Prepared by: Dr. James Rini, MD, MPH | Section Head, Ochsner Neurocognitive Program

Alzheimer's disease (AD) has long challenged the boundaries of medicine, given its slow, degenerative course and the limited efficacy of symptomatic treatments. However, the recent FDA approvals of two monoclonal antibodies-**Lecanemab (Leqembi™)** and **Donanemab (Kisunla™)**-mark a shift toward disease-modifying approaches. These agents target amyloid-beta (Aβ), a hallmark pathology in AD, but they differ in molecular target, trial design, efficacy profiles, and risk profiles.

Mechanisms of Action and Targets

- **Lecanemab** binds to **soluble Aβ protofibrils**, targeting early toxic species before plaques form. These protofibrils are believed to drive early neurotoxicity.
- **Donanemab** binds to a **pyroglutamate Aβ epitope**, present **only in deposited amyloid plaques**, directly engaging established pathology.

Head-to-Head Comparison Table

Metric	*Lecanemab (Leqembi™)*	*Donanemab (Kisunla™)*
Mechanism	Targets soluble Aβ protofibrils	Targets deposited plaques (N-terminal pyroglutamate Aβ)
Manufacturer	Eisai (lead), co-promoted with Biogen	Eli Lilly
FDA Approval Date	July 6, 2023	July 2, 2024
Trial Basis	Phase 2 and Phase 3 (Clarity AD)	Phase 2 and Phase 3 (TRAILBLAZER-ALZ 2)
Trial Duration	18 months	76 weeks (18 months)
Participants	~1,800	1,736
Primary Endpoint	CDR-SB (0–18 scale)	iADRS (0–144 scale)
Efficacy (CDR-SB)	0.45-point improvement (**27% slowing**)	0.67-point improvement (**36% slowing in low/medium tau**); **0.70-point / 28.9% slowing overall**
Efficacy (iADRS)	Not a primary endpoint	3.25-point difference (**35.1% slowing** in low/medium tau); **2.92-point / 22.3% slowing overall**
Amyloid Reduction	–59.1 Centiloids	–88 Centiloids
Dosing Schedule	IV infusion every 2 weeks	IV infusion every 4 weeks (stopped after plaque clearance)

ARIA-E (Brain Swelling)	12.6% overall; 2.8% symptomatic	24.0% overall; 6.1% symptomatic
ARIA-H (Microhemorrhage)	Severe bleeding in 5 cases	Severe bleeding in 7 cases; 3 fatal cases
Infusion Reactions	26.4%	8.7%
Deaths in Trial	5 treatment-related bleeding events	3 treatment-related deaths
Plasma Biomarkers	No clear tau lowering shown	Reduced plasma P-tau217
MRI Volume Changes	Data not highlighted	Accelerated brain atrophy noted (↓ brain volume, ↑ ventricles)
Eligibility	MCI or mild dementia due to AD with confirmed amyloid	Same, with additional **tau stratification by PET**
Exclusion Criteria	>4 microhemorrhages, superficial siderosis, seizures, etc.	Same + **extensive tau burden**, severe white matter disease
Cost Estimate	~$5,300/year (Medicare co-insurance)	~$6,400/year (Medicare co-insurance)

Clinical Interpretation and Considerations

While both lecanemab and donanemab demonstrated statistically significant effects in reducing amyloid plaque burden and slowing clinical progression in early-stage Alzheimer's disease, the **clinical significance** of these findings remains a subject of active discussion within the neurology community.

1. Modest Effect Sizes vs. Meaningful Change

The **minimal clinically important difference (MCID)** for both the **Clinical Dementia Rating–Sum of Boxes (CDR-SB)** and the **Integrated Alzheimer's Disease Rating Scale (iADRS)** exceeds the average treatment-placebo differences reported in the pivotal trials:

For CDR-SB, the MCID is generally estimated at **1.0 points for mild cognitive impairment (MCI)** and **1.6 points for mild dementia**. Lecanemab's treatment effect in the Clarity AD trial yielded a **0.45-point difference**, and donanemab's effect in TRAILBLAZER-ALZ 2 was **0.67 points** in the low/medium tau group—both **below thresholds typically considered perceptible to patients or caregivers**.

Similarly, **iADRS** changes of **3.25 points (donanemab)** also fall below the **MCID of 5 to 9 points**, depending on disease severity.

Thus, while percentage slowing (e.g., 27% or 36%) appears favorable, **absolute cognitive gains** remain **modest**. These effects may be more meaningful when compounded over time or used in conjunction with other interventions, but on their own, they may not translate to a noticeable change in day-to-day functioning for many patients.

2. Real-World Applicability and Safety Caveats

The safety profile of both agents—particularly regarding **amyloid-related imaging abnormalities (ARIA)** and **brain atrophy**—necessitates caution when translating these therapies to general clinical practice:

In trials, **MRI monitoring was intensive**, with prespecified imaging intervals and rapid management of ARIA events. In real-world settings, this level of surveillance may not be consistently feasible, particularly in resource-limited or rural clinics.

Rates of **ARIA-E** and **ARIA-H** were significantly higher in **ApoE ε4 carriers**, especially homozygotes, underscoring the importance of **genetic testing prior to initiation**. Yet in clinical settings, **access to ApoE genotyping** and **neurologist-led oversight** may be variable.

Accelerated brain atrophy, including decreased total brain volume and increased ventricular size, was observed in donanemab-treated patients. While amyloid removal may unmask underlying neurodegeneration, the phenomenon raises concerns about **net neuroanatomical impact** of these therapies, especially over longer durations.

In this context, **the number needed to harm (NNH)** has been estimated at approximately **3**, meaning for every three patients treated, one may experience a serious adverse effect, including ARIA-related bleeding or edema. This must be weighed carefully against the potential—but modest—clinical benefit.

3. Role of Biomarkers and Tau Stratification

Patient selection is key to maximizing benefit and minimizing harm:

Donanemab trials incorporated **tau PET imaging** to stratify participants by disease stage. Results suggested greater benefit in those with **low-to-moderate tau burden**, likely representing an **earlier, more modifiable disease stage**. This stratified approach supports more **precision-based prescribing**, though tau PET remains **costly and less accessible** than amyloid PET or CSF analysis.

In contrast, **lecanemab** showed **consistent efficacy** across a more generalized early AD cohort, suggesting broader applicability without the need for tau staging. This may make lecanemab more **clinically feasible** in diverse practice settings where tau PET is unavailable.

4. Caution in Interpreting Comparative Efficacy (27% vs. 32–36%)

While public and professional discussions often cite that **lecanemab slowed clinical decline by 27%** and **donanemab by 32–36%**, this apparent difference **does not represent a true head-to-head comparison** and should be interpreted with caution.

- The **27% figure for lecanemab** comes from the **Clarity AD trial**, which used the **Clinical Dementia Rating–Sum of Boxes (CDR-SB)** as its primary endpoint across a broad early Alzheimer's population (mild cognitive impairment or mild dementia due to AD) with amyloid confirmation via PET or CSF.
- The **35–36% figure for donanemab** comes from a **subgroup analysis** of the **TRAILBLAZER-ALZ 2 trial**, focusing on participants with **low/medium tau pathology** as determined by tau PET. This represents a **more narrowly defined, earlier-stage cohort**, excluding individuals with higher tau burden—a criterion not applied in the lecanemab trial.

Importantly, the **overall efficacy of donanemab** across the full population—including those with both low/medium and high tau levels—was:

- **28.9% slowing on CDR-SB**
- **22.3% slowing on iADRS**

This means that **the true CDR-SB-based average slowing across all donanemab-treated participants was 28.9%**, which is **comparable to lecanemab's 27%**, and that the oft-cited **22% figure applies to iADRS**, not CDR-SB.

Key Points for Interpretation:

- **CDR-SB and iADRS are different instruments**, each with distinct ranges, sensitivities, and minimal clinically important differences (MCIDs). Presenting percentage slowing without specifying the underlying scale can **create a misleading sense of comparative superiority**.
- The **effect sizes for both therapies are modest in absolute terms**, and **well below the MCID** for either instrument in most cases.
- These percentages reflect **group-level trends**, not the likely clinical experience of any individual patient. They **do not account for heterogeneity in patient trajectory, risk tolerance, or comorbidities**.

Bottom Line:

The difference between **27% and 28.9%** or even **35% in selected subgroups** is **not clinically decisive**. More importantly, these results:

- Reflect trials with **different designs, biomarkers, and outcome measures**
- Represent **average deltas**, not guaranteed outcomes
- Should not be interpreted as clear evidence of one agent's superiority

Until **direct comparative trials** or **individual patient-level meta-analyses** are available, decisions between these therapies should be made based on:

- **Patient eligibility and biomarker profile**
- **ARIA risk and ApoE genotype**
- **MRI access and clinical monitoring infrastructure**
- **Patient and caregiver goals of care**

In sum, **percent slowing alone is not a sufficient basis for choosing between agents**. Careful contextualization is essential.

Conclusion

Lecanemab and donanemab represent a promising new class of **anti-amyloid immunotherapies**, marking the beginning of disease-modifying treatment in Alzheimer's care. Despite a shared class effect, their **pharmacologic targets**, **administration schedules**, **treatment algorithms**, and **risk-benefit profiles** differ meaningfully.

- **Lecanemab** offers a **predictable, biweekly regimen** that targets protofibrils, potentially offering earlier intervention but requiring longer cumulative exposure.
- **Donanemab** aims for **aggressive plaque clearance**, with the possibility of treatment discontinuation, and demonstrates **greater relative efficacy** in **biomarker-selected subgroups**, but at the cost of more pronounced brain volume loss and a higher ARIA burden.

Ultimately, both agents require:

- **Rigorous patient screening**, including biomarker confirmation of amyloid pathology.
- **Baseline and serial MRI surveillance** for ARIA.
- **Genetic counseling and ApoE genotyping**, when available.
- **Close neurologic oversight**, ideally within multidisciplinary memory clinics or centers equipped for high-touch monitoring.

Their use should be guided not solely by FDA approval but by **individualized assessment of risk, benefit, access to monitoring infrastructure, and patient/family goals of care**. As more data emerge from **long-term open-label extensions** and **real-world cohorts**, clinicians will be better positioned to refine use of these agents in practice.

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