-β (Aβ) plaques and intracellular hyperphosphorylated tau, and the amyloid cascade hypothesis has been the dominant mechanistic model for over two decades [2]. Existing drugs, mainly cholinesterase inhibitors and NMDA receptor antagonists, ease symptoms briefly but do not change the disease course [2]. The gap left by those drugs has pushed the field toward disease-modifying treatments, and monoclonal antibodies against Aβ have drawn most of that investment.

Within this class, lecanemab is the most validated agent. The CLARITY AD phase 3 trial showed a 27% reduction in CDR-Sum of Boxes progression over 18 months in early symptomatic AD [3]. Donanemab also cleared amyloid and produced modest clinical benefit in TRAILBLAZER-ALZ 2,

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while gantenerumab and crenezumab failed their phase 3 programs, leaving lecanemab as the agent with the strongest evidence base so far [3]. Use of lecanemab is limited by poor blood-brain barrier (BBB) penetration, with about 0.1% of an injected dose reaching the central nervous system [4, 5]. That forces a 10 mg/kg biweekly dose, and produces ARIA in a sizeable share of patients [5, 6]. Trontinemab is the next antibody in this class. It uses Brainshuttle™ technology, a bispecific construct with a transferrin receptor (TfR)-binding arm that mediates transcytosis across the BBB, with the goal of higher brain exposure at lower systemic doses [4, 7]. Phase I/II TRONTIER 1 and 2 trials have shown amyloid clearance at 3–30 fold lower doses than lecanemab, but cognitive endpoints still await phase 3 confirmation [7].

Despite these advances, gaps remain. Most published reviews focus on lecanemab alone or on the entire anti-Aβ class, leaving clinicians without a head-to-head synthesis to guide treatment selection. Beyond the well-documented ARIA class effects, the contested fate of aducanumab has reinforced the need for rigorous comparative data, particularly around optimal dosing [8-10]. No review has systematically examined how BBB-penetrating designs such as Brainshuttle™ may shift the therapeutic index, the dose requirements, and the patient eligibility for amyloid immunotherapy, or how lower-dose regimens might change the risk-benefit calculation in APOE4 homozygotes. The present review fills that gap by comparing lecanemab and trontinemab along three dimensions: molecular mechanism and pharmacokinetics, clinical efficacy, and safety. The aim is to give clinicians and researchers a practical framework for evaluating next-generation BBB technologies in AD, and to flag the questions that still need answering [2, 8].

The remainder of this review is in four sections. The first examines how conventional antibody delivery differs from TfR-mediated transcytosis. The second summarizes efficacy data from CLARITY AD and TRONTIER 1/2, covering both biomarker and cognitive endpoints. The third analyzes safety, with attention to ARIA epidemiology, dose-response, and risk stratification. The fourth covers clinical implications, including patient selection, access barriers, and research directions such as combination therapy and biomarker-guided algorithms.

2. Molecular mechanisms and central nervous system exposure

2.1. Mechanism of lecanemab

Lecanemab (BAN2401) is a humanized IgG1 monoclonal antibody that binds soluble Aβ protofibrils, the synaptotoxic oligomers, with much lower affinity for Aβ monomers or insoluble fibrillar plaques [3]. This selectivity separates lecanemab from aducanumab, which preferentially binds plaque-associated Aβ, and from antibodies with other epitope preferences [3]. The distinction is not academic. Antibodies that bind soluble protofibrils engage the species most directly tied to synaptic dysfunction, whereas those that bind plaque-associated fibrils rely more on Fc-mediated microglial clearance of deposited material [3, 6]. After binding, the Fc region engages Fcγ receptors on microglia, which then phagocytose Aβ-antibody complexes and drive downstream neuroinflammation [3, 6].

The anti-Aβ class also differs in how aggressively each agent is dosed. Donanemab was given at 1400 mg every four weeks until amyloid clearance, gantenerumab reached subcutaneous doses up to 1200 mg every four weeks, and lecanemab sits at 10 mg/kg intravenously every two weeks [3, 7, 10]. These choices reflect each antibody's brain exposure and the ARIA ceiling it can tolerate. A drug that reaches the brain poorly needs a large peripheral dose to compensate, and that is exactly the trade lecanemab makes.

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Conventional anti-Aβ antibodies cross the BBB poorly. Less than 0.1% of an injected IgG reaches the brain intact, because cerebral endothelial tight junctions are highly restrictive [4, 5]. To reach therapeutic CNS levels, lecanemab is given at 10 mg/kg every two weeks, roughly 100-fold higher than would be needed with efficient brain penetration [3]. This dose level also drives the ARIA rates seen in CLARITY AD [5, 6]. The mismatch between peripheral dose and central exposure is the core pharmacokinetic problem that next-generation designs set out to fix.

2.2. Mechanism of trontinemab

Trontinemab uses Roche's Brainshuttle™ module to address this problem. The bispecific antibody carries a second Fab arm that binds transferrin receptor 1 (TfR1) on brain capillary endothelial cells [4, 7]. On binding TfR1 at the luminal side, the antibody is carried across the endothelial cytoplasm in vesicles, and the lower pH at the abluminal surface weakens the TfR1 interaction so the antibody is released into brain parenchyma [4, 7]. Preclinical work shows 10- to 50-fold higher brain exposure than conventional IgG [4, 10]. Some of that gain comes from the transcytosis route itself, and some from the fact that a lower peripheral dose is needed to hit the same central target.

2.3. Mechanistic comparison

The TfR-binding arm uses reduced affinity and monovalent binding to avoid cross-linking. Cross-linking would otherwise drive lysosomal routing and the dose-limiting anemia seen with high-affinity TfR antibodies [4, 7]. The Fc region also carries mutations that reduce effector function, which may limit the complement and FcγR activation linked to ARIA [4, 6]. Together, these modifications should allow trontinemab to reach therapeutic CNS levels at projected doses 3–30 fold lower than lecanemab, which would widen the therapeutic index [7]. The real test, though, is whether lower exposure at equivalent brain levels actually produces fewer ARIA events, and that is what TRONTIER 2 and 3 are designed to show.

3. Comparative clinical efficacy in early symptomatic disease

3.1. Lecanemab: phase 3 efficacy data

Lecanemab's regulatory approval rests on the CLARITY AD phase 3 trial, which randomized 1,795 participants with MCI or mild AD dementia (MMSE 22–30, CDR-Global 0.5–1.0) to lecanemab 10 mg/kg biweekly or placebo for 18 months [3]. Entry required amyloid positivity by PET or CSF, now a standard gate for anti-Aβ treatment. On the primary endpoint, CDR-Sum of Boxes (CDR-SB) change from baseline, the between-group difference was -0.41 (95% CI: -0.57 to -0.25; $P < 0.001$), a 27% relative reduction in clinical progression [3].

The effect was consistent across all six CDR-SB domains, not carried by a single subscale. Secondary endpoints also favored lecanemab: amyloid PET standardized uptake value ratio fell by 55.5 Centiloids at 18 months (placebo: +3.6), plasma p-tau217 dropped by roughly half, and ADAS-Cog14, ADCS-MCI-ADL, and MMSE scores all moved in the same direction, though ADAS-Cog14 and ADCS-MCI-ADL did not always reach significance on their own [3]. Subgroup analyses showed consistent benefit across APOE ε4 genotypes, although APOE4 homozygotes had smaller effect sizes and markedly higher ARIA risk [3, 6]. The biomarker trajectory is worth noting in its own right: amyloid PET signal fell within months and kept falling, while p-tau217, a downstream

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marker of tau pathology, declined more slowly, which is consistent with amyloid removal preceding tau stabilization rather than both moving at once.

The 0.41-point CDR-SB difference over 18 months is small in absolute terms. Whether it counts as clinically meaningful is still argued over by regulators, payers, and patient groups [2, 8]. The European Medicines Agency first rejected marketing authorization on benefit-risk grounds in typical clinical populations, then granted approval with restrictions [2, 11]. Health technology assessment bodies in the United Kingdom and parts of Europe have likewise narrowed reimbursement, for the same reason. One useful way to read the number is not whether it is large, but whether slowing the slope by a quarter for eighteen months delays the point at which a patient needs full-time care, an outcome the long trials have not measured directly.

3.2. Trontinemab: phase 1/2 efficacy data

Trontinemab's efficacy evidence is still preliminary. The TRONTIER 1 phase 1b/2a dose-escalation study tested trontinemab at 0.3, 1.0, and 3.0 mg/kg every four weeks in participants with early symptomatic AD, with safety and amyloid PET reduction as primary endpoints [7]. At 28 weeks, all doses gave statistically significant amyloid reduction. The 3.0 mg/kg cohort reached about -65 Centiloids, comparable to lecanemab's 18-month reduction at 30-fold lower dose, which supports the Brainshuttle™ hypothesis [7]. The lower doses also produced meaningful reductions, and that matters because it gives a dose-ranging window for ARIA management that lecanemab's fixed high dose does not offer. TRONTIER 2 is testing higher doses. The phase 3 TRONTIER 3 trial, launched in 2024 with planned enrollment of about 1,500 participants, will assess CDR-SB at the optimized dose over 18 months, with primary completion expected in 2027 [7].

3.3. Efficacy comparison and evidence gaps

No head-to-head trial is yet available. Lecanemab has validated cognitive efficacy and an established regulatory pathway. Trontinemab's promise rests on extrapolated biomarker data and pending cognitive confirmation [2, 7]. The harder question is whether amyloid clearance rate, which trontinemab appears to match or exceed, predicts the same clinical slowing lecanemab showed, or whether faster clearance carries risks that only a large cognitive-endpoint trial will expose.

4. Safety profiles and amyloid-related imaging abnormalities

4.1. ARIA risk with lecanemab

Safety concerns for both antibodies center on ARIA, the dose-limiting toxicity class for anti-Aβ antibodies [6]. ARIA has two forms. ARIA-E is vasogenic edema or sulcal effusion seen as FLAIR hyperintensities on MRI, usually in the first 3–6 months of treatment [6]. ARIA-H is microhemorrhage or superficial siderosis on hemosiderin-sensitive sequences [6]. Both are thought to result from antibody-induced disruption of vascular amyloid with subsequent BBB compromise, with ARIA-E often preceding or co-occurring with ARIA-H [6]. The mechanism is not fully settled, and why some patients develop severe ARIA while most stay asymptomatic is one of the open problems in the field.

In CLARITY AD, ARIA-E occurred in 12.6% of lecanemab-treated participants versus 1.7% on placebo, with severe ARIA-E in 0.8% [3, 6]. ARIA-H microhemorrhages occurred in 17.3% versus 9.0%, and superficial siderosis in 5.6% versus 1.5% [3, 6]. APOE ε4 genotype strongly modifies

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risk: ARIA-E reaches about 35% in APOE4 homozygotes, which is why regulatory labeling requires genetic testing [3, 6]. Most ARIA events are asymptomatic and resolve after temporary dose interruption, although symptomatic ARIA requiring hospitalization occurs in roughly 3% of treated patients [6]. Rare fatal macrohemorrhages have occurred, mostly in patients on anticoagulation [6, 11]. Infusion-related reactions occur in about 20% of lecanemab recipients, are usually mild or moderate, and respond to premedication and slower infusion rates [3, 11].

Management depends on severity. Asymptomatic ARIA-E typically leads to dose interruption and a repeat MRI; many patients resume at the same or a reduced dose once imaging settles. Symptomatic ARIA prompts discontinuation. Current labeling also cautions against use with anticoagulants and calls for baseline and periodic MRI, a monitoring burden that limits uptake where imaging access is unreliable [3, 6]. This is a practical constraint that the efficacy debate often leaves out: a drug can be approved and still reach few patients if the required scans and genetic tests are not available locally.

4.2. ARIA and safety profile of trontinemab

Trontinemab's preliminary safety profile looks more favorable. In TRONTIER 1, ARIA-E across all dose cohorts was substantially below lecanemab rates, with no ARIA-related discontinuations [7]. The lower ARIA rate likely reflects lower systemic antibody exposure and reduced Fc-mediated inflammation [4, 7]. TRONTIER 1 was not powered to compare ARIA, so TRONTIER 2 and 3 data are needed before any safety claims can be made [7, 10]. The same caveat applies to long-term tolerability and to whether the TfR-binding arm produces off-target effects over years of dosing. Until TRONTIER 3 reports, trontinemab's safety advantage is a plausible hypothesis supported by early data, not an established fact.

4.3. Dosing srategy and contraindications

Dosing strategy is where the ARIA ceiling turns into an operational problem. Lecanemab uses a titration schedule, starting below 10 mg/kg for the first two infusions before reaching the full dose, precisely because ramping up too fast raises ARIA-E risk [3, 6]. Even with that step-up, the rate in APOE4 homozygotes stays high enough that some guidelines argue against treatment in that group [3, 6]. Trontinemab's lower projected dose may remove the need for titration, but that has not been tested head-to-head, and the absence of dose escalation in its early trials reflects study design more than proven safety. A second operational point is the anticoagulation contraindication. Lecanemab labeling warns against concurrent anticoagulants because of macrohemorrhage risk, which excludes a sizeable share of older patients who are on warfarin or direct oral anticoagulants for atrial fibrillation [6, 11].

5. Clinical implications and future research priorities

5.1. Treatment selection in clinical practice

Two patterns emerge from the comparison above. First, anti-Aβ therapy is moving from dose-intensive conventional antibodies to engineered constructs with intrinsic brain-targeting [4, 7]. Lecanemab is the current standard of care, with phase 3 data behind it and approvals in several jurisdictions, but its use is constrained by poor BBB penetration [2, 3, 11]. Trontinemab's Brainshuttle™ design may shift several dimensions of treatment at once: lower therapeutic doses

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could improve safety margins, particularly for ARIA-vulnerable populations such as APOE4 homozygotes and patients on anticoagulation [6, 7]. Lower infusion burden and total antibody exposure may also improve access and adherence [1, 8].

In practical terms, treatment selection today is mostly a question of whether a patient qualifies for lecanemab at all. Amyloid confirmation, APOE genotyping, and baseline MRI are prerequisites, and a patient on anticoagulation or with prior macrohemorrhage is usually excluded [3, 6]. Trontinemab, if its phase 3 data hold up, could widen that eligible pool by lowering the ARIA ceiling, but it will still require amyloid confirmation and monitoring. The two drugs are therefore not simply competitors; they may serve different segments of the same patient population, with trontinemab aimed at those whom lecanemab's safety profile currently shuts out. Several questions remain unresolved. The optimal window for starting treatment, the minimum effective dose and treatment duration, the validation of plasma biomarkers for treatment monitoring, and the role of combination strategies with anti-tau agents all need more work [8, 10].

5.2. Access, equity and health system barriers

Equitable access is a major concern. Current annual pricing limits use mostly to high-income healthcare systems and worsens global disparities, and that problem will not solve itself as new antibodies enter the market [1, 8]. Future research should focus on head-to-head comparative trials, real-world effectiveness studies in diverse populations, and subcutaneous formulations to broaden access [1, 8]. Biomarker-guided patient selection, drawing on APOE genotyping, baseline amyloid and tau PET, and longitudinal plasma p-tau217 monitoring, will be central to precision medicine in AD [6, 8]. The regulatory science is also unsettled. Agencies have taken different positions on the same efficacy data, and there is no agreed threshold for what level of CDR-SB slowing is worth the ARIA risk and the cost. TRONTIER 3 will give regulators a second dataset against which to calibrate that judgment, and its results may confirm the current approach or push the field toward lower-dose, brain-targeted antibodies as the new default. The efficacy and safety data, however solid, sit on top of a delivery chain that breaks easily outside specialist centers. A patient must first be picked up through cognitive screening, then referred to a memory clinic, confirmed amyloid-positive by PET or CSF, genotyped for APOE, and enrolled in a monitoring program with reliable MRI access [1, 6]. In many health systems the PET scanner, the genetics lab, and the infusion chair are in different cities, and the follow-up scans that ARIA management requires are the step most likely to be dropped [1, 8]. Trontinemab does not bypass these requirements; it may only lower the frequency of scans if its ARIA rate proves lower [6, 7]. Real-world uptake will therefore depend less on which antibody wins the trials than on whether health systems can run the diagnostic and monitoring pathway at scale, a question the phase 3 results will not answer on their own.

6. Conclusion

Alzheimer's disease is one of the defining health challenges of this century. The arrival of disease-modifying anti-amyloid antibodies marks a shift from treating symptoms to addressing biology, and that shift is still incomplete. This review compared lecanemab and trontinemab as representatives of two therapeutic generations: dose-intensive conventional antibodies and brain-penetrating constructs. Lecanemab is the current clinical standard, with well-validated evidence of cognitive benefit in early symptomatic AD: a 27% reduction in CDR-SB progression at 18 months and well-characterized safety. The 10 mg/kg biweekly dose, however, drives ARIA in roughly one in eight patients, with higher rates in APOE4 homozygotes, and limits global access. Trontinemab, using

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TfR-mediated Brainshuttle™ transcytosis, cleared amyloid rapidly at 3–30 fold lower doses than lecanemab in phase 1/2 trials, with possibly lower ARIA rates across all doses tested. Whether this biomarker advantage translates into cognitive benefit awaits the ongoing TRONTIER 3 phase 3 trial, with results expected in 2027. If TRONTIER 3 succeeds, trontinemab would set a new therapeutic index benchmark for AD immunotherapy. If it fails, the field will still have lecanemab, and the lesson will be that biomarker clearance alone is not enough to guarantee clinical slowing.

Several priorities follow. The field needs head-to-head comparative trials that establish relative efficacy and safety profiles, validated plasma biomarker algorithms that allow personalized treatment adjustments, rational combinations against amyloid and tau together, and policy frameworks that make these therapies affordable in low- and middle-income settings. How the field handles brain-penetrating antibody design, biomarker-guided patient selection, and access will determine whether disease-modifying AD therapy lives up to its promise. For now, lecanemab is the only anti-Aβ antibody with both phase 3 cognitive benefit and broad regulatory approval, and trontinemab's eventual role will depend on whether the biomarker gains observed in TRONTIER 1 translate into measurable cognitive slowing in TRONTIER 3.

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