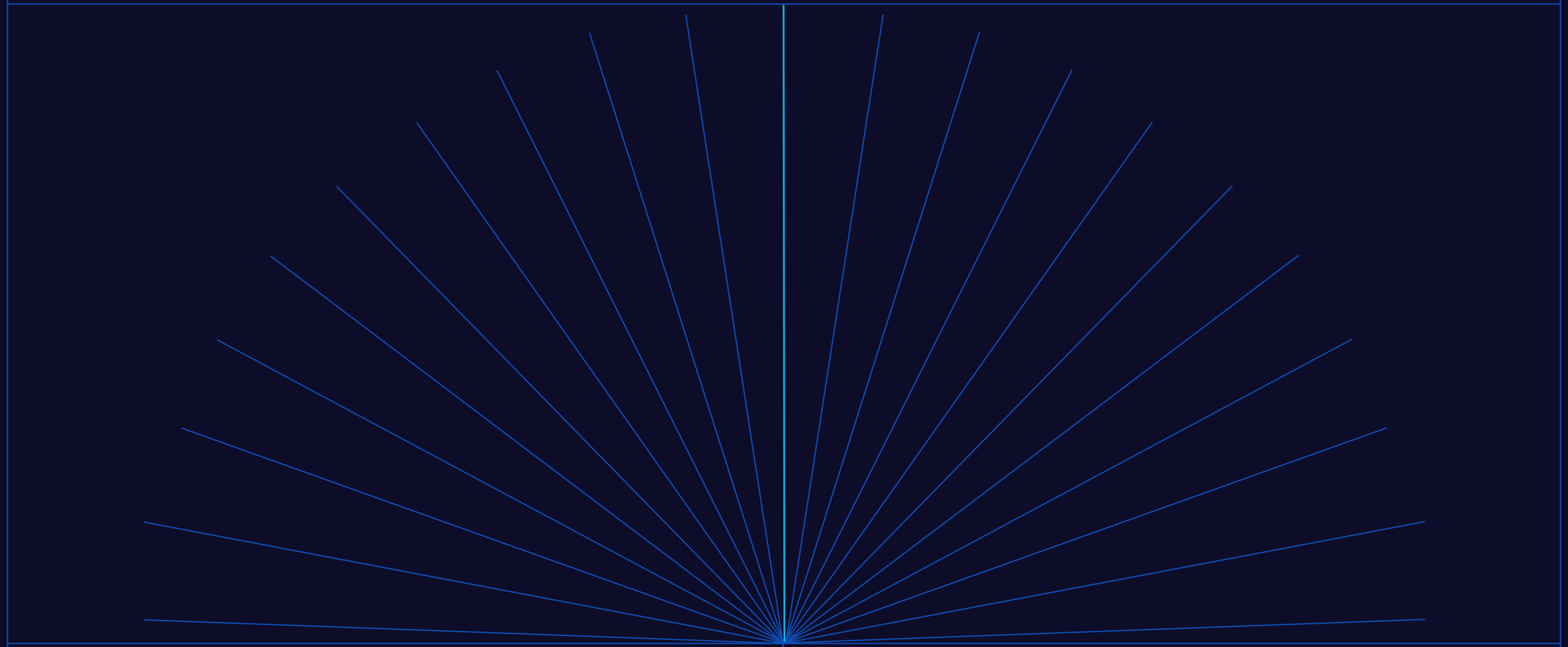


Sleuth

Novel approaches are arising and will be tested through early 2027

The pipeline is diversifying. Whether that converts to approvals is what the next year decides

THE PIPELINE

155

active programs

Neuroinflammation now leads with 31 programs, overtaking amyloid (28) for the first time.

Despite this shift, only amyloid-targeting drugs have reached approval, with no other class passing the approval bar.

THE PATTERN

70%

Phase 1 pass rate

Both amyloid and tau clear Phase 1 at 70%, well above the 48% CNS average.

But Phase 3 tells the real story: amyloid drops to 25% and tau falls to 0%.

THE TEST

4

binary catalysts by early 2027

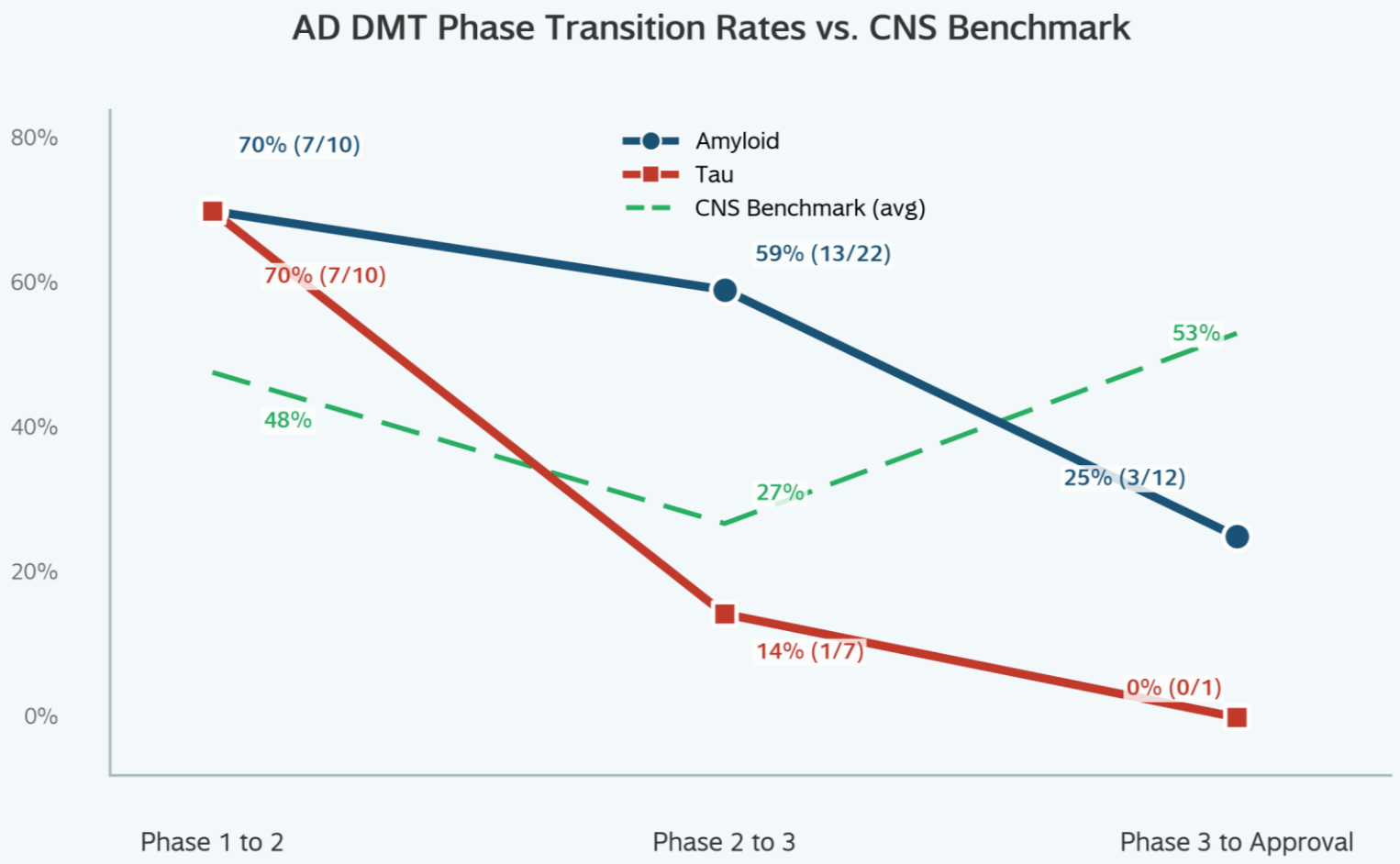
Four readouts will test whether non-amyloid biology can produce clinical proof.

Diranersen, XPro1595 and AR1001 read in 2H 2026. Buntanetap follows in early 2027.

Together they test whether oral and precision approaches can clear the bar.

Permissive Phase 1 gates mask a collapse that kills most AD programs

Amyloid and tau both clear Phase 1 at 70%, 22% above the CNS benchmark, then diverge sharply at Phase 3

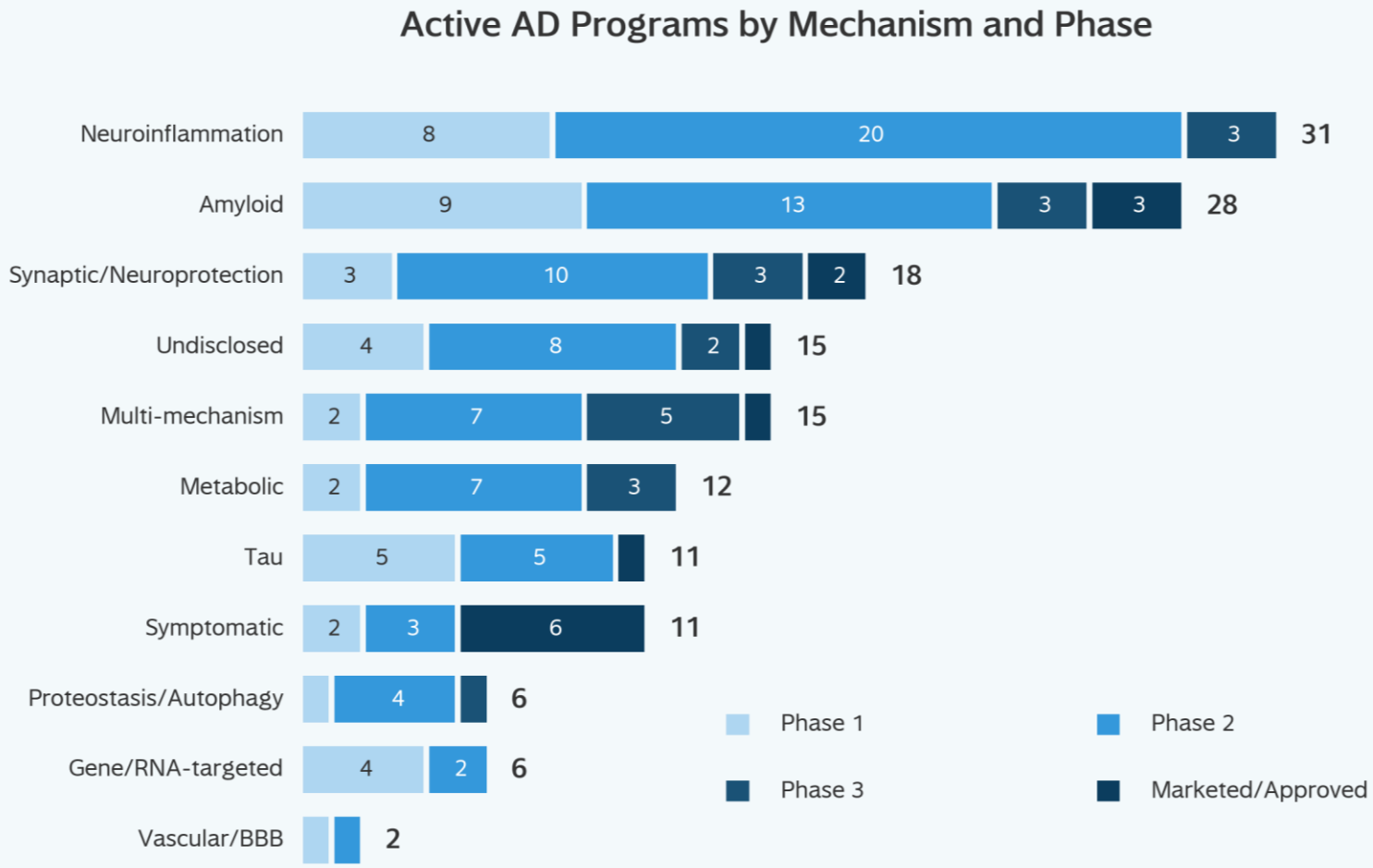


- 70% Phase 1 clearance for both classes runs 22% above the 48% CNS average, so early safety data inflates perceived viability
- Amyloid's 25% is 3 wins from 12 Phase 3 tries: lecanemab and donanemab slowed CDR-SB, validating the target at brutal cost
- Tau's 0% rests on one Phase 3 program, TauRx's LMTM, signaling the class as barely tested
- A 2% overall approval rate from 155 active programs signals that pipeline volume reflects low early bars, not validated biology

Transition success rates for AD disease-modifying therapies by target class against CNS and all-indication clinical development benchmarks (BIO/Informa/QLS 2011-2020). Each rate is computed on its own analyzable cohort of historical programs that reached that gate, not one cohort flowing through, so denominators differ by phase and do not sum sequentially. Data labels show passing/reaching counts; amyloid n=10 at Phase 1, 22 at Phase 2, 12 at Phase 3; tau n=10, 7, 1. The CNS benchmark is an external published rate, shown as a percentage only. Approved AD DMTs: lecanemab, donanemab, aducanumab (withdrawn). Mid-2026 pipeline cut.

Pipeline diversification has grown but has yet to produce approvals

Neuroinflammation overtakes amyloid in program count for the first time, yet only amyloid has converted



- Neuroinflammation leads with 31 programs to 28 for amyloid, a reversal that reflects capital flowing toward alternative approaches
- 43% of active programs sit in Phase 2 while only 19 reach Phase 3, so the pipeline is accumulating at the stage before proof-of-concept
- No class beyond amyloid is proven, meaning that PoC rests on a few early-2027 readouts
- Optionality is real, yet each non-amyloid bet remains pre-proof, making the next year crucial for validating alternative approaches

Analysis of 155 active Alzheimer's therapeutic programs tracked across 11 mechanism classes (neuroinflammation, amyloid, synaptic/neuroprotection, multi-mechanism, undisclosed, metabolic, tau, symptomatic, gene/RNA-targeted, proteostasis/autophagy, vascular/BBB) as of mid-2026. Phase distribution based on highest active phase per program. Approvals limited to post-2020 disease-modifying therapies with FDA action.

Even the best-validated class fails 75% of Phase 3 programs before approval

Only amyloid has cleared the approval bar, and every other class still stalls before Phase 3 proof

Phase Transition Success Rates by Mechanism Class

Target Class	Phase 1 to 2	Phase 2 to 3	Phase 3 to Appr.
Amyloid	70%	59%	25%
Tau	70%	14%	0%
Neuroinflammation	60%	33%	29%
Synaptic / Neuroprotection	55%	46%	N/A
Metabolic	14%	0%	0%
Other	33%	17%	25%
CNS Benchmark (avg)	48%	27%	53%

Rates = % of programs advancing to the next phase, higher is better.

Red marks rates below the CNS benchmark at that gate.

Other = 7 heterogeneous mechanisms (see source note), mapping to Slide 4 classes.

- Amyloid is the only validated class, yet 3 of 12 clear Phase 3, so approval pedigree does not de-risk a new entrant
- Neuroinflammation leads on program count but converts 2 of 7 at Phase 3, meaning that capital is running ahead of the evidence
- Tau sits unproven at 0 of 1 through Phase 3, leaving diranersen as the class's real test
- Metabolic posts 0 of 6 then 0 of 3 at the late gates, a biology-limited dead end, not a fixable trial-design problem

Phase transition success rates by mechanism class, AD disease-modifying programs, historical clinical-stage universe. Benchmarks from BIO/Informa/QLS Clinical Development Success Rates 2011-2020. Rates = % of programs advancing to the next phase, higher is better. CNS Benchmark = average transition rate across all CNS classes. Each rate is computed on its own analyzable cohort of historical programs that reached that gate, not one cohort flowing through, so denominators differ by phase and do not sum sequentially. Per-class Phase 3 analyzable n: amyloid 12 (3 approved), neuroinflammation 7, tau 1, metabolic 3 (and 6 at Phase 2 to 3). Other = 7 heterogeneous mechanisms: infection/gingipain, gut microbiome, regenerative/stem-cell, vascular, oxidative-stress/chelation, cortisol-axis, and multimodal or undisclosed. These map roughly to Slide 4's Gene/RNA, Proteostasis/Autophagy, Vascular, and Undisclosed classes.

Ten non-amyloid programs show positive signals, but none has cleared Phase 3

The gap between encouraging Phase 2 biomarker data and Phase 3 clinical proof remains the central risk

Non-Amyloid Programs by Signal and Current Phase

Program	Mechanism	Signal evidence	Signal stage	Current phase
Buntanetap	Multi-target	Cognition in pTau217+ subgroup	Phase 3	Phase 3
AR1001	PDE5 inhibitor	Tolerability, biomarker shifts	Phase 2	Phase 3
Masitinib	Mast cell / microglia	CDR-SB slowing (AB09004)	Phase 3	Phase 3
XPro1595	Soluble TNF	MRI myelin signal, biomarker	Phase 2	Phase 2/3
Diranersen	Tau ASO	CSF tau drop, cognitive trend	Phase 2	Phase 2
Etalanetug	MTBR tau antibody	Tau PET drop in DIAN-TU	Phase 2	Phase 2
MK-2214	pS413 tau antibody	CSF target engagement	Phase 1/2	Phase 2
Sargramostim	GM-CSF immune	MMSE gain, biomarker shifts	Phase 2	Phase 2
Lomecel-B	MSC cell therapy	Hippocampal volume held	Phase 2	Phase 2
Obicetrapib	CETP / cholesterol	Biomarker change in early AD	Phase 2	Phase 2

Current development phase: Phase 2 · Phase 2/3 · Phase 3

- Diranersen CELIA missed its primary dose-response endpoint but showed cognitive benefit in pre-specified secondary analyses
- XPro1595 MRI myelin stabilization shows precision TNF targeting can reach a structural endpoint beyond biomarker engagement
- Buntanetap cognitive benefit came from a pTau217-positive subgroup post hoc, so the oral DMT thesis needs prospective proof
- Non-amyloid evidence now spans biomarker-to-cognition links, structural MRI endpoints, target engagement and subgroup cognition

Positive-signal assessment based on published Phase 2 outcomes for approximately 20-25 non-amyloid programs with reported efficacy data. Signal stage is the trial phase that produced each signal. The colored tag is the program's current development phase. Diranersen CELIA missed its primary dose-response endpoint (CDR-SB, Week 76). Cognitive benefit appeared in pre-specified secondary analyses alongside robust CSF tau reduction. Named programs: diranersen (tau ASO), XPro1595 (soluble TNF, MRI signal), buntanetap (multi-target oral, cognition in pTau217+ subgroup), AR1001 (PDE5 inhibitor). Signal classification based on clinical and biomarker endpoints reported through mid-2026.

AAIC 2026 is a mechanism-selection meeting, not an amyloid lifecycle update

The confirmed slate is dominated by non-amyloid programs presenting first clinical data at a venue

AAIC 2026 Catalyst Assessment

Diranersen / BIIB080 — MUST-WATCH

Biogen / Ionis

Tau ASO (antisense oligonucleotide)

Full CELIA Phase 2 readout in mild AD

XPro1595 — MUST-WATCH

INmune Bio

Selective soluble TNF neutralization

MINDFuL MRI and clinical dataset

Spectris AD — WATCH

Cognito Therapeutics

Gamma entrainment / neural stimulation

Biomarker and clinical data from pivotal

Laromestrocel — WATCH

Longeveron

Allogeneic MSC cell therapy

CLEAR MIND Phase 2a full results

Donanemab — WATCH

Eli Lilly

Anti-amyloid antibody (lifecycle)

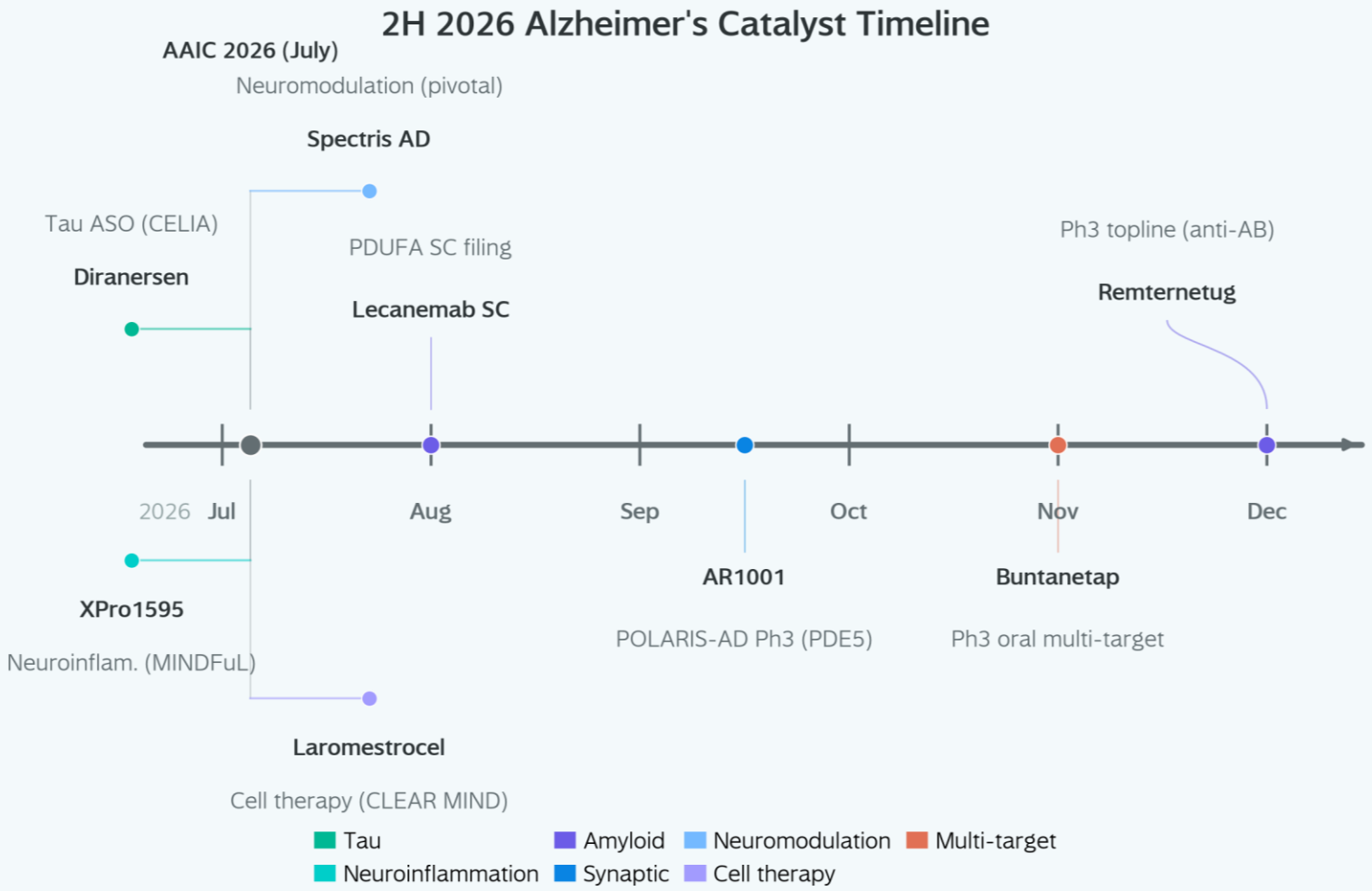
TRAILBLAZER-ALZ 5 prevention data

- Credible signals from both tau and neuroinflammation would shift the evidence base from amyloid monopoly to multi-mechanism
- MUST-WATCH means a first clinical read on a novel mechanism at a major venue that can validate a class and move consensus
- WATCH covers confirmatory or lifecycle data informing positioning rather than class viability, so paradigm stakes are lower

Based on 5 confirmed AAIC 2026 presentations with clinical data as of June 2026. n = 5 programs assessed. Priority classification: MUST-WATCH assigned to programs presenting novel mechanism data for the first time at a major venue (diranersen, XPro1595). WATCH assigned to programs with confirmatory data or lifecycle updates (Spectris AD, laromestrocel, donanemab). Rating reflects novelty of mechanism, data maturity stage, and potential to shift clinical consensus. Diranersen CELIA Phase 2 missed its primary dose-response endpoint (CDR-SB Week 76). The cognitive read came from pre-specified secondary analyses alongside robust tau-biomarker reduction.

2H 2026 concentrates more non-amyloid readouts than any prior half-year window

AAIC through year-end delivers 8 binary catalysts across tau, neuroinflammation, and oral DMT gates



- Four AAIC readouts cluster in one July week, concentrating non-amyloid verdicts on tau, neuroinflammation, and cell therapy.
- AR1001 and buntanetap are the first oral non-amyloid Phase 3 DMTs, with AR1001 reading Q3 2026 and buntanetap early 2027.
- By early 2027, these readouts collectively decide whether diversification converts or amyloid keeps its monopoly

Catalyst timeline for AD disease-modifying therapies with binary readouts from July 2026 onward. n = 8 events on a 2H 2026 calendar. Programs: diranersen (tau ASO, AAIC), XPro1595 (neuroinflammation, AAIC), Spectris AD (neuromodulation, AAIC), laromestrocel (cell therapy, AAIC), lecanemab SC (amyloid, PDUFA August 2026), AR1001 (PDE5, POLARIS-AD Phase 3 topline Q3 2026), buntanetap (multi-target oral, Phase 3 6-month readout guided to Q1 2027), remternetug (amyloid, TRAILRUNNER-ALZ 1 expected complete March 2026, topline pending at mid-2026 cut). Semaglutide EVOKE/EVOKE+ reported negative topline November 2025, excluded. Mid-2026 pipeline cut.

Oral Phase 3 is an amyloid graveyard that two non-amyloid DMTs now enter first

An oral non-amyloid win would differentiate AD treatment on access and convenience

Oral AD Phase 3 by Mechanism

Program	Mechanism	Modality	Ph3 Entry	Status
AMYLOID-PATHWAY ORAL				6 of 6 failed
Tramiprosate	Anti-aggregation	Small molecule	2005	FAILED
Tarenflurbil	Gamma-sec. mod.	Small molecule	2005	FAILED
Semagacestat	Gamma-sec. inh.	Small molecule	2008	FAILED
Verubecestat	BACE inhibitor	Small molecule	2013	FAILED
Atabecestat	BACE inhibitor	Small molecule	2015	FAILED
Lanabecestat	BACE inhibitor	Small molecule	2014	FAILED
NON-AMYLOID ORAL				1 failed, 2 pending
Idalopirdine	5-HT6 antagonist (symptomatic)	Small molecule	2015	FAILED
Buntanetap	Multi-target DMT	Small molecule	2024	PENDING
AR1001	PDE5 inhibitor DMT	Small molecule	2024	PENDING

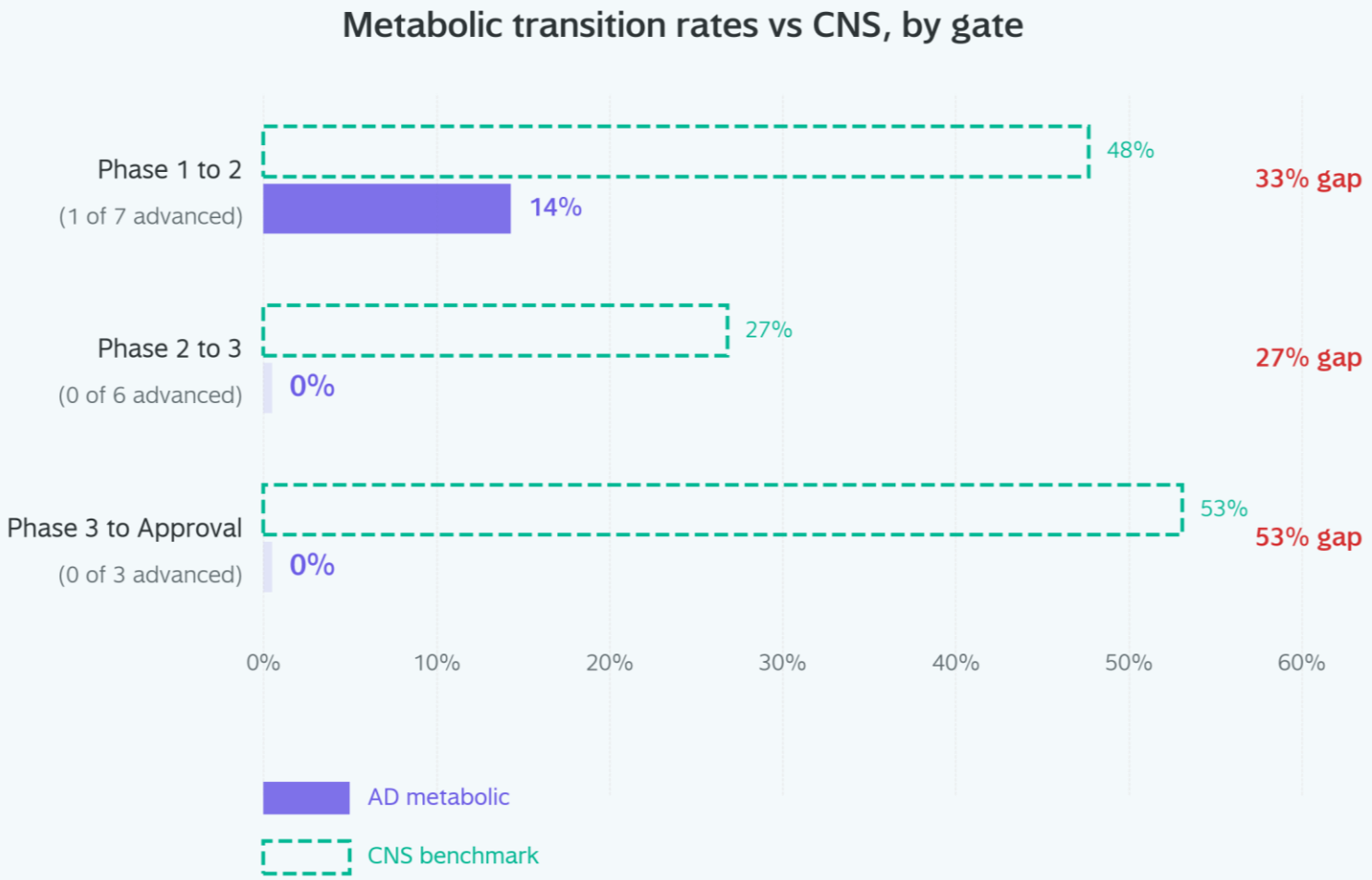
FAILED = Phase 3 failure PENDING = Phase 3 readout pending

- Buntanetap and AR1001 enter Phase 3 as the first oral non-amyloid DMTs, testing biology that amyloid oral never cleared
- A positive oral DMT would remove the infusion requirement from AD treatment, opening the market to primary-care prescribing
- Clearing that ceiling would pull capital and access past the infusion-bound amyloid antibodies and reset 2027 investment flows

Competitive-intelligence review of oral disease-modifying therapies that reached Phase 3 in Alzheimer's disease, classified by mechanism and Phase 3 entry year. n = 9 oral programs (6 amyloid-pathway, 3 non-amyloid). Of the 7 prior oral Phase 3 programs, 6 targeted amyloid via BACE or gamma-secretase and all 6 failed. Amyloid-pathway oral failures: tramiprosate (anti-aggregation, 2005), tarenflurbil (gamma-secretase modulator, 2005), semagacestat (gamma-secretase inhibitor, 2008), verubecestat (BACE inhibitor, 2013), lanabecestat (BACE inhibitor, 2014), atabecestat (BACE inhibitor, 2015). Non-amyloid oral: idalopirdine (5-HT6 antagonist, 2015, failed, classified as symptomatic), buntanetap (Annovis Bio, multi-target DMT, 2024, Phase 3 readout pending), AR1001 (AriBio, PDE5 inhibitor DMT, 2024, Phase 3 readout pending). All compounds are small-molecule oral agents.

No metabolic approach has cleared the Phase 2 bar despite repeated attempts

1 of 7 cleared Phase 1 to 2, then 0 of 6 and 0 of 3 in the separate cohorts reaching each later gate



- Semaglutide's EVOKE failure confirms the GLP-1 epidemiologic signal does not translate to cognitive benefit in AD trials.
- Named failures span GLP-1, insulin, SGLT2, and PPAR-gamma, covering every major metabolic hypothesis tested in AD.
- The 27% to 53% shortfall versus CNS benchmarks at each gate implicates mechanism-level biology over trial design.
- Future metabolic bets would need biomarker-selected cohorts and mechanism-specific endpoints that are not yet validated.

Transition success rates for the metabolic target class in Alzheimer's disease versus CNS clinical development benchmarks (BIO/Informa/QLS 2011-2020). Each rate is computed on its own analyzable cohort of programs that reached that gate, so the denominators differ by phase and do not sum sequentially. Phase 1 to 2: 14% (1 of 7) versus 47.7% CNS benchmark. Phase 2 to 3: 0% (0 of 6) versus 26.8% CNS benchmark. Phase 3 to approval: 0% (0 of 3) versus 53.1% CNS benchmark. The 3 programs at the Phase 3 gate (rosiglitazone, pioglitazone/TOMMORROW, intranasal insulin) reached Phase 3 historically and are not survivors of the 6 at the Phase 2 to 3 gate. Named failures include semaglutide (EVOKE/EVOKE+ Phase 3, negative topline November 2025), intranasal insulin, pioglitazone, liraglutide, and dapagliflozin. Metabolic class defined as programs whose primary mechanism targets insulin signaling, GLP-1, SGLT2, or related metabolic pathways. Mid-2026 pipeline cut.

Only amyloid has converted pipeline breadth into approvals across six classes

155 programs span 6 mechanism classes but non-amyloid Phase 3 attrition tops 70% with no approvals

AD Mechanism Scorecard by Target Class

Mechanism	Programs	Ph 3	Appr.	Ph 3 Attr.	Key 2026-27 Catalyst	Strategic Verdict
Amyloid	28	3	3	75%	Remternetug, Lecanemab SC	The only class that turned breadth into approvals. Compete on access
Neuro-inflam.	31	3	0	71%	XPro1595 AAIC readout	Biggest pipeline, zero approvals. XPro1595 is the proof-of-concept gate
Tau	11	0	0	100%	Diranersen AAIC readout	100% Phase 3 attrition to date. Diranersen is the last realistic shot
Synaptic / Neuroprot.	18	3	0	no data	AR1001 POLARIS-AD	Heterogeneous, thin, untested late. AR1001 is the only near-term signal
Metabolic	12	3	0	100%	Semaglutide (negative)	0% conversion at Phase 2 and 3. No credible path forward
Other	44	8	0	75-83%	Buntanetap Phase 3	Gene, vascular, multi-mechanism. Buntanetap is the standout Phase 3 test

- Amyloid is the only class that turned breadth into approvals. Neuroinflammation leads on count at 31 yet still sits at zero, the field's largest unproven bet.
- Tau and metabolic both post 100% Phase 3 attrition, which points to biology limits the trial design cannot fix. Diranersen is tau's last realistic shot.
- Four readouts by early 2027 decide whether any non-amyloid class clears the Phase 3 conversion ceiling.

Mechanism scorecard for the Alzheimer's disease pipeline by target class, scoped to the six target classes the historical attrition analysis supports: amyloid, neuroinflammation, tau, synaptic/neuroprotection, metabolic, and a heterogeneous Other class that rolls up gene/RNA-targeted, vascular/BBB, proteostasis/autophagy, multi-mechanism, and undisclosed programs. Columns: total active programs, current Phase 3 programs, approved disease-modifying therapies, Phase 3 attrition rate, key 2026-27 catalyst, and strategic verdict. n = 155 active AD programs across all phases, of which 144 are disease-modifying. Phase 3 attrition computed on the analyzable historical cohort that reached the Phase 3 to registration gate for each class, so denominators differ by class and do not sum sequentially. Symptomatic programs (11) are tracked in the landscape but excluded from the mechanism-class count. Mid-2026 pipeline cut; catalyst dates company-guided.

Four binary catalysts by early 2027 will resolve whether AD diversity converts

Pipeline breadth across 155 programs is real, but zero non-amyloid approvals means the proof is ahead

Four themes from the AAIC 2026 pipeline

THE PIPELINE HAS DIVERSIFIED

Neuroinflammation leads with 31 programs, ahead of amyloid at 28.

DIVERSIFICATION HAS NOT CONVERTED

Outside amyloid, no mechanism class has converted pipeline breadth into a single approval.

THE TEST IS SPECIFIC AND TIME-BOUND

Diranersen, XPro1595, AR1001, and buntanetap report by early 2027. These programs will signal whether non-amyloid approaches can produce a Phase 3 win.

AAIC 2026 SETS THE TONE

AAIC 2026 London concentrates more non-amyloid binary data presentations than any prior conference in AD development.

Synthesis slide drawing on pipeline analysis, transition success rates, and catalyst timing presented in this data package. Four editorial themes: pipeline diversification is real with neuroinflammation leading in program count, diversification has not yet converted outside amyloid, the conversion test is specific and time-bound across four programs reporting by early 2027, and AAIC 2026 sets the tone for the catalyst window. No new data introduced on this slide. Mid-2026 pipeline cut.