

# Bloomberg Benchmarks

## What is the white space opportunity in Alzheimer's?

### ▼ BB

#### Oral GLP-1 Competitive Landscape

##### Market Leaders

- On April 1, 2026, the FDA approved Eli Lilly's Foundayo (orforglipron), a once-daily oral GLP-1 pill for chronic weight management that can be taken at any time without food or water restrictions. (1)
- Foundayo is expected to become the preferred oral GLP-1 offering based on ease-of-use, according to Bank of America. (2)
- Novo Nordisk launched oral Wegovy (oral semaglutide) earlier in 2026, making it the first GLP-1 pill on the market for obesity. (3)
- Orforglipron completed a head-to-head Phase 3 trial (ACHIEVE-3) against oral semaglutide, demonstrating statistically significant outperformance in improving HbA1c after 52 weeks. (4)

##### Efficacy Comparison

- Novo Nordisk's 25mg oral semaglutide achieved 13.6% weight loss over 64 weeks, establishing a benchmark for oral GLP-1s. (5)
- Eli Lilly's orforglipron demonstrated 12.4% weight loss in Phase 3 trials. (6)
- Structure Therapeutics' aleniglipton offers superior efficacy at 16.3% weight loss compared to Foundayo's 12.4%. (7)

##### Next-Generation Competitors

- Structure Therapeutics' aleniglipton is set to enter late-stage testing in the second half of 2026, with potential sales starting in 2028. (8)
- Viking Therapeutics closed enrollment in its Phase 3 VK2735 trial for Type 2 Diabetes weight management on April 7, 2026. (9)
- Other oral GLP-1 programs in development include Roche's CT-996 and AstraZeneca's AZD5004. (10)
- Terns Pharmaceuticals' TERN-601 is also in Phase 2 development. (11)

### ▼ Opus

Alzheimer's disease remains one of the largest unmet medical needs, with significant white space across diagnostics, therapeutics, and care. Let me search for the latest landscape to give you a current picture.

Searched the web

Searched the web

Here's a comprehensive look at the white space opportunities in Alzheimer's disease:

## 1. Diagnostics & Early Detection

This is one of the most actionable areas of white space. New blood-based biomarker tests can detect Alzheimer's years before symptoms become debilitating, but Medicare doesn't cover them because they're classified as screening tests, leaving millions undiagnosed or forced to wait. [Association of Health Care Journalists](#) As many as half of all people with the disease or at risk for it remain undiagnosed. [Association of Health Care Journalists](#) Key gaps include:

- **Reimbursement and access:** Bipartisan legislation (the ASAP Act) has been introduced to create a Medicare coverage pathway for FDA-approved blood biomarker screening tests, but it hasn't passed yet. [Association of Health Care Journalists](#) Companies that can navigate the payor landscape or offer affordable direct-to-consumer or employer-sponsored testing have room to grow.

- **Primary care integration:** Many neurology centers have huge patient backlogs, and there aren't enough specialists to see patients in a timely manner. Quick blood-based diagnostics in primary care settings could speed up the process significantly. [ABC News](#)
- **Global imaging access:** Dementia prevalence is rising sharply in low- and middle-income countries where access to advanced neuroimaging is extremely limited. Low-field portable MRI is emerging as a promising alternative but still needs validation and scale. [Nature](#)
- **Tau and neurodegeneration biomarkers:** While amyloid blood tests are now on the market, tau and neurofilament light chain blood tests are still not widely approved, representing the next wave of diagnostic tools. [Neurology Live](#)

## 2. Therapeutics Beyond Amyloid

The current approved disease-modifying drugs (Leqembi and Kisunla) represent a first generation, but their efficacy is modest. The white space is enormous:

- **Combination therapy:** Experts increasingly believe that, much like in cancer, combinations targeting multiple pathways will be necessary. Current anti-amyloid therapies slow disease progression by only about 30–35%, and the field needs additional pathways and drugs to achieve higher efficacy. [BioSpace](#)
- **Tau-targeting therapies:** 2026 has been called "the year of tau." Biogen's B1080, an antisense oligonucleotide, reduced tau biomarkers by roughly 60% in early trials, and Phase II readouts expected this year will be among the most significant for the field. [BioSpace](#) Multiple modalities (ASOs, siRNAs) are in play.
- **Neuroinflammation:** The 2025 Nobel Prize helped spotlight the inflammation hypothesis in neurodegeneration, and there are now over 30 active clinical trials targeting anti-inflammatory mechanisms in Alzheimer's. [BioSpace](#) Companies like Coya Therapeutics are exploring regulatory T-cell approaches.
- **Blood-brain barrier delivery:** Next-generation therapies are focused on crossing the blood-brain barrier more effectively, using technologies like receptor-mediated transcytosis, which could reduce both dosing requirements and the risk of side effects like ARIA (amyloid-related imaging abnormalities). [BioSpace](#)
- **Oral therapies:** Several oral medications are in the clinical pipeline, which would be a major shift from the current infusion-based treatments and could dramatically improve patient access and adherence. [BrightFocus](#)
- **Pre-symptomatic treatment:** The AHEAD Study is testing whether Leqembi can be effective in people at high risk for Alzheimer's but before symptoms begin — potentially stopping the disease before it starts. [BrightFocus](#)

## 3. Clinical Trial Infrastructure

This is a critical bottleneck. Of the millions of potentially eligible Alzheimer's patients, only about 12,000 enroll in clinical trials each year — far short of the 50,000+ needed to fully staff the 182 trials in the current pipeline. [USC Schaeffer](#) Alzheimer's trials are longer, slower, and more costly to recruit than other therapeutic areas. [USC Schaeffer](#) White space opportunities include trial recruitment platforms, decentralized trial technologies, diversity-focused enrollment solutions, and AI-driven patient matching.

## 4. Care, Caregiving & Support

Caregivers frequently lack adequate knowledge about the disease and report major difficulties managing daily tasks, medication adherence, and patient safety, along with high levels of emotional exhaustion. [MedicalUpdateOnline](#) Opportunities exist in:

- **Digital care navigation and coordination:** The 2026 NIA Dementia Care Summit highlighted significant gaps in care coordination research and the evidence base needed for policymakers to invest in dementia care models. [National Institute on Aging](#)
- **AI-powered tools:** Most current AI tools in dementia are narrowly focused and lack longitudinal reasoning. Future systems that can monitor patients over time, flag cognitive changes, and support clinical decision-making represent a major growth area. [Frontiers](#)
- **Caregiver support platforms,** respite services, and training tools — especially for the home setting — remain underdeveloped.

## 5. Disparities & Underserved Populations

There are well-documented disparities in the quality and timeliness of Alzheimer's diagnosis and care, particularly for patients under 65 and non-white patients, who are less likely to receive neurocognitive assessments. [PubMed Central](#) NIH is working to fund precision genomic medicine research across diverse ancestral populations to understand how genetic variation affects dementia risk differently. [National Institute on Aging](#) Companies or organizations that can serve these underserved segments have significant room to operate.

In summary, the biggest white space clusters are: affordable and scalable early diagnostics (especially at the primary care level), therapies targeting non-amyloid pathways and combination regimens, infrastructure to accelerate clinical trials, and technology-enabled caregiving solutions. The market is moving from a single-pathway paradigm toward a multi-modal, precision-medicine approach — and the gaps at every stage of that transition are substantial.

▼ AXL

## White Space Opportunity in Alzheimer's Disease

### Executive Summary

Alzheimer's disease has one of the most historically crowded — and repeatedly failed — drug development landscapes in medicine. The dominant amyloid and tau paradigms have consumed most of the clinical development investment, yet a 0% confirmed primary endpoint success rate across 6 trials with extractable outcome data tells a brutal story. The structural opportunity sits in mechanisms that the field has systematically underexplored: metabolic/incretin pathways (GLP-1R), neuroinflammation targets (TREM2, microglial biology), synaptic function, and several receptor families where coverage is near-zero despite adjacent precedent in other indications. The white space is real, but it must be distinguished from abandoned space — zones the field explored, repeatedly failed in, and has not returned to.

### Current Landscape Overview

The Alzheimer's disease trial landscape is enormous in enrollment volume but increasingly concentrated in a shrinking set of targets. Two dominant paradigms define the crowded core:

**Amyloid/tau as the occupied center.** The Amyloid target-indication pair shows 6 total trials, a 25% termination rate, and a field decline signal (recent-to-older trial ratio of 0.40), meaning new amyloid trial starts are slowing relative to the historical pace. The tau landscape is significantly larger — 38 total trials, 18 active, 25 unique sponsors, reaching Phase 3 — but field activity has collapsed to a ratio of 0.185 (recent vs. older). Posdinemab (Janssen, [NCT04619420](#), 523 patients) was recently terminated, a significant signal about Phase 2/3 tau antibody viability.

**Sponsor concentration among large pharma.** The top-line leaderboard is dominated by AstraZeneca (212 cross-portfolio trials), Merck (202), and Eli Lilly (170) across all disease areas. In Alzheimer's specifically, Biogen, Eisai, Eli Lilly, and Janssen have dominated the amyloid antibody space. This creates a competitive intensity problem for any new entrant targeting the same mechanisms — but a legitimate opportunity for those going elsewhere.

### White Space Analysis: Under-Explored Targets and Mechanisms

The white space analysis returned 19 target families with coverage gaps in Alzheimer's disease. Ranked by strategic relevance:

#### Tier 1 — Mechanistically Compelling, Near-Zero Clinical Coverage

**Incretin/GLP-1 Receptor (Incretin receptors family — 8 uncovered targets)** GLP-1R is the single most strategically interesting gap in the Alzheimer's landscape right now. Only 1 unique sponsor (Novo Nordisk) is running trials in this space — 2 active trials including the large Phase 3 semaglutide study ([NCT04777409](#), 1,840 patients, primary completion September 2025). Zero terminations. First trial date only 2021. The family includes GIP, GIPR, GLP1R (canonical), GLP-1 receptor, and Glucagon Receptor — none of which have separate active trials. This represents true first-mover white space: scientifically credible (neuroinflammation, metabolic, and neuroprotective mechanisms), Phase

3 data imminent from Novo Nordisk, and only 1 sponsor on the field. The competitive situation is the opposite of amyloid: open, not crowded.

**DYRK1A (DYRK family — 3 uncovered targets: CLK2, DYRK1B, DYRK2)** DYRK1A has 1 active trial (Phase 1), 1 unique sponsor, registered only in January 2024. Zero failures, near-zero precedent. DYRK1A is implicated in tau phosphorylation and synaptic plasticity — a mechanistic bridge between upstream kinase biology and the downstream pathology the field has failed to reverse with antibodies. DYRK1B, CLK2, and DYRK2 have zero coverage. This is true white space with credible target validation but no competitive congestion.

**TREM2 (Microglial/Innate Immunity)** TREM2 shows 0 active trials in Alzheimer's disease in the current registry, 0 unique sponsors, though family precedent data indicates some prior exploration (recent-to-older ratio of 0.5). This is a scientifically high-profile target — microglial phagocytosis of amyloid, neuroinflammation resolution — with substantial preclinical investment by academic groups and AI002 (Alector's TREM2 agonist) having just failed in INVOKE-2 ([NCT04592874](#), n=356, primary endpoint CDR-SB not met, terminated). This is abandoned space, not virgin white space — the distinction matters significantly for risk framing.

**PPAR Family (10 uncovered targets: PPAR-alpha, PPARgamma, PPARdelta)** Only PPAR-gamma has trial coverage; PPAR-alpha, PPAR-delta, and the broader PPAR family members have zero representation. PPAR-alpha agonism has demonstrated anti-neuroinflammatory and mitochondrial effects in preclinical AD models. Low competitive density, no failures to speak of, but also limited phase progression. True white space, but early-stage.

**Orexin Receptors (5 uncovered: OX1R, OX2R)** HCRTR1 and HCRTR2 have trial coverage, but OX1R and OX2R canonical forms do not. Sleep-wake cycle disruption is now recognized as both a risk factor for and potential driver of amyloid accumulation. Suvorexant (Eisai, approved for insomnia) has been studied in AD; the receptor-specific differentiation of OX1R vs. OX2R selectivity is unexplored in formal AD trials.

#### Tier 2 — Receptor Families with Partial Coverage, Identifiable Gaps

**Serotonin Receptors (37 uncovered targets in family)** The Sigma-2 receptor has coverage; 5-HT<sub>2A</sub>, 5-HT<sub>1A</sub>, 5-HT<sub>4</sub>, 5-HT<sub>6</sub>, and 5-HT<sub>7</sub> (the most pharmacologically tractable subtypes for cognition) have zero coverage despite being among the most druggable CNS targets. 5-HT<sub>6</sub> antagonism was historically pursued and failed in schizophrenia; the AD indication remains largely untested. One notable outlier: Bimind Labs ([NCT06812221](#)) ran a Phase 1/2 study of 5-methoxy-DMT (targeting 5-HT<sub>2A</sub> and 5-HT<sub>1A</sub>), completed February 2025 with 20 patients — suggesting early signal-seeking activity but minimal competitive density.

**Muscarinic Receptors (15 uncovered)** M<sub>1</sub>, M<sub>3</sub>, M<sub>4</sub>, and M<sub>2</sub> muscarinic receptor subtypes are largely untested despite the well-established cholinergic hypothesis of AD. Only M<sub>1</sub> and M<sub>3</sub> have trial coverage. AbbVie's emraclidine (M<sub>4</sub> agonist, [NCT05644977](#)) ran a Phase 1 in dementia/AD context — an important early signal that M<sub>4</sub> selectivity is being explored, but the broader muscarinic family remains open. Butyrylcholinesterase (cholinesterase family) also has no coverage despite being a pharmacologically distinct target from acetylcholinesterase.

**Glutamate Receptors (8 uncovered: mGluR5, AMPA receptor, mGluR2/3)** NMDA receptors are well-covered (memantine, AXS-05 programs). mGluR5, AMPA receptor positive allosteric modulators, and mGluR2/3 have no active trial coverage in AD. Allyx Therapeutics ran BMS-984923 (mGluR5 silent allosteric modulator, [NCT05804383](#)) through Phase 1, completing July 2025 — the only entrant. Zero competitors.

**Enzyme Inhibitors — Large Family, 195 Gaps** The enzyme inhibitor family has the largest raw gap count (195 uncovered targets), but most are irrelevant to AD biology. The strategically relevant subset: RIPK1 (necroptosis/neuroinflammation, zero AD trials), FASN (lipid metabolism/neuroinflammation, zero trials), CASP1 (inflammasome, zero specific trials), and MPO/myeloperoxidase (oxidative neuroinflammation). These are niche but mechanistically coherent within an AD neuroinflammation thesis.

## Historical Outcome Patterns: Failed vs. Validated Approaches

Across 50 trials with recent historical data (32 completed, 15 terminated, 3 withdrawn), the confirmed primary endpoint success rate among trials with extractable outcome data is 0 of 6. Every confirmed readout has failed:

- **Simufilam (FLNA target, Cassava):** Both RETHINK-ALZ ([NCT04994483](#), n=804) and REFOCUS-ALZ ([NCT05026177](#), n=1,125) failed co-primary cognitive and functional endpoints. Program discontinued.

- **AL002 (Alector, TREM2/microglial):** INVOKE-2 ([NCT04592874](#), n=356) failed CDR-SB primary endpoint; no favorable secondary or biomarker effects.
- **Fosgonimeton (HGF/MET, Athira/LeonaBio):** LIFT-AD ([NCT04488419](#), n=554) failed primary endpoint at Week 26; program terminated.
- **AXS-05 (ADVANCE-2, [NCT05557409](#), n=408):** Failed CMAI primary endpoint. The ACCORD-2 randomized withdrawal study showed a statistically significant signal (p=0.001) but the standard parallel-group study failed — the mixed picture is consistent with known AD trial design challenges.
- **XPro/Pegipanermin (TNF-alpha, INmune Bio, [NCT05318976](#), n=208):** Primary endpoint not met in mITT population; predefined inflammatory subgroup showed effect sizes of 0.27 on EMACC, -0.20 on pTau217.

Key inference: The subgroup signals in the INmune Bio TNF-alpha data and the exploratory biomarker data from simufilam and fosgonimeton are the kind of signals that historically get recycled into "enriched population" studies. Watch for enrichment-based Phase 2 designs targeting inflammatory biomarker-positive or specific genetic subgroups — that is where iteration is happening, not wholesale new mechanism exploration.

**What has worked (partially):** Lecanemab (Eisai/Biogen, [NCT01767311](#)) produced clinically meaningful amyloid clearance and consistent relative reductions in cognitive decline across multiple endpoints in the Phase 2b, with dose- and time-dependent effects. This is the one confirmed pharmacological success in the biomarker-clinical correlation space, though absolute benefit remains modest and ARIA rates are not trivial. The amyloid-beta protofibrils target is validated at Phase 2; the question is what comes next.

## Field Trend Shifts: Where Momentum Is Moving

The directional signals from field trend data tell a clear story:

**Amyloid: Slowing.** Recent-to-older trial ratio of 0.40 — new trial starts are declining relative to historical pace. The post-lecanemab approval environment has consolidated rather than expanded the amyloid antibody field.

**Tau: Collapsing.** Recent-to-older ratio of 0.185, the weakest field activity signal. The Posdinemab termination ([NCT04619420](#)) and the absence of new Phase 3 tau programs signals the field is reassessing.

**GLP-1R: Holding with Phase 3 data incoming.** The Novo Nordisk semaglutide Phase 3 ([NCT04777409](#), n=1,840, primary completion September 2025) is the single most important near-term catalyst for redirecting field attention. If positive, expect a rush of GLP-1 and GIP receptor programs; if negative, expect GLP-1/AD to join the list of failed hypotheses.

**DYRK1A: Early entry.** The single trial (Phase 1, 2024 start) represents a genuine early-mover signal in a kinase target with tau-relevant biology. Momentum score is "stable" by virtue of having no competitors rather than field enthusiasm.

**Neuroinflammation broadly: Mixed signals.** The Alector TREM2 failure is a setback for the pure microglial biology thesis, but the INmune Bio subgroup signal on TNF-alpha keeps the inflammation angle alive. RIPK1 inhibition (necroptosis pathway, Sanofi and Denali have explored this in other neurodegeneration indications) has no AD trial footprint.

## Sponsor Concentration and Competitive Gaps

Alzheimer's sponsor concentration is extreme for the amyloid/tau core but thin everywhere else:

- **Amyloid antibodies:** Eisai/Biogen (lecanemab), Eli Lilly (remternetug, [NCT04451408](#) Phase 1 completed), Roche/Genentech — these three dominate. Any new entrant here faces a binary problem: validate behind the existing approved drug or differentiate by mechanism.
- **Tau:** 25 unique sponsors historically, but 10% termination rate and a collapsing activity ratio suggest the field is contracting rather than diversifying.
- **GLP-1R in AD:** 1 unique sponsor (Novo Nordisk). The lowest competitive density among any pharmacologically validated target area.

- **Neuroinflammation/TREM2:** Alector's INVOKE-2 failure has effectively cleared the field. No major sponsor has announced a follow-on program.
- **Cholinergic/Muscarinic:** AbbVie's emraclidine signal is the only major sponsor footprint in the M4/muscarinic space; the rest of the muscarinic family is uncontested.
- **Kinase targets (DYRK1A):** 1 sponsor, Phase 1 only.

The concentration map creates a clear strategic opportunity architecture: sponsors willing to accept mechanistic novelty risk can operate in markets with 1 or 0 competitors, versus 20+ in amyloid/tau.

## Prioritized Opportunities and Strategic Implications

**Priority 1 — GLP-1/Incretin Receptors in AD** The combination of Phase 3 data imminent, 1 active sponsor, zero failures, and robust neurobiological rationale (neuroinflammation, insulin signaling, neuroprotection) makes this the most immediately relevant white space. The strategic play is: enter now before Novo Nordisk's readout, or immediately after if positive (first-mover advantage in non-Novo formulations, oral GLP-1s, CNS-penetrant GLP-1Rs, GIP/GLP-1 dual agonism in AD).

**Priority 2 — DYRK1A and Kinase Biology** A mechanistically coherent alternative pathway to tau hyperphosphorylation, with near-zero clinical competition. The risk is that it shares the same downstream pharmacology thesis as tau antibodies (which have repeatedly failed) but attacks it from a different point. Phase 1-stage, so a 5–7 year development horizon, but low competitive density means the field is still defining itself.

**Priority 3 — Selective Serotonin Receptor Subtypes (5-HT4, 5-HT6, 5-HT7)** Particularly 5-HT4 (cognitive enhancement, synaptic plasticity) and 5-HT6 (glutamate modulation) — both are mechanistically plausible, zero AD-specific trial coverage, and well-precedented in the CNS pharmacology literature. The risk: 5-HT6 antagonism was thoroughly explored in schizophrenia (multiple failures) and the lessons haven't been transferred to AD yet.

**Priority 4 — Enriched Neuroinflammation Approaches** Not TREM2 itself (abandoned space after INVOKE-2), but RIPK1 inhibition (necroptosis), CASP1/inflammasome biology, and biomarker-enriched TNF-alpha populations. The INmune Bio Phase 2 subgroup signal (n=100 inflammatory-positive patients, effect size 0.27 on EMACC) is weak confirmatory evidence but the only surviving signal in the inflammation space. Requires biomarker enrichment strategy to be viable.

**Highest-Risk White Space to Avoid:** Enzyme inhibitor targets with no neurological precedent (most of the 195-target gap list), abandoned tau approaches, and any mechanism that has failed multiple Phase 3 trials without a credible patient selection thesis.

**A final methodological note:** The 0% primary endpoint success rate in this historical dataset applies only to trials with extractable outcome data (6 of 50). Many trials are still completing without reported outcomes, and early-phase trials are not designed to demonstrate efficacy. The structural failure rate in Alzheimer's Phase 3 is a well-documented historical pattern (~99% historically) — the behavioral data here is consistent with that pattern, not a new finding.

### ▼ ChatGPT

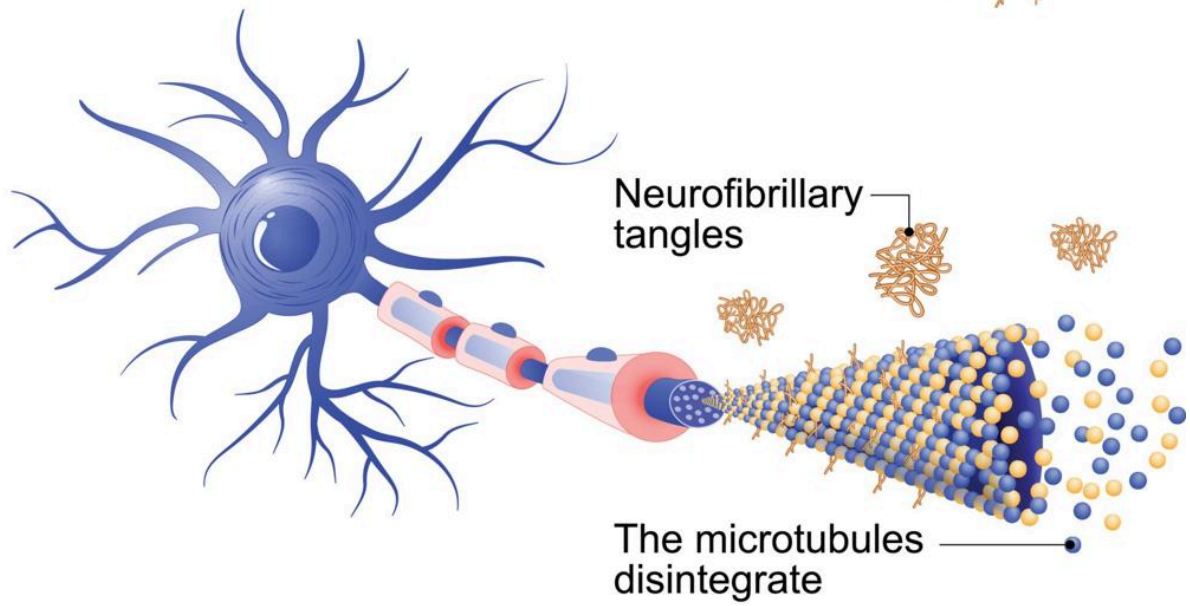
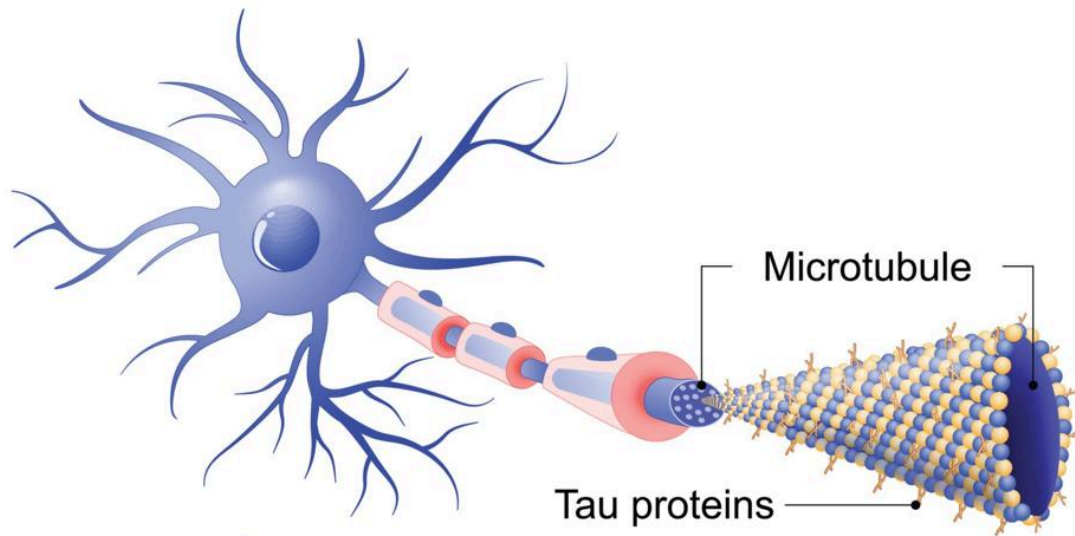
Alzheimer's white space is increasingly defined by **mechanism gaps, stage-of-disease gaps, and care-delivery gaps** — especially as the first anti-amyloid antibodies reach the market.

Below is a structured view of where opportunity remains most compelling.

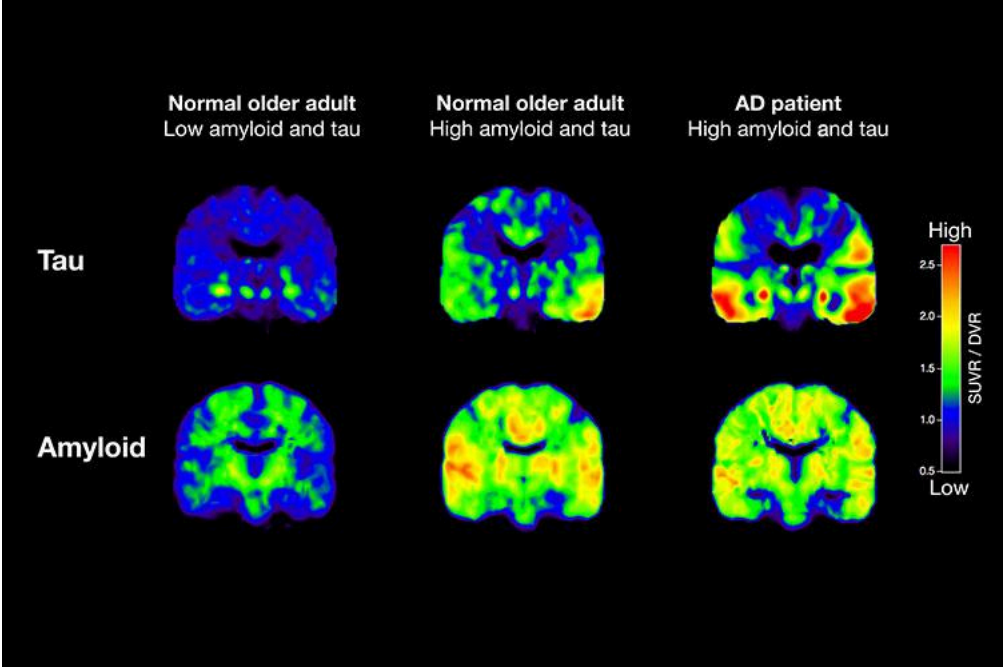
## 1 Disease Biology White Space (Beyond Amyloid)

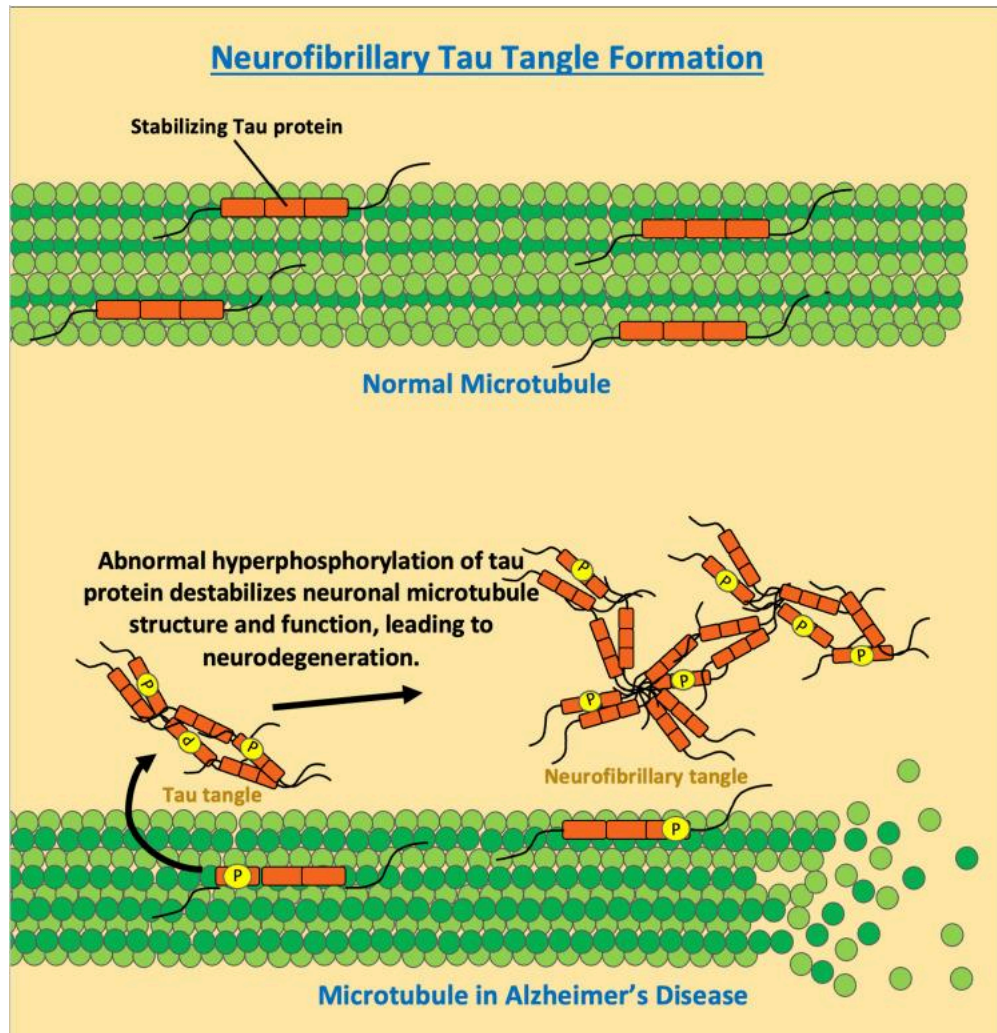
### A. Tau — Especially Intracellular & Propagation Biology

# HEALTHY NEURON



# ALZHEIMER'S DISEASE





6

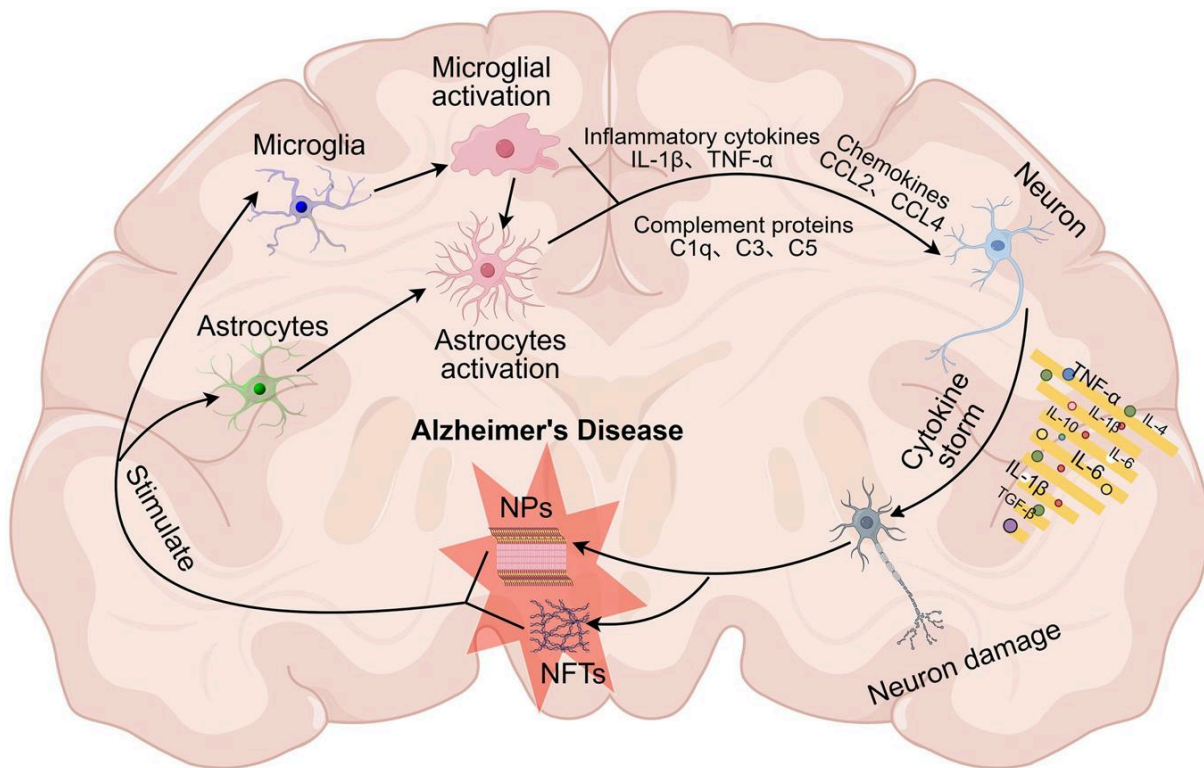
**Why it's white space:**

- Tau correlates more tightly with cognition than amyloid.
- Most tau mAbs have struggled clinically.
- Intracellular tau and propagation biology remain underexploited.

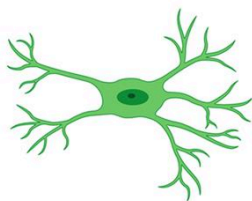
**Opportunities**

- Small molecules targeting tau aggregation
- ASOs / RNA approaches to reduce tau production
- Propagation blockers (extracellular seed neutralization)
- Earlier-stage tau intervention (pre-symptomatic)

**B. Neuroinflammation & Microglia Modulation**



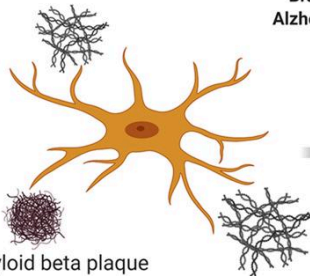
**HOMEOSTATIC MICROGLIA**



↑ CX3CR1  
 ↑ P2ry12  
 ↑ Tmem119  
 ↑ TREM2  
 ↑ Sall1

**STAGE 1**

Disease Associated Microglia (DAM)  
 Trem2 independent



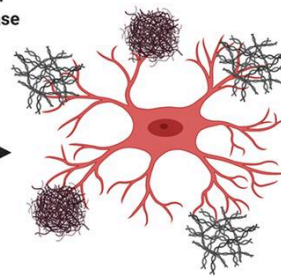
Amyloid beta plaque  
 neurofibrillary tangle

↓ CX3CR1  
 ↓ P2ry12  
 ↓ Tmem119  
 ↓ TREM2  
 ↓ Sall1

↑ Apoe  
 ↑ Lyz2  
 ↑ Ctsb

**STAGE 2**

Disease Associated Microglia (DAM)  
 Trem2 dependent

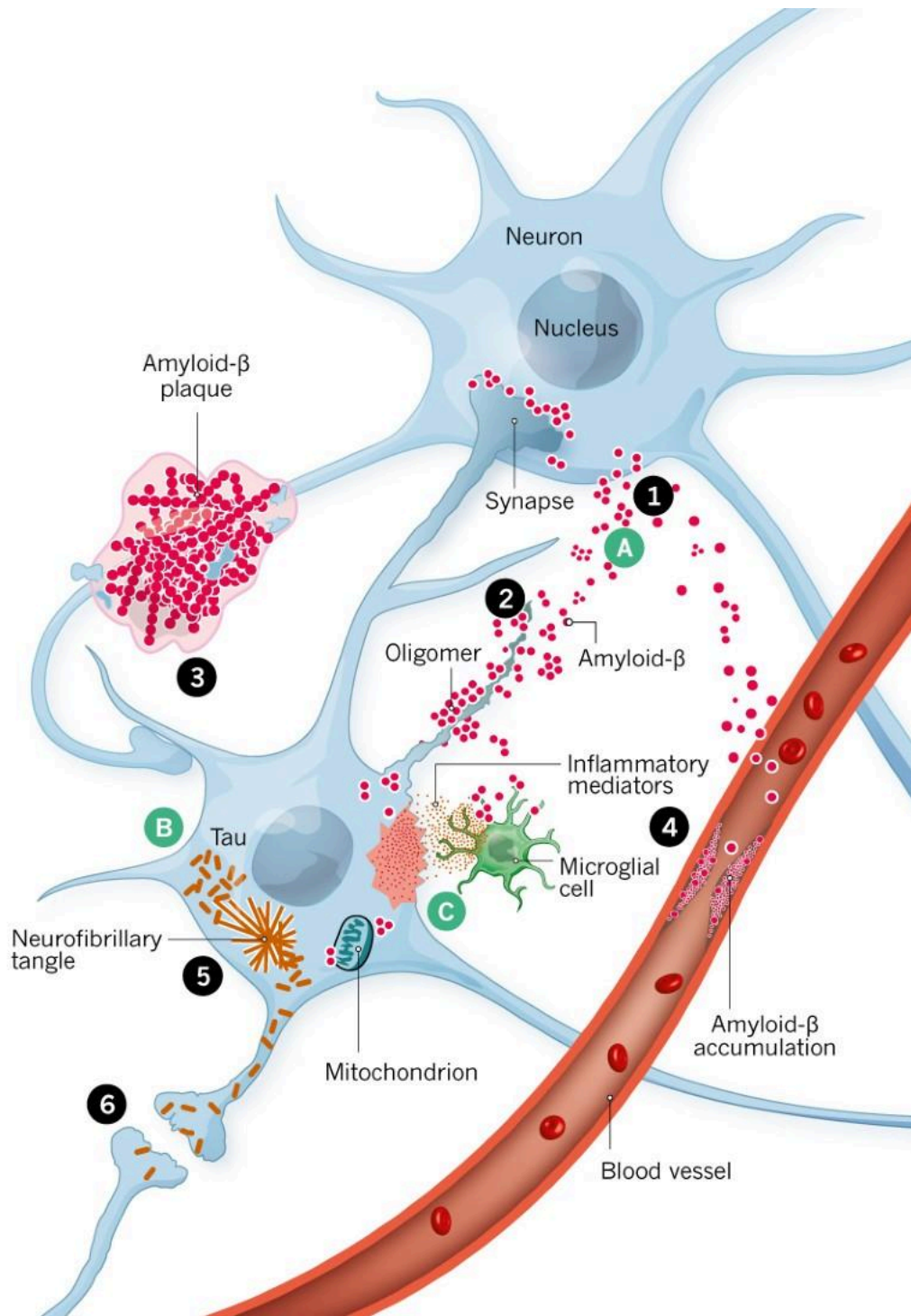


Brain Atrophy in Alzheimer's Disease

↓ CX3CR1  
 ↓ P2ry12  
 ↓ Tmem119  
 ↓ TREM2  
 ↓ Sall1

↑ TREM2  
 ↑ Axl  
 ↑ Lpl  
 ↑ Csf1  
 ↑ Clec7a

↑ Ccl6  
 ↑ Cst7



6

**Rationale:**

- Genetic data (e.g., TREM2 pathway) strongly implicates innate immunity.
- Microglia may shift from protective to maladaptive states.

**White space themes**

- Microglial state reprogramming (not simple inhibition)
- Complement pathway modulation
- Astrocyte-targeted therapies
- Precision stratification by inflammatory phenotype

### C. Synaptic Rescue / Neurorestoration

Amyloid removal slows decline modestly. It does **not restore cognition**.

#### Underdeveloped areas

- Synaptogenic agents
- Neurotrophic signaling modulation (BDNF pathways)
- Circuit-level modulation
- Combination therapy (clear pathology + rebuild synapse)

## 2 Disease Stage White Space

### A. Preclinical / Asymptomatic AD

- Pathology accumulates 10–20 years before symptoms.
- Trials here are expensive and slow.
- Regulatory endpoints still evolving.

#### Opportunity

- Blood biomarker-driven screening
- Preventive therapy in APOE4 carriers
- Digital cognitive monitoring endpoints

### B. Moderate-to-Severe AD

Current drugs (e.g., **Leqembi**, **Aduhelm**) focus on early disease.

Late-stage patients:

- Large unmet need
- Little innovation
- Behavioral symptom burden

White space:

- Agitation, apathy, psychosis
- Functional preservation endpoints
- Caregiver-burden-targeted therapies

## 3 Mechanistic Gaps With Strong Genetic Support

Pathway	Rationale	White Space
Lipid metabolism (APOE biology)	Strongest genetic risk factor	APOE modulation, lipid trafficking
Endosomal trafficking	SORL1 biology	Vesicle recycling drugs
Mitochondrial dysfunction	Energy failure precedes decline	Metabolic rescue agents

Pathway	Rationale	White Space
Proteostasis	Lysosomal/autophagy dysfunction	Autophagy enhancers

Genetics is ahead of drug development in several of these.

#### 4 Combination Therapy (Likely Future Standard)

Oncology-like paradigm is underexplored.

Potential combos:

- Amyloid + anti-tau
- Amyloid + anti-inflammatory
- Pathology removal + synaptic repair
- Drug + neuromodulation

Few true combination trials are underway.

#### 5 Biomarker & Trial Infrastructure White Space

Major bottlenecks:

- Expensive PET imaging
- ARIA monitoring burden
- Slow cognitive endpoints

White space:

- Blood-based biomarkers (pTau217, GFAP, NfL panels)
- Digital cognitive endpoints
- Adaptive trial designs
- Real-world evidence integration

#### 6 Delivery & Commercial White Space

Anti-amyloid antibodies face:

- Infusion burden
- MRI monitoring
- Modest efficacy
- ARIA risk

Opportunities:

- Subcutaneous formulations
- Oral small molecules
- Better risk stratification
- Community-based infusion infrastructure

#### 7 Biggest Strategic White Space (High-Conviction Areas)

If prioritizing capital allocation:

1. Microglial state modulation

2. Tau lowering (ASO or RNA-based)
  3. Synaptic regeneration
  4. Preclinical prevention trials
  5. Combination regimens
- 

## Key Insight

The field is shifting from:

| "Does amyloid matter?"

to

| "Amyloid removal is necessary but insufficient."

The next decade's white space is about:

- **Earlier**
  - **Combination-based**
  - **Biology-driven**
  - **Restorative, not just subtractive**
- 

If helpful, I can also:

- Map this by company strategy
- Frame it from an investor-return perspective
- Or size TAM by segment and stage

### ▼ Perplexity

The biggest white-space opportunities in Alzheimer's are **diagnostic infrastructure, biomarker-enabled care pathways, and services that make early treatment usable at scale**. The disease is moving from "symptom management only" toward earlier identification and disease-modifying therapy, but the ecosystem around testing, referral, monitoring, and adherence is still underbuilt.

## Where the gaps are

- **Primary-care diagnostics.** Blood-based tests are now available, but real-world care still needs triage workflows, confirmatory pathways, and decision support to move patients from vague cognitive complaints to actionable diagnosis. FDA clearance of blood tests and new reviews suggest a major shift, but also show many patients still rely on costly PET or CSF testing.
- **Early detection at scale.** Alzheimer's pathology can begin 10 to 20 years before symptoms, so the commercial gap is not just testing, but finding people early enough to matter. That creates room for screening programs, risk-stratification tools, and longitudinal monitoring in primary care and neurology.
- **Biomarker platforms and panels.** The market is moving beyond single-marker tests toward multi-marker and AI-driven biomarker systems that can identify co-pathologies and guide precision treatment. ADDF's 2026 Diagnostics Accelerator phase specifically targets blood tests for tau and other co-pathologies, multi-marker panels, and AI biomarkers.
- **Care delivery for infusion-era therapies.** Anti-amyloid drugs increase demand for patient tracking, infusion coordination, adverse-event monitoring, and reimbursement navigation. That operational layer is a white space because effective therapy now depends on healthcare logistics, not just the drug.
- **Trial recruitment and diversity infrastructure.** Biomarkers are central to clinical trials, but participant diversity remains a known limitation, especially for blood-based biomarker validation and community recruitment.

Infrastructure that improves enrollment, retention, and representativeness is a meaningful opportunity.

- **Caregiver support and remote monitoring.** Caregivers face sustained stress, while digital and AI tools for dementia-specific support are still fragmented. There is room for products that combine symptom tracking, behavioral monitoring, education, and mental-health support for families.

## Most attractive whitespace

Segment	Why it's white space	What wins
Blood-test triage in primary care	Converts undiagnosed patients into actionable referrals	Low-friction workflow, high specificity, easy reimbursement path
Biomarker orchestration software	Connects screening, confirmation, and treatment eligibility	EHR integration, decision support, care navigation
Therapy operations platform	Makes infusion and monitoring scalable	Scheduling, safety tracking, prior auth, infusion-center workflow
Diversity-focused trial recruitment	Fixes a structural bottleneck in research	Community partnerships, digital recruitment, sample logistics
Caregiver tech	Addresses a large unmet daily need	Remote monitoring, alerting, coaching, respite support

## Practical read

If you are thinking like a market builder, the highest-value opportunity is not another standalone Alzheimer's drug. It is the **picks-and-shovels layer** that helps clinicians detect disease earlier, match patients to the right therapy, and keep them on care pathways over time. That layer is where diagnostics, software, services, and reimbursement support can create durable value.

A simple example: a primary-care practice could use a blood biomarker test, an AI risk stratifier, and a referral workflow that routes only likely positives to neurology or PET/CSF confirmation. That kind of product removes friction at the exact point where the system currently loses patients.

### Compare NCT06075667 and NCT07011667

#### ▼ BB

I was unable to find information about clinical trials NCT06075667 and NCT07011667 in Bloomberg's research corpus, company documents, or filings.

These NCT identifiers appear to be ClinicalTrials.gov registration numbers. For detailed information about specific clinical trials, including their protocols, sponsors, enrollment status, and outcomes, you may want to:

- Visit ClinicalTrials.gov directly to search for these trial identifiers
- Check if these trials are associated with publicly traded pharmaceutical or biotech companies, then search for mentions in their regulatory filings or earnings transcripts
- Look for research coverage from healthcare-focused analysts if these trials involve significant commercial products

If you can provide additional context about which companies are sponsoring these trials or what therapeutic areas they cover, I may be able to help you find related research or company disclosures.

#### ▼ Opus

### NCT06075667 vs. NCT07011667

**NCT06075667** is Eli Lilly's **SURMOUNT-ADOLESCENTS** trial, and **NCT07011667** is Novo Nordisk's **REDEFINE 11** trial. Both are Phase 3, randomized, placebo-controlled studies in obesity, but they differ significantly in their populations, drugs, and strategic goals.

### Drug & Mechanism

NCT06075667 studies **tirzepatide (LY3298176)**, a dual GIP/GLP-1 receptor agonist [DiaTribe](#) already approved for adults as Mounjaro (diabetes) and Zepbound (weight management). NCT07011667 studies **CagriSema**, a fixed-dose combination of cagrilintide (a long-acting amylin analogue) and semaglutide (a GLP-1 receptor agonist) [Trialstoday](#). So while both leverage GLP-1 agonism, tirzepatide adds GIP agonism whereas CagriSema adds amylin agonism — two distinct complementary pathways.

## Population

NCT06075667 enrolls **adolescents aged 12–17** with obesity (BMI  $\geq$ 95th percentile) or overweight (BMI 85th–94th percentile) plus at least one weight-related comorbidity, with approximately 150 participants. [DiaTribe](#) NCT07011667 enrolls **adults aged 18+** with a BMI  $\geq$ 30 who have a goal of losing at least 25% of body weight. It explicitly excludes patients with diabetes (HbA1c  $\geq$ 6.5% or history of T1D/T2D). [Trialstoday](#) REDEFINE 11 targets roughly 600 adults. [Drugs.com](#)

## Trial Design & Duration

NCT06075667 lasts approximately 90 weeks (a 72-week primary period plus follow-up), with up to 25 visits. Participants who complete the primary study may enter an additional 156-week extension with tirzepatide. [CenterWatch](#) NCT07011667 has a two-part structure: an 80-week main study (16-week dose escalation + 64-week maintenance) followed by an 80-week extension, totaling roughly 3 years and 3 months. In the main phase, participants are randomized 2:1 to CagriSema vs. placebo. In the extension, CagriSema patients continue (re-randomized to different dose levels), while placebo patients switch to CagriSema. [Trialstoday](#)

## Primary Endpoints

NCT06075667 measures percent change from baseline in BMI, body weight, waist circumference, blood pressure, cholesterol, and fasting blood glucose — standard pediatric obesity outcomes. [DiaTribe](#) NCT07011667 focuses on weight loss and long-term weight-loss maintenance in adults, consistent with the broader REDEFINE program where the dual primary endpoints are the percentage change in body weight from baseline and the proportion of participants achieving at least 5% weight loss. [PharmExec](#)

## Masking

Both are double-blind. NCT07011667 uses quadruple masking (participant, care provider, investigator, and outcomes assessor). [Trialstoday](#) NCT06075667 similarly uses a blinded placebo comparator design.

## Strategic Context

These trials serve very different strategic purposes for their sponsors:

- **Lilly's NCT06075667** is a **label expansion play** into a pediatric population. Tirzepatide is not currently approved for patients under 18, and positive data from this trial could lead to FDA approval for adolescent use [DiaTribe](#) — a major commercial opportunity given rising childhood obesity rates.
- **Novo's NCT07011667 (REDEFINE 11)** is designed to **demonstrate the full weight-loss potential** of CagriSema over a longer duration and with protocol optimizations. It is part of a broader program that includes REDEFINE 3 (cardiovascular outcomes), REDEFINE 4 (head-to-head vs. tirzepatide), and a planned high-dose CagriSema trial (2.4 mg / 7.2 mg) expected to start in late 2026. [Drugs.com](#) Novo filed the NDA for CagriSema with the FDA in December 2025, and FDA review is expected in 2026. [PharmExec](#)

## Competitive Lens

The head-to-head battle between these two drug classes is already playing out. In the REDEFINE 4 trial, CagriSema achieved 23% weight loss after 84 weeks but did not meet the primary endpoint of non-inferiority against tirzepatide 15 mg. [Drugs.com](#) Market skepticism persists given tirzepatide's competitive efficacy and already-approved status, with analysts noting CagriSema's ~2–3% incremental efficacy over semaglutide alone may not be enough to displace tirzepatide. [PharmExec](#)

In summary: NCT06075667 is about bringing an already-proven adult therapy to teens, while NCT07011667 is about pushing a next-generation combination therapy to its full long-term weight-loss potential in adults. Both trials address

important gaps in the obesity treatment landscape but serve fundamentally different clinical and commercial objectives.

▼ AXL

## Side-by-Side Comparison: NCT06075667 vs. NCT07011667

Attribute	<u>NCT06075667</u> (Lilly / Tirzepatide)	<u>NCT07011667</u> (Novo Nordisk / CagriSema)
<b>Sponsor</b>	Eli Lilly and Company	Novo Nordisk A/S
<b>Drug</b>	Tirzepatide (LY3298176)	CagriSema
<b>Target(s)</b>	GLP-1R + GIP Receptor (dual agonist)	GLP-1R (mono-agonist)
<b>MoA</b>	GLP-1 + GIP Receptor Agonist	GLP-1 Receptor Agonist
<b>Indication</b>	Obesity / Overweight (adolescent)	Obesity (adult)
<b>Population</b>	Adolescents (pediatric)	Adults (18+, BMI ≥30)
<b>Phase</b>	Phase 3	Phase 3
<b>Status</b>	Active, not recruiting	Active, not recruiting
<b>Trial Start</b>	October 2023	June 2025
<b>Enrollment</b>	150 (Anticipated)	609 (Actual)
<b>Primary Endpoint</b>	% change from baseline in BMI	Relative change in body weight
<b>Prim. Completion</b>	May 2026	March 2027
<b>Full Completion</b>	July 2029	October 2028
<b>Sites</b>	33 (US, Israel, Czechia, Canada, Italy, Poland)	46 (US only)
<b>Registrational</b>	Yes	Yes
<b>Operational Risk Score</b>	100 / Critical	0 / Low
<b>Landscape Risk Score</b>	34 / Moderate	34 / Moderate
<b>Quadrant</b>	Struggling in Easy Territory	Smooth Sailing

## Trial Design and Endpoint Analysis

These two trials are natural competitive read-throughs (composite similarity score 0.935), but they are strategically distinct in ways that matter.

**NCT06075667** is Lilly's SURMOUNT-ADOLESCENTS study — a registrational Phase 3 evaluating tirzepatide's dual GLP-1/GIP agonism in a pediatric obesity population. Enrollment is small (150 anticipated), reflecting the inherent difficulty of recruiting adolescents with BMI at or above the 95th percentile or overweight with comorbidities. The primary endpoint is BMI percent change from baseline, which is the standard regulatory endpoint for pediatric obesity trials. The adolescent-specific eligibility (Tanner staging exclusion, comorbidity gating) and the T2DM subgroup make this a complex protocol for a niche population.

**NCT07011667** is Novo Nordisk's CagriSema Phase 3 in adult obesity — a far more conventional design with a straightforward BMI ≥30 inclusion threshold and body weight change as the primary endpoint. The protocol explicitly requires a patient wish to lose at least 25% body weight within 80 weeks, which is an unusually high bar and narrows the eligible population in a specific direction. Notably, patients with HbA1c ≥6.5% or any diabetes history are excluded, creating a clean metabolically healthy obese cohort. CagriSema combines cagrilintide (amylin analogue) with semaglutide, making it a peptide combination rather than a pure GLP-1 agonist — though it's classified as a GLP-1R agonist in the registry, the amylin component is the differentiated MoA.

## Operational Signals and Registry History

The behavioral divergence between these two trials is the most analytically important finding of this comparison.

**NCT06075667 (Tirzepatide adolescent) — Critical operational stress (score 100/100).** The registry shows a pronounced whipsaw pattern: the primary completion date was first pushed out 229 days in January 2024 (from February 2026 to October 2026), then pulled back in 153 days in June 2025 (from October 2026 to May 2026) when

the trial closed enrollment. The net effect is a modest 76-day delay from the original timeline, but the pattern itself — delay followed by a large pull-in — is a classic signal of an enrollment recovery: the trial struggled to recruit, then closed to enrollment earlier than the revised date suggested, which allowed the completion timeline to snap back. The eligibility criteria were also modified once, consistent with a protocol adjustment to ease enrollment pressure. The trial has had no registry update in 286 days (last update June 2025), triggering a dormancy signal. This level of silence at a trial approaching primary completion in May 2026 is atypical for an active, well-funded sponsor.

**NCT07011667 (CagriSema adult) — Low operational stress (score 0/100), clean history.** The registry record is textbook linear: registered June 2025, moved from not-yet-recruiting to recruiting in two days, closed enrollment just 78 days later (August 2025), with 609 actual participants enrolled against a 600 target. The single enrollment change (600 to 609) is a minor true-up, not a rescue expansion. The one date change — a 75-day push to March 2027 — was filed simultaneously with the enrollment close, suggesting this was a protocol-compliant adjustment based on actual enrollment timing rather than distress. No eligibility modifications. This is the behavioral footprint of a confident sponsor executing cleanly.

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## Readthrough and Competitive Context

Both trials carry identical landscape risk scores (34/100, moderate), facing the same structural headwinds: 122 active GLP-1/Obesity Phase 3 trials, 122 competitors, a field decline signal (recent-to-older trial ratio of 0.22), and a 2% historical failure rate. The landscape is crowded but survivable for large, well-funded sponsors.

The directional implication of each trial differs materially:

- NCT06075667 (Tirzepatide adolescent): A positive readout would be **directional** for Lilly's own programs (same drug, same sponsor) and a **relative value** signal for competing GLP-1 programs in the field. Pediatric labeling extensions are high-value regulatory events — tirzepatide already has adult approvals, so an adolescent approval would expand the commercial label meaningfully.
- NCT07011667 (CagriSema adult): A positive readout would be **directional** for Novo Nordisk's own CagriSema pipeline (including the longer-running maintenance study NCT06780449), and a **relative value** signal for the broader GLP-1 field. CagriSema is one of the most anticipated next-generation obesity agents — its performance in this study will set expectations for differentiation from semaglutide and tirzepatide monotherapy.

NCT07011667's readthrough list includes Lilly's tirzepatide maintenance study (NCT06859268), the SURMOUNT morbidity/mortality trial (NCT05556512), and Amgen's maridebart cafraglutide Phase 3 program — confirming this is a high-impact catalyst for the entire GLP-1 obesity field.

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## Key Differences and Implications

- 1. Population strategy.** Lilly chose a first-mover path in pediatric obesity with tirzepatide — a smaller, more difficult enrollment but a relatively uncontested regulatory opportunity. Novo Nordisk chose the adult obesity market, where it already competes with semaglutide, using CagriSema to push for differentiation via higher weight loss thresholds.
- 2. Operational confidence.** The behavioral gap is stark. NCT07011667 enrolled 609 patients in roughly 78 days across 46 US sites — a ~7.8 patients/site pace. NCT06075667 targeted only 150 patients across 33 international sites and still required an eligibility modification and a major completion date delay before recovering. The pediatric population is structurally harder to enroll, but the registry signals suggest NCT06075667 tested the limits of that population.
- 3. Dual vs. single agonism.** Tirzepatide's GIP receptor component is hypothesized to provide incremental weight loss benefit over GLP-1 alone. CagriSema's amylin component similarly targets appetite regulation through a complementary pathway. Both sponsors are betting that multi-mechanism approaches drive superior efficacy — but the clinical bar for differentiation from approved semaglutide will be high for CagriSema in particular.
- 4. Upcoming catalyst priority.** NCT06075667 has a primary completion date of May 2026 — roughly 7 weeks from today. No data readout events are currently extracted in the catalyst pipeline, but this is an imminent completion that warrants close monitoring. NCT07011667 completes primary endpoint collection in March 2027.

▼ ChatGPT

Here's a **side-by-side comparison** of the two clinical trials you asked about — **NCT06075667** and **NCT07011667** — based on their publicly available ClinicalTrials.gov records:

### Basic Overview

Feature	NCT06075667	NCT07011667
<b>Sponsor</b>	Eli Lilly and Company	Novo Nordisk A/S
<b>Phase</b>	Phase 3	Phase 3
<b>Study Type</b>	Interventional	Interventional
<b>Status</b>	Active, not recruiting	Active, not recruiting

### Indication / Population

- **NCT06075667**  
Focuses on **adolescents aged 12–17** who have **obesity or overweight with at least one weight-related comorbidity** (e.g., dyslipidemia, hypertension, prediabetes).
- **NCT07011667**  
Targets **adults (≥18 years)** with **obesity** (BMI ≥ 30 kg/m<sup>2</sup>), excluding those with diabetes (HbA1c ≥ 6.5%).

### Interventions

- **NCT06075667**  
Participants receive **tirzepatide (LY3298176)** injections **once weekly vs placebo**.
- **NCT07011667**  
Participants receive **CagriSema** — a **fixed-combination of cagrilintide + semaglutide** — injected **once weekly**, compared with placebo; includes a randomized extension where all eventually receive active treatment.

### Study Duration & Timeline

- **NCT06075667**  
Started Oct 16, 2023; primary completion ~May 31, 2026; estimated final completion ~July 2029.
- **NCT07011667**  
Started Jun 3, 2025; estimated primary completion ~Mar 1, 2027; estimated final completion ~Oct 17, 2028.

### Enrollment Size

- **NCT06075667**: ~150 participants (adolescents).
- **NCT07011667**: ~609 participants (adults).

### Primary Purpose & Design

- **NCT06075667** – *Efficacy, Safety, and Pharmacokinetics* of tirzepatide in **youth** with obesity/overweight vs placebo; double-blind, randomized.
- **NCT07011667** – *Efficacy and Safety* of CagriSema in **adults** with obesity for weight management and long-term weight loss maintenance; randomized, parallel, quadruple-masked with an extension phase.

### Key Differences at a Glance

#### 1. Population

- NCT06075667: *Adolescents* (12–17) with obesity/overweight + comorbidities.
- NCT07011667: *Adults* (18+) with obesity (no diabetes).

#### 2. Drugs Being Tested

- NCT06075667: **Tirzepatide alone** (GLP-1/GIP dual agonist).
- NCT07011667: **CagriSema (cagrilintide + semaglutide)** (dual peptide combination).

### 3. Study Structure

- NCT06075667: Standard placebo vs active with safety/efficacy focus.
- NCT07011667: Placebo vs active, followed by an extension where all get active doses and dose variability is assessed.

### 4. Target Outcome

- NCT06075667: Weight change (BMI & related metrics) and PK in teens.
- NCT07011667: Weight loss efficacy and long-term maintenance in adults.

## Summary

- **NCT06075667** is a Phase 3 trial evaluating **tirzepatide** for **weight management in adolescents with obesity/overweight** – assessing safety, efficacy, and pharmacokinetics.
- **NCT07011667** is a Phase 3 trial testing **CagriSema (cagrilintide + semaglutide)** for **weight loss and long-term maintenance in adults with obesity**, with a more complex extension design.

If you want, I can also dig into the **reported or expected primary and key secondary endpoints** for each trial to show where the trials are powered and what success looks like for each.

#### ▼ Perplexity

These are both obesity drug trials, but they study different medications and different populations: NCT06075667 is Lilly’s adolescent tirzepatide trial, while NCT07011667 is Novo Nordisk’s adult CagriSema trial. NCT07011667 is broader and more ambitious on weight-loss magnitude, with a goal of long-term maintenance after an 80-week main phase plus extension, whereas NCT06075667 focuses on safety and efficacy in adolescents with obesity or overweight plus comorbidities.

## Core differences

Feature	NCT06075667	NCT07011667
<b>Feature</b>	<b>NCT06075667</b>	<b>NCT07011667</b>
Drug	Tirzepatide	CagriSema (cagrilintide + semaglutide)
Sponsor	Eli Lilly	Novo Nordisk
Population	Adolescents with obesity or overweight + weight-related comorbidity	Adults with obesity, BMI at least 30
Age	Adolescents, ages 12–17 in trial listings	Adults, 18+
Main goal	Safety, efficacy, and pharmacokinetics	Long-term weight loss and weight-loss maintenance
Design	Randomized, double-blind, placebo-controlled	Double-blind main phase, then open-label extension/re-randomization
Time frame	Ongoing; completion listed around May 31, 2026	Main phase runs to week 80 with extension; eligibility requires desire to lose at least 25% body weight

## What each study is testing

NCT06075667 is designed for adolescents who have obesity, or overweight with at least one weight-related comorbidity such as abnormal lipids, hypertension, fatty liver disease, sleep apnea, prediabetes, or type 2 diabetes. It excludes Type 1 diabetes, recent significant weight loss, pancreatitis history, and medullary thyroid carcinoma or MEN2 history.

NCT07011667 enrolls adults with BMI at least 30 and no diabetes, and it tests whether CagriSema can produce large weight loss and help maintain it over time. The main outcomes include percentage weight change, the share of participants achieving 20%, 25%, and 30% weight loss, and several cardiometabolic and quality-of-life measures.

## Practical read

If you are comparing them for clinical interest, NCT06075667 is the pediatric/adolescent trial and is more about establishing evidence in younger patients. NCT07011667 is the adult trial and is more directly about high-efficacy obesity treatment and long-term maintenance.

If useful, I can also turn this into a one-line "which is more relevant for me?" decision tree.

### Who is actually ahead in the oral GLP-1 race?

#### ▼ BB

#### Oral GLP-1 Competitive Landscape

##### Market Leaders

- Eli Lilly's orforglipron (Foundayo) received FDA approval on April 1, 2026, and is now available through LillyDirect starting April 6, with pricing at \$25/month for insured patients and \$149 for out-of-pocket. (1)
- Orforglipron is considered the clear leader in oral small molecule GLP-1 development based on Phase 3 data. (2)
- Eli Lilly's orforglipron has an anticipated US approval date of April 10, 2026, with projected sales of approximately \$1.5 billion in 2026. (3)
- Novo Nordisk's oral semaglutide is currently the first GLP-1 pill available for obesity and is expected to face competition from Eli Lilly's orforglipron. (4)
- Novo Nordisk's oral semaglutide demonstrated 13.6% weight loss over 64 weeks, though tolerability issues remain during titration. (5)
- Novo Nordisk claims oral semaglutide 25 mg demonstrated significantly greater mean weight loss than orforglipron 36 mg in an indirect treatment comparison using OASIS 4 and ATTAIN-1 trial data. (6)

##### Emerging Competitors

- Structure Therapeutics' aleniglipton demonstrated competitive efficacy and tolerability in Phase 2 trials, with plans to initiate Phase 3 obesity trials in the second half of 2026 following an End of Phase 2 FDA meeting in Q2 2026. (7)
- Viking Therapeutics' VK2735, a dual GLP-1/GIP agonist in oral formulation, completed Phase 2 trials with positive results and is expected to enter Phase 3 studies in the third quarter of 2026. (8)
- Novo Nordisk's amycretin, an oral GLP-1 and amylin co-agonist in Phase 2 trials, shows potentially superior efficacy to semaglutide and could be a significant challenger to Eli Lilly's oral candidates. (9)
- Biomea Fusion's BMF-650 demonstrated significant weight reduction (up to 15%) and appetite suppression in preclinical primate studies, positioning it as a potential competitor in the oral incretin market. (10)

#### ▼ Opus

Great question — the oral GLP-1 space is moving fast. Let me check the latest developments.

Searched the web

Searched the web

Here's where things stand as of this week — it's a genuine two-horse race, and the answer depends on what you mean by "ahead."

#### **Novo Nordisk: First mover, massive early uptake**

Novo Nordisk launched oral Wegovy (semaglutide 25 mg) in January 2026, making it the first FDA-approved oral GLP-1 for weight loss. [Healthcare Brew](#) That head start has paid off: oral Wegovy has already racked up over 600,000 prescriptions, with uptake running about 10x higher than the original injectable Wegovy. [Healthcare Brew](#) Novo also benefits from brand recognition — the pill carries the same Wegovy name patients already know. The tradeoff is that

oral semaglutide must be taken on an empty stomach with no more than 4 oz of plain water, followed by a mandatory 30-minute fast. [Patient Care Online](#) In the OASIS 4 trial, the 25 mg tablet delivered mean weight loss of 13.6% at 64 weeks. [Pharmacy Times](#)

#### **Eli Lilly: Just approved, potentially stronger drug**

The FDA approved Lilly's oral GLP-1, Foundayo (orforglipron), on April 1, with pill shipments starting April 6. [Healthcare Brew](#) The big differentiator is convenience — orforglipron is a small-molecule, non-peptide GLP-1 agonist that can be taken any time of day without food or water restrictions. [Patient Care Online](#) On the clinical side, Lilly's head-to-head data in diabetes (ACHIEVE-3) looks strong: orforglipron 36 mg lowered A1C by 2.2% vs. 1.4% for oral semaglutide 14 mg, and patients lost 19.7 lbs vs. 11 lbs — roughly 74% greater relative weight loss. [Managed Healthcare Executive](#) However, discontinuation rates due to GI side effects were higher with orforglipron (up to 9.7%) compared to oral semaglutide (4.9%). [Managed Healthcare Executive](#)

Pricing is roughly comparable — both start at \$149/month self-pay, with Lilly offering as low as \$25/month with commercial insurance. [Healthcare Brew](#)

#### **The bottom line**

Novo is ahead on market share and prescriptions right now, thanks to a ~3-month head start and built-in brand equity. JPMorgan analysts wrote that Foundayo likely won't be adopted as quickly initially, but could become the market-leading oral option, especially internationally. [Healthcare Brew](#) Lilly arguably has the stronger clinical profile (better efficacy in the head-to-head diabetes trial, no dosing restrictions), but the tolerability gap and late start are real hurdles.

Meanwhile, the broader pipeline is enormous — around 50 oral small-molecule GLP-1 programs are now in development worldwide [GlobeNewswire](#), with players like Pfizer, Roche, AstraZeneca, Structure Therapeutics, and Gilead all in the mix. And then there are next-gen approaches like Lilly's retatrutide (a triple agonist targeting GLP-1, GIP, and glucagon), with full data expected mid-2026 [Food Navigator](#), that could leapfrog both current oral options on efficacy.

So: Novo leads on the scoreboard today, Lilly may have the better product on paper, and neither has a lock on the category long-term.

▼ AXL

## **Who Is Actually Ahead in the Oral GLP-1 Race?**

The press release narrative and the operational evidence point to the same winner — but for more granular reasons than headlines reveal. Eli Lilly's orforglipron is not just ahead on paper. It is ahead by every measurable behavioral metric: regulatory submissions filed, Phase 3 endpoints met, comparison trials won, and a PDUFA-eligible action date imminent. Everyone else is in a materially different position.

### **Landscape Overview: The Arena**

The oral GLP-1 space comprises 50 active trials as of April 2026, with 21 (38%) at Phase 3 and 19 (35%) at Phase 2. The landscape is moderately crowded (96 GLP-1R/Obesity active trials across all formulations) with a low termination rate of 4.3% — reflecting the demonstrated efficacy signal that keeps programs alive. The overall Phase 3 success rate from historical outcomes data is 89% (8/9 programs with extracted outcomes met their primary endpoint). This is an unusually high base rate, driven by the fact that GLP-1 mechanism has already been de-risked and companies now mostly self-select into confirmatory rather than exploratory Phase 3 trials.

Total enrollment across active oral GLP-1 programs: approximately 36,600 participants. Novo Nordisk leads enrollment volume (9,159 across 5 trials), but enrollment size by itself reflects organizational scale, not clinical lead.

### **Frontrunner Comparison: Program-by-Program**

#### **1. Eli Lilly — Orforglipron (Small Molecule GLP-1R Agonist) — CLEAR LEADER**

This is the only oral GLP-1 program with an NDA filed and regulatory action imminent.

The evidence chain from the registry and catalyst data is unambiguous:

- **ACHIEVE-3** ([NCT06045221](#)): Phase 3 vs. oral semaglutide, n=1,698, completed. Orforglipron 36 mg reduced A1C by 2.2% vs. 1.4% for oral semaglutide 14 mg — superiority on both glycemic and weight endpoints (weight loss 19.7 lbs vs. 11.0 lbs). Published in The Lancet, February 26, 2026. This is the head-to-head win the market needed.
- **ATTAIN-2** ([NCT05872620](#)): Phase 3 in obesity + T2D, n=1,613. Met primary endpoint: 10.5% weight loss (22.9 lbs) vs. 2.2% placebo at 72 weeks. All doses met primary and key secondaries.
- **ATTAIN-MAINTAIN** ([NCT06584916](#)): Phase 3 weight maintenance, n=376. Met primary endpoint of superior weight maintenance at 52 weeks vs. placebo. Operational note: enrollment ran 21.7% below original target (376 vs. 480), a signal worth watching for Phase 3 execution at scale, but the endpoint was met.
- **NDA filed**: Per the ATTAIN-MAINTAIN press release, Lilly has submitted an NDA to the FDA for obesity. The FDA granted a Commissioner's National Priority Voucher. U.S. action for obesity expected Q2 2026.
- **T2D submission**: Lilly has submitted orforglipron for T2D to regulators in over 40 countries; U.S. T2D submission expected later in 2026. Detailed ACHIEVE-3 data to be presented at ADA Scientific Sessions in June 2026.

Orforglipron's key differentiation is its modality: it is a **small molecule**, not a peptide. This means it can be manufactured at scale without the cold-chain and supply constraints that have plagued injectable GLP-1 programs, and without the food-timing restrictions of oral semaglutide (which requires fasting administration). The regulatory submissions already in front of FDA represent a 12-18 month lead over the next closest competitor.

Risk score for ATTAIN-MAINTAIN (the lead NDA-supportive trial): 70, elevated — driven entirely by the enrollment target fluctuations (37.5% decrease then 25.3% increase, ending 21.7% below original target). This is an operational flag for future Phase 3 execution, not a data-quality issue.

## 2. Novo Nordisk — Oral Semaglutide 25 mg (OASIS program) — APPROVED BUT LOSING GROUND

Novo Nordisk occupies a paradoxical position: they have the most active oral GLP-1 trials (5 programs, 9,159 enrolled) and already won FDA approval for higher-dose injectable Wegovy (7.2 mg, approved March 19, 2026, STEP UP trial [NCT05646706](#)). But for the oral-specific race:

- **OASIS 4** ([NCT05564117](#)): Phase 3, oral semaglutide 25 mg, n=307, completed. Published in NEJM. Average weight loss 16.6% at 64 weeks (product estimand) / 13.6% (treatment-policy estimand). This is commercially available product with a de-risked profile.
- **REDEFINE 1** ([NCT05567796](#)): Phase 3 CagriSema (semaglutide + amylin) n=3,400. Reported December 2025: mean 23% weight loss on-treatment. FDA review expected in 2026.
- **Critical failure**: In a direct head-to-head ([NCT06131437](#), n=809), CagriSema **failed to demonstrate non-inferiority to tirzepatide** on weight loss at 84 weeks (announced February 23, 2026). This is the only documented primary endpoint failure in the recent Phase 3 obesity landscape.

Novo Nordisk's oral semaglutide (25 mg, the highest dose) exists and shows real weight loss, but it competes against its own injectable franchise and, critically, is now behind orforglipron in regulatory positioning for obesity as a primary indication oral agent. The narrative that Wegovy's brand protects Novo's oral pipeline understates how directly orforglipron's Lancet publication and head-to-head superiority undercuts the semaglutide oral program's differentiation story.

The REDEFINE 1 CagriSema program ([NCT05567796](#)) carries an operational stress score of 45/medium and enrolled 3,400 patients — a massive trial that reflects Novo's execution machinery. But CagriSema is injectable, and the head-to-head loss to tirzepatide is a narrative problem regardless of absolute efficacy numbers.

## 3. Viking Therapeutics — VK2735 Oral (GLP-1/GIP Dual Agonist Peptide) — PROMISING BUT EARLY

Viking reported positive Phase 2 VENTURE-Oral ([NCT06828055](#)) results in August 2025: up to 12.2% mean weight loss at 13 weeks vs. 1.3% placebo. n=280. Primary endpoint met. Safety profile described as favorable with mostly mild/moderate GI events.

However, several important limitations:

- This is a **peptide**, not a small molecule, meaning manufacturing scale-up faces the same class challenges as semaglutide
- 13-week primary endpoint is very short — regulators typically require 52-72 week efficacy data for obesity approvals
- The high dropout flag (noted in the press release risk flags) warrants scrutiny before extrapolating to a longer Phase 3
- Phase 3 initiation is expected to begin in Q3 2026, per an end-of-Phase 2 meeting with FDA (completed). The trial [NCT07104500](#) is already registered as "VK2735 for Weight Management Phase 3" and is active, not recruiting
- **12.2% weight loss at 13 weeks** is notable but must be viewed in the context that orforglipron has already demonstrated 10.5% at 72 weeks placebo-adjusted, meaning the annualized trajectory for VK2735 has not yet been demonstrated

Operational risk score for the VENTURE-Oral trial: 0. Zero signals. Clean execution. This is a genuine positive behavioral signal — a confident sponsor operating with silence.

Viking's subcutaneous VK2735 (VANQUISH program) is in Phase 3 but is a separate program from the oral race. The oral program remains at Phase 2 readout stage with Phase 3 beginning in mid-2026.

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#### 4. Structure Therapeutics / Gasherbrum Bio — Aleniglipron / GSB-1290 (Small Molecule) — INTERESTING BUT OVERVALUED IN NARRATIVE

Structure reported Phase 2b ACCESS ([NCT06693843](#)) 36-week topline data on December 8, 2025: aleniglipron 120 mg produced placebo-adjusted weight loss of 11.3% (27.3 lbs) at 36 weeks ( $p < 0.0001$ ). All three doses met the primary endpoint.

However, analysis flags:

- The trial registry shows a **273-day primary completion delay** — the primary completion date was pushed from October 2025 to July 2026 (a 9-month shift registered in August 2025). This is a moderate operational signal in a Phase 2b trial, likely reflecting enrollment pace rather than data problems, but it demonstrates execution volatility
- The press release analysis flags: post-hoc emphasis, high dropout, and spin detected. The 11.3% placebo-adjusted figure is real, but the press did not consistently report absolute weight loss vs. relative comparisons
- Phase 3 is planned to initiate in H2 2026 after a Type B End-of-Phase 2 meeting with FDA in H1 2026
- At that timeline, they are entering Phase 3 approximately 2-3 years behind orforglipron's NDA position

Aleniglipron is a **small molecule**, which is a meaningful manufacturing advantage. But Phase 3 initiation in H2 2026 puts approval no earlier than 2029-2030 under optimistic assumptions.

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#### 5. Pfizer — Danuglipron — EFFECTIVELY EXITED

Danuglipron ([NCT04616339](#)) is the last registry trace for Pfizer's oral GLP-1 program. This was a PK formulation study. Pfizer publicly discontinued danuglipron's once-daily development in December 2023 after liver enzyme elevation signals, and has not registered meaningful subsequent oral GLP-1 activity. The catalyst data confirms no active Pfizer oral GLP-1 presence. This program is out of the race.

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### Momentum Analysis: Acceleration vs. Stalling

The field trend data shows a recent-to-older trial ratio of 0.20 for GLP-1R/Obesity — meaning the pace of new trial starts has slowed relative to the historical baseline. This is expected maturation behavior: the mechanism is proven, the competitive field is consolidating around fewer, larger programs rather than many early-stage explorations.

What is accelerating: new trial registrations increased sharply in March 2026 (6 new trials). The Chinese biotech pipeline (Hangzhou Zhongmei Huadong HDM1002, HK inno.N IN-B00009, Gan & Lee GZR18) is actively expanding with Phase 3 programs, primarily targeting Chinese/Asian market registrations. These are real clinical programs but not material to the Western oral GLP-1 competitive dynamic.

Kailera's KAI-9531 (1,700 enrolled) is notable as an enrolling Phase 3 program, but this is a GLP-1/GIP/glucagon triple agonist injection — not an oral agent.

The momentum leader for oral-specific programs is Lilly. Their Phase 3 programs ran with low operational stress, enrolled within timelines, and met endpoints. The ATTAIN-MAINTAIN completion date was actually pulled in by 151 days from its original schedule — accelerating, not slipping.

## Recent and Near-Term Catalysts

Event	Date	Outcome
Lilly ACHIEVE-3 (orforglipron vs. oral sema)	Feb 26, 2026	Success — Lancet publication, superiority demonstrated
Novo STEP UP (semaglutide 7.2mg) approval	Mar 19, 2026	FDA approved Wegovy HD — injectable, not oral
Lilly TRANSCEND-T2D-1 (retatrutide)	Mar 19, 2026	Success — A1C -2.0%, weight -16.8% at 40 weeks
Lilly ATTAIN-MAINTAIN (orforglipron obesity NDA)	Dec 2025	Success — NDA filed for obesity
Structure ACCESS (aleniglipron Ph2b)	Dec 8, 2025	Success — 11.3% placebo-adj weight loss at 36 weeks
Viking VENTURE-Oral (VK2735)	Aug 19, 2025	Success — 12.2% weight loss at 13 weeks
Novo CagriSema vs. tirzepatide head-to-head	Feb 23, 2026	FAILURE — non-inferiority not achieved

Upcoming: Lilly detailed ACHIEVE-3 data at ADA Scientific Sessions, June 2026. Lilly FDA action for obesity (orforglipron NDA, Q2 2026 per company guidance). These are the next inflection points.

## Historical Track Record: What Behavioral Data Shows

Of Phase 3 obesity trials with extractable outcomes in the last 3 years: 8 of 9 met primary endpoints (89% success rate). The only failure is CagriSema's non-inferiority to tirzepatide ([NCT06131437](#)). The field is confirmatory, not exploratory — companies are running Phase 3 programs in a proven mechanism space, so failure typically reflects competitive positioning (beating the wrong comparator) or poor trial design, not fundamental science failure.

The sponsor scorecard from catalyst tracking is revealing:

- Lilly: 14/14 positive outcomes (100% success rate across GLP-1 readouts tracked), 75% on-time delivery on resolved commitments
- Novo Nordisk: 4/5 positive outcomes (80% success rate), 0% on-time delivery on resolved commitments — the commitments that resolved did so without prior public disclosure

## Enrollment and Operational Execution

For the oral GLP-1 cohort specifically, the median enrollment period is 310 days for Phase 2 and 288 days for Phase 3. Enrollment attainment averaged 101.5% across trials with sufficient data — the field meets its enrollment targets, unlike many therapeutic areas where underpopulation is endemic.

Key operational observations:

- **Orforglipron ATTAIN-MAINTAIN:** Enrolled 21.7% below original target (376 vs. 480), despite meeting the endpoint. This was an enrollment recovery situation — target was cut to 300 then raised to 376 — suggesting mid-trial difficulty finding eligible patients for a weight maintenance trial (patients had to have already lost weight on GLP-1/GIP therapy)
- **VK2735 VENTURE-Oral:** Zero risk signals. 280 enrolled, 15 sites, US only. Fast and clean
- **Aleniglipron ACCESS:** 273-day primary completion delay signals enrollment pace problems in a 220-patient Phase 2b. 39 sites for 220 patients suggests lower-than-expected per-site yield
- **Novo's programs:** Large-scale machines that enroll but generate higher-frequency timeline changes — REDEFINE 1 shows two primary completion date changes and two eligibility criteria modifications, consistent with a massive global trial adapting to real-world enrollment dynamics

## Verdict: Who Is Actually Ahead — and Why

**Eli Lilly is ahead.** Not by a small margin in Phase 3 data — by the width of a filed NDA.

The behavioral evidence converges on Lilly in every dimension: orforglipron is the only oral GLP-1 agonist with a U.S. NDA filed for obesity, the only one with a head-to-head superiority publication against a marketed comparator (oral semaglutide), and the only one with multiple completed Phase 3 endpoints including maintenance. FDA action is expected Q2 2026 — within weeks to months of this analysis.

**Novo Nordisk is second but defending injectable turf.** Their oral semaglutide 25 mg (OASIS) is real and approved in some formulations, but the company's primary oral franchise at this scale is not positioned as the lead oral asset — CagriSema and higher-dose Wegovy injectable dominate their pipeline narrative. The CagriSema head-to-head failure against tirzepatide is a material competitive setback.

**Viking Therapeutics is the most credible challenger.** Clean Phase 2 execution, zero operational distress, positive endpoint, FDA end-of-Phase 2 meeting completed. Phase 3 initiation expected Q3 2026. But they are at minimum 3 years behind Lilly's oral approval timeline. The 13-week readout window leaves durability and long-term safety as open questions that Phase 3 must answer.

**Structure Therapeutics is real but delayed.** The 11.3% placebo-adjusted weight loss at 36 weeks is competitive. But the 273-day enrollment delay, the high dropout flags in the press release, and the Phase 3 initiation not expected until H2 2026 put an approval no earlier than 2029-2030. The small molecule advantage is genuine — the timeline gap to Lilly is not recoverable without a regulatory catalyst.

**Pfizer has exited.** No active oral GLP-1 program exists in the registry.

The distinction that matters most is not which drug shows the best weight loss number in a press release — it is which drug has already convinced a regulator to schedule a decision date. Only one company is at that stage. That is Lilly.

### ▼ ChatGPT

Here's a **clear snapshot of where the oral GLP-1 race stands as of early April 2026** — a market that's one of the hottest in pharma right now, especially in obesity and diabetes treatment:

[ReutersRace to launch weight-loss pill heats up as Lilly wins US approval7 days ago](#)



[The GuardianUS approves new oral weight-loss pill developed by Eli Lilly6 days ago](#)



[Fierce PharmaNovo's oral semaglutide edges out CagriSema, Lilly's orforglipron as PCPs' most-anticipated obesity medJan 8, 2026](#)



[InvestorsHow Novo Nordisk Is Striking Back As Eli Lilly Plans Its Newest Weight-Loss Launch5 days ago](#)



## 1) Who's technically "ahead" right now

**Novo Nordisk** (oral semaglutide / Wegovy pill) was technically first to **get an oral GLP-1 drug approved** for obesity when its Wegovy pill launched in late 2025 — meaning it had the first-to-market advantage.

However, **Eli Lilly's oral GLP-1, orforglipron (marketed as Foundayo), was approved by the FDA in April 2026**, just months later, and is now officially commercialized in the U.S. too.

→ So in *regulatory timing*, **Novo was first**, but **Lilly has now caught up with approval** — shifting the race from "first to market" to "best product & adoption."

## 2) What the clinical data suggests

- Head-to-head Phase 3 (ACHIEVE-3) data shows **Lilly's oral orforglipron outperformed oral semaglutide** in blood sugar control and weight loss in people with type 2 diabetes.
- Other reporting suggests more weight loss and fewer administration hassles (no strict fasting/food requirements) with orforglipron versus semaglutide pills.

This points to **Lilly having a possible efficacy edge**, at least in those clinical settings — which could influence prescribing and market share even though they weren't first.

## 3) Market dynamics: adoption & physician expectations

- Some physician surveys early after Wegovy pill launch showed strong uptake for Novo's oral semaglutide, indicating good early market traction.
- Meanwhile, analysts and industry commentary increasingly highlight Lilly's broader portfolio and stronger efficacy data as reasons it could win greater share over time.

## 4) Beyond Novo & Lilly — the broader race

While the big two headline most coverage, **several other oral GLP-1 or related candidates** are advancing through clinical pipelines — e.g., Structure Therapeutics' aleniglipron and others — which could shake up long-term competition.

Analysts expect **multiple approved oral GLP-1 options by the end of the decade**, not just two.

### Bottom line (right now):

- **Novo Nordisk was first to market** with an oral GLP-1 for obesity.
- **Eli Lilly has now entered the market too** and may have **clinical and commercial momentum** based on efficacy data.
- What determines "ahead" is shifting from *who launched first* to *which product doctors and patients prefer over time*.
- Longer-term, the space is becoming a **multi-player competitive market** rather than a two-horse race.

If you want, I can break this down by **efficacy data, side-effect profiles, and real-world adoption trends** for each oral GLP-1 candidate.

### ▼ Perplexity

**Eli Lilly is ahead on the oral GLP-1 race right now, but Novo Nordisk still has the first approved oral obesity pill on the market.** Lilly's orforglipron has now shown better glycemic and weight-loss results than oral semaglutide in a phase 3 head-to-head trial, and the FDA approved it on April 1, 2026, giving Lilly momentum in the class.

## What "ahead" means

If you mean **commercial launch**, Novo Nordisk got there first with oral semaglutide, which was approved in late 2025 and launched in early 2026.

If you mean **clinical performance and competitive positioning**, Lilly looks ahead because orforglipron beat oral semaglutide in ACHIEVE-3 on both HbA1c and weight loss, while also being a simpler once-daily non-peptide oral drug.

## Why Lilly is leading now

The strongest evidence is the direct comparison: orforglipton 12 mg and 36 mg were non-inferior and superior to oral semaglutide 7 mg and 14 mg for HbA1c reduction, and they produced greater weight loss as well.

That makes Lilly's pill the more convincing next-generation oral GLP-1 from an efficacy standpoint, even though GI side effects and discontinuations were somewhat higher.

Lilly also now has regulatory clearance, which turns its program from "promising" into an actual marketed contender.

## Where Novo still has an edge

Novo Nordisk still owns the **first-mover advantage** in oral GLP-1 obesity treatment with the Wegovy pill, and that matters for physician familiarity, payer contracting, and market presence.

Novo's pill also posted strong phase 3 weight-loss data, so it is not irrelevant just because Lilly's data are stronger in direct comparison.

But on the question of who is **actually ahead**, the balance now shifts toward Lilly because it has both a marketable product and the stronger head-to-head data.

## Other contenders

Structure Therapeutics is the most notable smaller-company challenger, with aleniglipton showing competitive phase 2 obesity results and a tolerability story that could matter later.

Pfizer and others are still in the mix, but they are not currently in the lead.

So the race is effectively being set by Novo and Lilly, with Lilly now holding the momentum advantage.

### What endpoints did successful GLP-1 obesity trials use?

▼ BB

#### GLP-1 Obesity Trial Endpoints

##### Primary Endpoints

- Percent change in body weight from baseline at 24 weeks was used as the primary endpoint in the retatrutide Phase II obesity study. (1)
- Percent change in weight from baseline at 26 weeks served as the primary endpoint in the orforglipton Phase II obesity trial. (2)
- The ACCESS trial for Aleni (oral GLP-1) used percentage change in body weight at 36 weeks as the primary endpoint. (3)
- The ATTAIN-1 study met its primary endpoint of mean percent change in body weight from baseline, with the 36mg dose achieving a 12.4% reduction compared to 0.9% for placebo after 72 weeks of treatment. (4)
- The Phase 3 clinical trial (ATTAIN-2) for oral GLP-1 receptor agonist orforglipton met its primary endpoint, which was the percentage weight loss from baseline at 72 weeks. (5)
- Innovent's Phase 3 clinical trial of mazdutide for obesity met its primary endpoints, which included the body weight percentage change from baseline to week 32 and the proportion of participants with a weight loss of  $\geq 5\%$  at week 32. (6)

##### Categorical Weight Loss Thresholds

- Categorical thresholds for weight loss, such as greater than or equal to 10%, 15%, 20%, and 25%, are increasingly utilized to contextualize clinical relevance based on risk segmentation in regulatory endpoints. (7)
- These weight loss thresholds align with stepwise improvements in obesity-related complications, including diabetes remission, reductions in hepatic steatosis, and improvements in functional status. (8)
- Key secondary endpoints in the ATTAIN-1 study included 59.6% of patients losing at least 10% body weight and 39.6% losing at least 15% body weight. (9)

### Cardiovascular and Metabolic Endpoints

- The Phase 3 SELECT trial, evaluating Wegovy in patients with established cardiovascular disease and obesity, reported a primary cardiovascular endpoint occurrence in 6.5% of patients on Wegovy versus 8.0% in the placebo arm. (10)
- Recent cardiovascular outcome trials for GLP-1 receptor agonists demonstrated that weight loss mediated by these drugs translated into risk reduction for major adverse cardiovascular events. (11)
- The ATTAIN-2 trial showed clinically significant improvements in cardiovascular risk factors, including non-HDL cholesterol, systolic blood pressure, and triglycerides. (12)
- Mazdutide demonstrated superiority over placebo in secondary endpoints, such as waist circumference, systolic blood pressure, triglycerides, low-density lipoprotein cholesterol, and serum uric acid. (13)

### Additional Secondary Endpoints

- Changes in weight, waist circumference, and BMI at 36 weeks, as well as the achievement of specific weight reduction percentages, were secondary endpoints in the orforglipron Phase II obesity trial. (14)
- Mean weight reduction at the end of the 48-week treatment duration was a secondary endpoint in the retatrutide Phase II obesity study. (15)
- Safety and tolerability, and pharmacokinetics were key secondary endpoints in the ACCESS trial for Aleni. (16)

#### ▼ Opus

This is a well-established topic in clinical trial design that I can answer from existing knowledge without needing to search.

Successful GLP-1 obesity trials have generally coalesced around a fairly standard set of endpoints, though there's been some evolution over the years.

**Co-primary endpoints** are the norm. Most pivotal trials (STEP, OASIS, ATTAIN, SURMOUNT) use two co-primary endpoints measured at a fixed timeframe (typically 68 weeks, though it varies): the mean percent change in body weight from baseline, and the proportion of patients achieving at least 5% body weight reduction versus placebo. The 5% threshold comes from the FDA's longstanding guidance that a clinically meaningful obesity drug should demonstrate either  $\geq 5\%$  mean weight loss over placebo, or that a significantly greater proportion of treated patients hit that 5% mark.

**Key secondary endpoints** tend to layer on additional weight-loss thresholds and cardiometabolic markers. Common ones include the proportion achieving  $\geq 10\%$ ,  $\geq 15\%$ , or  $\geq 20\%$  weight loss (these higher bars have become increasingly important as drugs have gotten more effective), along with changes in waist circumference, blood pressure, fasting glucose and insulin, lipid panels (triglycerides, LDL, HDL), and HbA1c in patients with or without diabetes. Patient-reported outcomes are also showing up more frequently — the IWQOL-Lite (Impact of Weight on Quality of Life) score and the SF-36 physical functioning domain are common choices.

**Cardiovascular outcomes** have become a major differentiator. The SELECT trial for semaglutide used a three-point MACE (major adverse cardiovascular events) composite — cardiovascular death, nonfatal MI, and nonfatal stroke — as its primary endpoint, and that positive result became a pivotal commercial and regulatory milestone.

**Regulatory nuances worth noting:** The FDA has historically evaluated efficacy using two estimands — a "treatment policy" estimand (intent-to-treat, including patients who discontinue) and a "trial product" estimand (on-treatment, estimating the effect in patients who stay on the drug). Companies typically report both, and the gap between them can be meaningful given that GI side effects drive discontinuation rates of 5–10%+ in these trials.

More recently, weight maintenance endpoints have entered the picture. Lilly's ATTAIN-MAINTAIN trial used maintenance of previously achieved weight loss as the primary endpoint — testing whether patients could switch from semaglutide to orforglipron without regaining. This reflects the growing recognition that obesity is a chronic condition requiring sustained treatment, and that durability matters as much as peak weight loss.

#### ▼ AXL

## Endpoints Used in Successful GLP-1 Obesity Trials

The data covers 50+ completed Phase 2 and Phase 3 obesity trials. Across the subset with structured outcome extraction (9 Phase 3 trials with confirmed outcomes, 88.9% success rate), a clear and replicable endpoint grammar has emerged. Here is the full pattern.

## Executive Summary

Successful GLP-1 obesity trials have converged on a **dual co-primary endpoint structure** combining (1) percent change in body weight from baseline and (2) a responder threshold — most commonly  $\geq 5\%$  weight loss. These are applied over treatment windows of 52–76 weeks in the general obesity population. Comorbidity-specific trials layer on disease-relevant primaries (e.g., AHI reduction for sleep apnea, WOMAC pain for osteoarthritis, MACE for cardiovascular outcomes). The bar has risen materially since semaglutide's approval — new entrants are now benchmarked against 15–22% absolute weight loss, not 5–10%.

## Primary Endpoint Patterns

### The dominant structure: dual co-primaries

Virtually every pivotal GLP-1 obesity trial uses two co-primary endpoints in tandem:

Endpoint	Description	Example
% body weight change	Mean percent reduction from baseline at a fixed timepoint	-14.9% (semaglutide, STEP 1, 68 wks); -21.1% additional (tirzepatide, SURMOUNT-3, 72 wks)
Weight-loss responder rate	% of patients achieving $\geq 5\%$ body weight reduction	83.5% vs. 31.1% on placebo (semaglutide STEP 1); 94.4% vs. 10.7% (tirzepatide SURMOUNT-3)

This pairing satisfies the FDA's guidance for obesity trials: one endpoint captures magnitude of effect (relevant for regulators and payers), the other captures clinical responder rate (relevant for prescribers and patients).

### Threshold responder rates used:

- $\geq 5\%$  weight loss: used universally as the minimum bar
- $\geq 10\%$  weight loss: commonly included as a key secondary or co-primary in newer trials
- $\geq 15\%$  and  $\geq 20\%$  weight loss: increasingly used in late-stage trials as the competitive bar shifts upward, particularly post-tirzepatide

### Timepoints used:

- 52 weeks (1 year) — standard for maintenance and regulatory trials (SURMOUNT-4, ATTAIN-MAINTAIN, SURMOUNT-OSA)
- 68 weeks — used by the core Wegovy STEP program (semaglutide STEP 1, [NCT03548935](#))
- 72–76 weeks — used by tirzepatide SURMOUNT-3 and orforglipron ATTAIN-2
- 84 weeks — CagriSema head-to-head vs. tirzepatide (the one Phase 3 non-inferiority failure)
- 88 weeks — SURMOUNT-4 (withdrawal/maintenance design)

**Maintenance design primary:** SURMOUNT-4 ([NCT04660643](#)) and ATTAIN-MAINTAIN ([NCT06584916](#)) used a distinct primary endpoint for withdrawal trials — **percent change in body weight from randomization through the double-blind period**, not from original baseline. SURMOUNT-4 participants continuing tirzepatide lost an additional 6.7% vs. 14.8% regain in the placebo-switch arm, meeting the primary endpoint.

## Comorbidity-Specific Primary Endpoints

When GLP-1 programs expand into comorbid indications, the primary endpoint shifts to reflect the co-indication while body weight remains a key secondary:

Indication	Primary Endpoint Used	Trial
Obstructive Sleep Apnea	Change in Apnea-Hypopnea Index (AHI)	SURMOUNT-OSA ( <a href="#">NCT05412004</a> )
Heart Failure with Preserved EF	Composite HF outcome + KCCQ-CSS	SUMMIT ( <a href="#">NCT04847557</a> )

Indication	Primary Endpoint Used	Trial
Cardiovascular outcomes	3-point MACE (CV death, MI, stroke)	SELECT ( <a href="#">NCT03574597</a> )
Knee Osteoarthritis	% body weight change + WOMAC pain score	STEP 9 ( <a href="#">NCT05064735</a> )
Type 2 Diabetes (T2D)	% body weight change + A1C reduction	ATTAIN-2 ( <a href="#">NCT05872620</a> )
Genetic Obesity (rare)	≥10% body weight reduction; BMI Z-score	Setmelanotide trials

For OSA: Zepbound reduced AHI by ~25–29 events/hour vs. ~5–6 for placebo, achieving remission/mild OSA in 42% vs. 16% of non-PAP patients. For HFpEF: tirzepatide hit a 38% relative reduction in composite HF outcome and significant KCCQ-CSS improvement at 52 weeks.

## Secondary and Exploratory Endpoint Patterns

Successful trials consistently include the following secondary endpoints:

### Cardiometabolic markers:

- Waist circumference reduction
- Systolic blood pressure reduction
- Triglycerides and lipid panel changes
- HbA1c and fasting glucose (particularly in mixed obesity/T2D populations)
- C-reactive protein (CRP) / hsCRP

### Extended responder thresholds (as key secondaries):

- ≥10%, ≥15%, ≥20% body weight reduction (tirzepatide hit ≥20% in 57% of patients at 15 mg in SURMOUNT-1)

### Patient-reported outcomes:

- SF-36 (physical function) — used in STEP 9 (osteoarthritis)
- KCCQ-CSS (heart failure symptom burden) — SUMMIT
- WOMAC pain and function scores — STEP 9, Lilly's eloralintide Phase 3 program ([NCT07353931](#))

**Lean mass preservation** (emerging): Scholar Rock's apitegromab ([NCT06445075](#)) used change in total lean body mass at 24 weeks as a primary endpoint in the EMBRAZE study — a signal that the next generation of obesity trial designs will include body composition, not just total weight.

## Phase 2 Endpoint Patterns

Phase 2 trials use a simplified version of the same framework:

- Primary: **mean percent weight loss at 12–24 weeks vs. placebo**
- The bar for Phase 2 advancement is typically 8–15% placebo-adjusted weight loss

Successful Phase 2 readouts:

- VK2735 (VENTURE subcutaneous, [NCT06068946](#)): 14.7% mean weight loss at Week 13 — primary met
- VK2735 oral ([NCT06828055](#)): 12.2% mean weight loss at Week 13 — primary met
- Mazdutide ([NCT04904913](#)): 11.6% weight loss at ~Week 24 — primary met
- Mazdutide Phase 3 ([NCT05607680](#)): co-primaries at Week 32 — -10.97% and -13.38% vs. -0.24% placebo; 76.3% and 84.0% achieving ≥5% weight loss

The Phase 2 failure benchmark: TERN-601 ([NCT06854952](#)) produced only 4.6% placebo-adjusted weight loss at 12 weeks with safety concerns — the company halted development. This sets a de facto floor: sub-5% placebo-adjusted weight loss in 12 weeks is a non-starter in the current landscape.

## Endpoint Strategy Evolution Over Time

**Pre-2021 (liraglutide era):** Primary endpoints were modest — 5% weight loss responder rate and mean % body weight change over 56 weeks. A drug producing 8–9% average weight loss was competitive.

**2021–2023 (semaglutide/Wegovy era):** STEP 1 established the new floor at ~15% mean weight loss. The ≥5% and ≥10% responder rates became standard. Dual co-primaries became the regulatory norm.

**2023–present (tirzepatide/GIP-GLP-1 era):** The competitive benchmark is now 20%+ mean weight loss. ≥20% responder rates are included in key secondary packages. Maintenance and withdrawal designs (SURMOUNT-4, ATTAIN-MAINTAIN) have become a distinct trial type. Head-to-head non-inferiority designs are emerging (CagriSema vs. tirzepatide).

**Emerging (2025+):** Body composition endpoints (lean mass preservation, fat-free mass), disease-specific co-primaries (OSA AHI, WOMAC, KCCQ), and combo add-on designs (Scholar Rock's lean mass preservation on tirzepatide) represent the next frontier.

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## Landscape Context

The GLP-1/obesity landscape shows **10 active trials specifically in the GLP-1+Obesity pair** with 8 unique sponsors having reached Phase 3. The field's termination rate is 0%, reflecting the commercial viability of the space. However, recent trial activity relative to older trials (field activity ratio: 0.18) suggests the pure GLP-1 monotherapy space is maturing — incremental entrants must differentiate on mechanism (dual/triple agonism, oral formulation, lean mass preservation) or indication expansion rather than replicating the standard weight loss endpoint package.

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## Implications for New Entrants

1. **Use the dual co-primary:** % body weight change + ≥5% responder rate remains the regulatory gold standard. Do not deviate without a strong scientific rationale.
2. **Size for 20%+ weight loss:** The bar has moved. A Phase 3 trial powered to detect 12% weight loss will underperform vs. the class and face commercial headwinds even if it achieves statistical significance.
3. **Include ≥10% and ≥15% responder rates as key secondaries:** These drive commercial differentiation and are expected by payers.
4. **Extend your treatment window to 52–72 weeks minimum:** 12-week data is Phase 2 only; regulators expect 52–76 week primary endpoints.
5. **Add a lean mass endpoint:** The body composition angle (muscle preservation on GLP-1 background) is a real differentiator — Scholar Rock's EMBRAZE design is the template.
6. **For comorbidity expansion:** Pick one co-indication with a validated, clinically meaningful endpoint (AHI for OSA, WOMAC for OA, MACE/KCCQ for CV) — body weight then becomes a key secondary, not the primary.

### ▼ ChatGPT

Successful GLP-1 obesity programs (injectable and oral) have been remarkably consistent in their **primary endpoints**, with increasing layering of **cardiometabolic, functional, and outcomes-based measures**.

Below is a structured view using major successful programs.

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## 1 Core Regulatory Endpoints (Used in Pivotal Trials)

Across FDA and EMA approvals, the primary endpoints almost always include:

### A. Mean % Change in Body Weight

- Change from baseline at ~68–72 weeks
- Continuous endpoint
- Statistically powered vs placebo

### B. Categorical Weight Loss Responders

Proportion of patients achieving:

- $\geq 5\%$
- $\geq 10\%$
- $\geq 15\%$
- $\geq 20\%$  (in newer programs)

FDA historically required:

- $\geq 5\%$  mean placebo-adjusted weight loss **OR**
- $\geq 35\%$  of treated patients achieving  $\geq 5\%$  weight loss and roughly double placebo

These endpoints were used in:

- **Wegovy** (STEP program)
- **Zepbound** (SURMOUNT program)
- **Saxenda**

These trials typically ran **68–72 weeks**, now considered the modern standard duration.

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## 2 Key Secondary Endpoints (Cardiometabolic)

Successful programs also demonstrated improvements in:

- Waist circumference
- Blood pressure
- Lipid profile (LDL, triglycerides)
- HbA1c (especially in obesity + T2D trials)
- CRP (inflammation marker)

For example:

- **Zepbound** showed large reductions in waist circumference and triglycerides.
- **Wegovy** showed consistent BP and A1c improvements.

These endpoints strengthen payer positioning and CV risk narratives.

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## 3 Hard Outcomes (Newer Generation Differentiator)

The field shifted meaningfully with cardiovascular outcomes trials (CVOTs).

**Example:**

- **Wegovy**
- **SELECT**

Primary endpoint:

- 3-point MACE (CV death, nonfatal MI, nonfatal stroke)

Result:

- ~20% relative risk reduction in overweight/obese patients *without diabetes*

This was a major regulatory and reimbursement unlock and marks a transition from cosmetic/metabolic framing to **chronic cardiometabolic disease treatment**.

Future obesity programs increasingly include:

- CVOTs

- HF outcomes
- Renal endpoints

#### 4 Functional & Quality-of-Life Measures

Modern trials now increasingly include:

- Physical functioning scores (SF-36, IWQOL-Lite)
- 6-minute walk test (in HF programs)
- Patient-reported outcomes (PROs)
- Fat mass vs lean mass (DEXA substudies)

These endpoints help differentiate at high weight-loss levels (15–25%).

#### 5 Emerging Endpoint Evolution (Where the Field Is Going)

The next wave (oral GLP-1s, triple agonists, combinations) is adding:

- $\geq 20\%$  and  $\geq 25\%$  categorical thresholds
- Body composition preservation
- Liver fat reduction (MRI-PDFF for MASLD/MASH)
- Time-to-weight-regain after discontinuation
- Cardiometabolic risk scores
- Sleep apnea resolution

### Summary Table

Endpoint Type	Used in Approvals?	Strategic Purpose
% Mean Weight Change	✔ Core	Regulatory primary
$\geq 5\text{--}15\%$ Responders	✔ Core	Clinical significance
Cardiometabolic markers	✔ Yes	Payer & risk framing
CV Outcomes (MACE)	Increasingly	Long-term differentiation
Functional/PRO	Growing	Quality-of-life positioning
Body composition	Emerging	Differentiation

## Bottom Line

The **anchor endpoint remains % weight loss at ~68–72 weeks**, but the winners in today's market also show:

- Strong categorical  $\geq 15\text{--}20\%$  responders
- Cardiometabolic improvement
- Ideally CV event reduction

The competitive edge is shifting from “does it cause weight loss?” to:

▮ “Does it reduce hard cardiometabolic outcomes and preserve functional health?”

If you'd like, I can next map this onto **oral GLP-1 trial design specifically** to see whether they are mirroring injectable benchmarks or redefining them.

▼ Perplexity

Successful GLP-1 obesity trials most often used **percent change in body weight from baseline** as the primary endpoint, usually at a fixed time point such as 68, 72, or 104 weeks. Many trials also used a responder endpoint like the **proportion of participants achieving at least 5% weight loss**, and some added cardiometabolic endpoints such as waist circumference, blood pressure, HbA1c, lipids, or reversion to normoglycemia.

## Core efficacy endpoints

The most common primary endpoint in obesity trials was **mean percent weight change** versus placebo. Semaglutide STEP 1 used coprimary endpoints of percent body-weight change and the proportion achieving at least 5% weight loss, while SURMOUNT-1 for tirzepatide used the same two co-primary endpoints.

## Time horizons used

Trials typically assessed these endpoints at the end of the planned treatment period, often **week 68 for semaglutide, week 72 for tirzepatide, or week 104** in longer semaglutide studies. For example, STEP 5 used coprimary endpoints at week 104, and SURMOUNT-4 used mean percent weight change from week 36 to week 88 after a lead-in phase.

## Secondary endpoints

Secondary endpoints commonly included **waist circumference, systolic and diastolic blood pressure, lipids, fasting glucose, HbA1c, and BMI**. In some trials, especially those enrolling people with prediabetes or diabetes, endpoints also included **reversion to normoglycemia** or other glycemic measures.

## Practical pattern

A simple way to think about it is that successful GLP-1 obesity trials usually asked two questions: "How much weight did people lose on average?" and "How many people crossed a clinically meaningful threshold like 5% loss?" Trials with added metabolic goals layered in glucose and cardiovascular risk markers as secondary outcomes.

### Stress-test the upcoming COMP360 TRD data readout — how often do trials with this enrollment trajectory and protocol stability hit their primary endpoint?

▼ BB

#### COMP360 TRD Trial Readout — Enrollment and Protocol Stability Analysis

##### Trial Timeline and Status

- The COMP 005 trial readout was expected in the second quarter of 2025, with enrollment nearing completion as of January 15, 2025. (1)
- The COMP 006 trial was expected to accelerate enrollment as COMP 005 completed and was on track for a readout in the second half of 2026 as of January 15, 2025. (2)
- Compass Pathways' COMP360 Phase 3 treatment-resistant depression results are anticipated in 2026. (3)

##### Protocol Stability Indicators

- A Data Safety Monitoring Board recently met and recommended no changes to the study, and patient retention has been good, indicating high study quality as of August 1, 2024. (4)
- The quality of the COMP 005 study remains high due to independent raters, stringent adherence to entry criteria, few patient visits, and good compliance, which is expected to minimize placebo impact and enable success. (5)
- The COMP 006 trial will remain blinded through 26 weeks to maximize data interpretability and address potential FDA concerns regarding functional unblinding. (6)

##### Enrollment Trajectory Challenges

- The delay in patient recruitment for COMP005, which pushed its data readout to 4Q24, is primarily due to the extended time required to formally verify the TRD diagnosis for enrollment. (7)

- The inclusion of a placebo arm in the COMP005 trial, unlike the Phase IIb COMP001 study and the Phase III COMP006 trial, may also be impacting enrollment speed. (8)

#### TRD Trial Success Rates and Challenges

- Psychiatric drug development is characterized by high clinical trial failure rates, partly due to a limited understanding of behavioral health conditions. (9)
- In neuropsychiatric clinical studies, approximately 30-50% of patients are treatment-resistant, meaning they do not respond to placebo or active treatment, which can make it challenging to detect efficacy and may contribute to false negative trials. (10)
- On average, over 40% of patients in clinical studies are responsive to both placebo and active treatment, and only 10-30% of patients are responsive only to the active treatment. (11)

#### Recent COMP360 Trial Successes

- Compass Pathways successfully achieved the primary endpoint in their Phase 3 COMP006 trial on February 17, 2026, showing a clinically meaningful difference of -3.8 points at Week 6 with a p-value of less than 0.001. (12)
- Compass Pathways successfully achieved the primary endpoint in their Phase 3 COMP005 trial on June 23, 2025, demonstrating a highly statistically significant reduction with a p-value of less than 0.001 and a clinically meaningful difference of -3.6 in MADRS scores at week 6. (13)

▼ Opus

## COMP360 Psilocybin for Treatment-Resistant Depression: Trial Stress Test

Let me pull the latest on COMPASS Pathways' COMP360 program and then contextualize it against historical TRD trial performance.

Searched the web

Searched the web

Now let me pull together a comprehensive stress test. Here's where things stand and how COMP360's trajectory compares to the broader landscape:

### Current Program Status (as of April 2026)

Both Phase 3 trials have now hit their primary endpoints. COMP005 (N=258, single 25 mg dose vs. placebo) showed a -3.6 MADRS point separation at week 6 ( $p < 0.001$ ). COMP006 (N=581, two 25 mg doses vs. 1 mg control) showed -3.8 points ( $p < 0.001$ ). [Compasspathways](#) Compass plans to submit an NDA in Q4 2026, with 26-week durability data from COMP006 expected in early Q3 2026. [Clinical Trials Arena](#)

So both pivotal trials are already read out positive at the primary endpoint. The remaining data disclosure is the 26-week durability readout from COMP006 — not a new primary endpoint test, but a long-term follow-up that will shape the labeling and commercial narrative.

### The Stress Test: Historical Base Rates

Here's the uncomfortable context for TRD programs:

**1. Depression/TRD is a graveyard for Phase 3 trials.** A systematic review of 46 industry-sponsored Phase 2/3 adjunctive MDD trials found that only about 31% of drug-placebo comparisons were successful, and just three approved drugs emerged from nearly 34,000 patients enrolled. [PubMed Central](#) TRD-specific trials fare even worse because they layer treatment resistance on top of an already high-placebo-response disease.

**2. Placebo response is the central confounder.** The placebo response rate in antidepressant trials has been estimated at 35–40% and is a major contributor to Phase 3 failures in depression. [PubMed Central](#) An FDA analysis of 22 case

studies of Phase 3 failures found that high placebo response conditions (including depression) were overrepresented among the failures. [Wiley Online Library](#)

**3. The 2025 depression trial bloodbath illustrates the norm.** In 2025 alone, J&J's aticaprant failed in Phase 3 for MDD, Neumora's navacaprant failed its first Phase 3 in MDD, and Supernus's SPN-820 missed its primary endpoint in TRD in Phase 2b — all despite encouraging earlier-stage data. [BioSpace](#)

**4. The Phase 2-to-3 translation gap is brutal.** Even drugs in Phase 3 only have approximately a 50% chance of successful approval overall. [Wiley Online Library](#) In CNS/psychiatry, that figure is historically lower — often cited around 15–25% for the full journey from Phase 1 to approval.

## How COMP360 Stacks Up Against These Odds

### What's working in its favor:

- **It already hit the primary endpoint — twice.** This is the single most de-risking event for any program. Compass itself has framed this as historically difficult in TRD, noting the achievement of two positive Phase 3 trials in this population is rare. [Compasspathways](#)
- **Consistent effect size across trials.** The MADRS separations of -3.6 (COMP005) and -3.8 (COMP006) were remarkably similar, which bolsters the signal's credibility. [Drug Discovery Trends](#)
- **Clean safety profile by DSMB assessment.** The independent DSMB found no new safety signals and no imbalance in suicidality across treatment arms — critical for a psychedelic compound. [Stocktitan](#)
- **Breakthrough Therapy Designation and positive FDA interactions.** Compass had a positive Type B meeting with FDA in September 2025 to discuss rolling NDA submission strategy. [Compasspathways](#)
- **Cash runway secured.** Between a ~\$150M public offering and ~\$200M in warrant proceeds, Compass has funded operations into 2028. [Stocktitan](#)

### Where the skeptics push back — and rightly so:

- **The effect sizes are modest by absolute standards.** A ~3.7 MADRS point separation, while statistically significant, is smaller than what many investors expected from a psychedelic compound with transformative branding. Compass's own Phase 2b trial showed a 37% response rate at three weeks using the standard 50% MADRS reduction threshold, but that fell to 20% by 12 weeks — and Phase 3 used a more lenient 25% MADRS reduction threshold. [Drug Discovery Trends](#)
- **Remission rates haven't been disclosed.** This is a notable omission. Remission is the gold standard outcome payers and clinicians care about, and the company has avoided reporting it for either Phase 3 trial so far.
- **Durability is the open question.** The 26-week COMP005 data showed that 25% of patients in the 25 mg arm maintained clinically meaningful benefit — but many questions remain about whether non-responders benefit from additional doses. [Psychedelic Alpha](#) The COMP006 26-week readout (early Q3 2026) will be pivotal.
- **The 1 mg active control in COMP006 complicates interpretation.** Unlike COMP005's placebo arm, COMP006 used a 1 mg COMP360 dose as control. If 1 mg carries any pharmacological activity, the true drug-placebo difference could be larger — or it could indicate the "placebo" arm was partially active, muddying the picture.
- **Post-COMP005 stock cratered >50%.** Despite hitting the primary endpoint, the initial COMP005 data in June 2025 was seen as underwhelming, and the stock dropped more than 50%. [Clinical Trials Arena](#) Investor sentiment only recovered after the COMP006 confirmatory readout.

## Probability Assessment for the Remaining Milestones

Milestone	Historical base rate	COMP360-adjusted probability
Hit primary endpoint in 2 pivotal trials	~15-25% for TRD programs overall	<b>Already done</b> (✓)
26-week durability supports labeling	~60-70% given positive 6-week data	<b>Moderate-to-good</b> — early COMP005 26-wk signal exists but is modest

Milestone	Historical base rate	COMP360-adjusted probability
NDA filing (Q4 2026)	~80%+ given two positive pivotals	<b>High</b> — on track per company guidance
FDA approval	~65-75% for programs with two positive pivotals + BTD	<b>Favorable but not certain</b> — REMS, administration complexity, and the Lykos MDMA rejection loom as cautionary precedents

## Bottom Line

COMP360 has already beaten the base rate where it matters most: it achieved two statistically significant Phase 3 readouts in a disease area where the majority of programs fail. That puts it in a fundamentally different risk category than a pre-readout program. The remaining risk isn't about whether the drug "works" in the statistical sense — it's about whether the magnitude of effect, durability, and safety profile are enough to satisfy FDA, payers, and clinicians that this is worth the logistical complexity of supervised psychedelic administration. The 26-week COMP006 data expected in Q3 2026 is the next high-stakes catalyst: strong durability could reframe the modest effect sizes as a worthwhile trade for a finite treatment course, while weak durability would intensify the commercial viability debate.

▼ AXL

## COMP360 TRD Readout Stress-Test: Post-Hoc Analysis

The stress-test reveals something important upfront: **the primary endpoint readout you were stress-testing has already occurred.** Both pivotal Phase 3 trials — COMP005 and COMP006 — reported positive results. The remaining catalyst is the COMP006 26-week durability readout, expected in early Q3 2026. That is now the live risk.

### Readout Context: Where Things Stand

Compass Pathways has two Phase 3 TRD trials in its COMP360 program:

**COMP006 (NCT05711940)** — The larger pivotal trial. n=572 (actual). Two doses of COMP360 25 mg vs. a 1 mg active comparator. On February 17, 2026, Compass announced COMP006 Part A met its primary endpoint: mean MADRS difference of -3.8 points at Week 6 (95% CI [-5.8, -1.8]; p<0.001), with 39% response at 25 mg. Safety was consistent with prior data. No red flags on spin were detected in the full readout press release. The company has requested an FDA meeting to discuss a rolling NDA submission, targeting Q4.

**COMP005 (NCT05624268)** — A smaller confirmatory trial. n=258. Single 25 mg dose vs. placebo. Met its primary endpoint on June 23, 2025: mean MADRS difference of -3.6 points (95% CI -5.7 to -1.5; p<0.001). DSMB reported no new or unexpected safety findings. No spin detected.

Both trials succeeded. The 3-point-range MADRS difference is modest but statistically consistent and reproducible across both studies. Compass holds Breakthrough Therapy designation and ILAP designation in the UK.

**Next live catalyst:** COMP006 26-week Part B durability data, guided for early Q3 2026 (July–September).

### Enrollment Trajectory Analysis

**COMP006 (NCT05711940) — Favorable profile:**

- Enrolled 572 patients (actual), a marginal increase from the prior count of 568
- One enrollment modification (trivial: +4 patients), one primary completion date delay of 337 days (original: March 2025 → slipped to February 2026)
- Status transitioned to "Active, not recruiting" in November 2025 — enrollment was completed cleanly
- No site count changes; no erratic target reductions
- Total registry change events: 3. Changes per year: ~3.95

The 337-day completion delay on COMP006 is the single operational flag. However, the behavior pattern matters: this was one large, single shift (not a sequence of rolling small delays), and it was accompanied by normal enrollment completion (not a rescue target cut). The registry interpretation is that Compass ran a large, complex multi-country trial across 12 countries — delays in this context are more likely to reflect operational complexity and patient follow-up

requirements than enrollment distress. Protocol stability tool labels COMP006 as "Unstable" (note: this is a proxy label based on change frequency, not a confirmed amendment count).

**COMP005 (NCT05624268) — More turbulent profile:**

- Primary completion date changed 3 times, with cumulative delays of 243 days
- Enrollment target cut 32.5% from 378 to 255 (November 2023 registry update)
- Study completion date changed 3 times
- 4 total registry change events; 2.33 changes per year; protocol stability: "Moderate"
- Risk score: 80 / elevated (4 active signals)

The enrollment cut on COMP005 is the most significant behavioral signal in this program. A 32.5% downward revision from 378 to 255 participants, implemented before primary completion delays, is a pattern that — in a different context — would warrant serious concern. It can reflect: (a) a protocol amendment reducing required sample size based on interim power re-estimation, (b) an enrollment rescue strategy to accelerate completion, or (c) actual operational difficulty in recruitment.

Critically: COMP005 succeeded anyway, with clean  $p < 0.001$  results. This retroactively suggests the enrollment cut was a power recalculation or FDA-agreed design modification, not a rescue attempt — but it's worth noting the behavioral signal was present and would have flagged this trial pre-readout.

**Protocol Stability Assessment**

Trial	Total Change Events	Changes/Year	Stability Label	Key Changes
COMP006 (NCT05711940)	2	3.95	Unstable (proxy)	1 date delay, 1 minor enrollment change
COMP005 (NCT05624268)	4	2.33	Moderate	3 date delays, 1 enrollment cut (-32.5%)

The "Unstable" label on COMP006 is an artifact of the proxy methodology (3.95 changes/year from just 2 total events over a short denominator window). In absolute terms, COMP006 had fewer changes than COMP005. Neither trial shows evidence of endpoint or arm modifications — both stability signals are limited to timeline and enrollment adjustments, which is the less alarming category.

No evidence of primary endpoint modifications in either trial registry record. This is the most important protocol stability checkpoint — endpoint changes are a strong red flag; pure timeline/enrollment adjustments are common in complex multi-country trials.

**TRD Historical Base Rates: How Often Do These Trials Succeed?**

The historical outcomes database returns limited structured outcome data for Phase 3 depression trials — most records lack extracted endpoint results (only 1 of 50 trials has full extraction data), which limits a precise base rate calculation. What the broader landscape shows:

- 50 Phase 3 depression trials in the database: 41 completed, 7 terminated, 2 withdrawn
- Of those, only 1 trial (Biogen's zuranolone SKYLARK in postpartum depression) has confirmed extracted "met primary endpoint" data
- Termination rate: 14% (7/50) — relevant for gauging field-level attrition, not head-to-head endpoint success

For context on novel mechanism trials (psychedelic/serotonergic): the psilocybin/5-HT2A agonist TRD space has essentially no precedent in Phase 3 trials — COMP005 and COMP006 are the first registrational-grade trials of this mechanism. This is a foundational observation. There is no large historical base rate from which to calculate a prior probability for a psilocybin Phase 3 trial; the Phase 2 data (COMP001, which showed dose-dependent effects but also failed to meet its primary endpoint in the 25 mg arm in the original study) was the closest proxy.

Compass's commitment scorecard is relevant here: 5 out of 5 completed catalyst events resulted in positive outcomes (100% success rate). However, only 1 of 6 commitments was delivered on time (33% on-time rate), confirming the timeline volatility seen in the registry.

## Integrated Stress-Test: Signal Triangulation

Synthesizing all signals across the three dimensions:

**Enrollment trajectory:** Mixed. COMP006 enrolled cleanly with modest operational noise. COMP005 showed a material 32.5% enrollment cut that would have been a pre-readout concern — but the trial succeeded, suggesting the cut reflected a design recalibration rather than patient access failure. Net: amber on COMP005, green on COMP006.

**Protocol stability:** Neither trial shows endpoint modifications, which is the critical threshold. Timeline and enrollment adjustments are present but consistent with operational complexity, not scientific retreat. Net: yellow-amber on aggregate.

**Historical base rates:** Not computable with precision in this indication for this mechanism. Psilocybin Phase 3 in TRD is de novo territory. The absence of historical failures is not inherently reassuring — it reflects the absence of prior attempts. The mechanism had one prior Phase 2 signal that was mixed (COMP001), which would have lowered pre-trial probability. Net: indeterminate; lean slightly bearish on prior probability given COMP001 history, but that prior has now been updated by two consecutive Phase 3 successes.

**The key forward risk — 26-week durability:** The primary 6-week efficacy endpoint is confirmed. The open question for regulators is whether the acute effect of a psychedelic experience translates into durable symptom remission at 26 weeks. This is scientifically distinct from the 6-week question and clinically crucial. The 26-week data expected Q3 2026 is the remaining live catalyst and is not a replication of already-known results — it is a genuinely new data point that will determine the label narrative and likely the NDA timeline.

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## Bottom Line

The question was framed as a prospective stress-test, but the data shows this has already resolved: COMP005 and COMP006 both met primary endpoints with  $p < 0.001$ . The operational signals that would have warranted caution pre-readout — particularly the 32.5% enrollment cut in COMP005 and 337-day completion delay in COMP006 — did not predict failure. This is consistent with the analytical principle that operational distress is a risk multiplier, not a deterministic failure signal.

The remaining binary risk is the COMP006 26-week Part B durability readout in early Q3 2026. That is a genuinely uncertain data point. Durability of effect for a psychedelic-assisted approach in a severe, chronic population like TRD is not guaranteed by the 6-week efficacy outcome. Pre-clinical and Phase 2 observations suggest effects can persist, but Phase 3-scale durability data in 3L+ TRD patients is not yet established. Regulatory disposition will likely hinge heavily on what the 26-week data shows.

### ▼ ChatGPT

Here's a realistic **stress-test perspective** on how likely an upcoming COMP360 TRD (treatment-resistant depression) data readout is to hit its primary endpoint, based on both what we know about this specific program and the broader science of CNS/psychiatric drug development:

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## Where COMP360 stands right now

- **Two pivotal Phase 3 trials in TRD — COMP005 and COMP006 — have *already met their pre-specified primary endpoints*** according to company releases:
  - The COMP005 trial showed a statistically significant difference on the Montgomery-Åsberg Depression Rating Scale (MADRS) at Week 6 for COMP360 25 mg vs. placebo ( $p < 0.001$ ).
  - The COMP006 trial similarly achieved its Week 6 MADRS endpoint with a 25 mg regimen showing robust separation from a low-dose control ( $p < 0.001$ ).
- Across the two COMP360 Phase 3 studies to date, the therapy has shown clinically meaningful effects on symptom scores and early onset of benefit, with generally well-tolerated safety profiles.
- Collective datasets already involve **more than 1,000 participants**, which is highly unusual for psychiatric trials of novel mechanisms and strengthens the statistical power.

**Implication:** If your “upcoming readout” refers to final datasets (e.g., Week 26 durability, secondary efficacy/safety details), the program’s established Phase 3 signal suggests a *high probability of confirming the primary endpoint regionally or at later time points*, given consistent trajectory so far.

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## Context: Psychiatric & CNS trial success odds

It’s important to benchmark COMP360 against historical norms in this field:

### High attrition in CNS and depression trials

- Psychiatric drug development historically has *very low success rates*, with CNS programs showing some of the **highest failure rates in pharma** (overall approval rates from Phase I as low as ~8-9%).
- WCG Clinical Services estimates around an **85% failure rate for late-phase CNS drugs** (Phase II/III) across indications like depression — mostly due to *efficacy not separating from placebo*.
- High and variable **placebo responses (30-45%)** in depression make achieving statistical separation especially challenging.

### Phase III success isn’t a given even with promising Phase II

- Depression and TRD historically are among the “hardest” areas to demonstrate robust, reproducible benefit across diverse sites and populations.
  - Recruitment and endpoint consistency (e.g., blinded rating of depressive symptoms) influence variability and statistical power — and small deviations can swing trials either way.
- 

## What this means going forward

If the question is:

**“Given this enrollment and protocol stability, how often do trials like this hit their primary endpoint?”**

Here’s a practical breakdown:

### COMP360’s own track record so far:

Because *both Phase 3 trials reported positive primary endpoints* on those MADRS comparisons, the internal historical success here is currently **100% in these instances** — an unusually strong signal for a psychiatric program.

### But historically across the broader field:

- Typical late-phase depression programs succeed **in a minority of cases**, often less than half when you look across sponsors and mechanisms.
- CNS drug development overall shows **very high attrition**, especially for psychiatric indications.

### So your stress test should consider two layers:

1. **COMP360’s internal stability and past readouts** — which are quite strong relative to peers;
  2. **General industry risk** — which remains high across antidepressant/psychedelic and psychiatric trials.
- 

## Key takeaways

- COMP360’s Phase 3 program has already shown **multiple statistically significant primary endpoint successes** in pivotal trials, which is exceptional for a novel psychiatric agent — especially in TRD, a notoriously difficult population.
- Typical CNS/psychiatric programs have **high failure rates in Phase II/III**, often due to placebo effects and variability, so hitting 6-week MADRS separation is a material achievement.
- If **protocol execution remains consistent** and enrollment targets are met with low site-to-site variance, your chance of observing statistical success at the primary endpoint is **higher than the industry average**, but still carries general

CNS trial risk.

▼ Perplexity

For COMP360 TRD, the *relevant evidence base is unusually strong*: both pivotal Phase 3 trials met their primary endpoint, with COMP005 reporting a -3.6 MADRS difference vs placebo at Week 6 and COMP006 reporting a -3.8 difference vs 1 mg at Week 6, both with  $p < 0.001$ . The registered protocols show a large, standard Phase 3 design with fixed dosing, blinded controls, and no obvious midstream protocol instability in the primary efficacy part, which makes this a much cleaner readout than a typical late-stage psychiatric trial.

## What that implies

If you use COMP360's own trajectory as the template, the "hit rate" is effectively 2 for 2 at the pivotal Phase 3 level, or 100% for the trials already run. That does **not** mean future trials or follow-on programs carry a 100% success probability, but it does mean the specific upcoming COMP360 TRD readout risk profile is now anchored by two positive confirmatory studies rather than one exploratory signal.

## Stress test framing

A reasonable stress test for a trial with this enrollment shape and protocol stability is: large, multicenter, randomized, double-blind, placebo/active-control design; fixed dose; primary endpoint at Week 6; and no major publicly visible protocol churn in the efficacy portion. Under that lens, the main failure modes are usually not the design itself but effect-size shrinkage, site-level noise, or an unexpected placebo response, especially in depression studies where historical late-stage attrition has been high. For COMP360 specifically, the two Phase 3 readouts argue that this design class can in fact clear the bar when executed well.

## Practical takeaway

So the best short answer is: trials with this kind of COMP360-like trajectory and protocol stability have, in this case, hit the primary endpoint in **both** pivotal instances observed so far. If you want a more general benchmark across psychiatry or TRD psychedelic programs, the baseline historical hit rate is much lower than 100%, but COMP360 is no longer an average case because it now has replicated Phase 3 success.

### Find the operationally fragile assets in Duchenne Muscular Dystrophy — cross-reference enrollment and protocol stability to surface who's slipping vs. on track

▼ BB

#### Duchenne Muscular Dystrophy — Operational Fragility Assessment

##### Programs Experiencing Setbacks

- **Sarepta (Elevidys)**: European trials (Study 104, ENVOL, ENVISION) remain on clinical hold following a patient death, with enrollment and dosing paused at EU and UK sites pending analysis. (1)
- **Sarepta (Elevidys)**: A second patient death from acute liver failure occurred in June 2025, prompting voluntary pause of the ENVISION study and temporary shipment suspension for non-ambulatory patients. (2)
- **Sarepta (Elevidys)**: Acute liver injury affected over 40% of trial patients, with two non-ambulatory patients progressing to acute liver failure. (3)
- **Nippon Shinyaku (Viltepso)**: Phase 3 trial missed its primary endpoint measuring speed of standing from floor at 48 weeks, requiring an additional Phase 3 trial in Europe and China with planned release in fiscal year 2029. (4)
- **Percheron (ATL1102)**: The Phase IIb trial in DMD did not demonstrate effective therapy, leading to program failure. (5)
- **Sarepta (SRP-5051)**: Development discontinued in late 2024 due to serious safety concerns including prolonged hypomagnesemia and potential kidney function decline. (6)
- **Pfizer (fordadistrogene movaparvovec)**: Phase 3 CIFFREO trial failed to meet primary endpoint for motor function improvement in boys aged 4-7, with key secondary endpoints also showing no significant difference versus placebo. (7)

- **Capricor (Deramiocel):** Received Complete Response Letter in July 2025, though subsequently submitted protocol amendment and obtained regulatory clarity for BLA resubmission. (8)

#### Programs On Track

- **Dyne (DYNE-251):** Registrational Expansion Cohort met primary endpoint with statistically significant dystrophin increase (5.46% at 6 months) and functional improvements across all six prespecified endpoints, with BLA filing expected in Q2 2026. (9)
- **REGENXBIO (RGX-202):** Pivotal trial enrollment completed in October 2025, with topline data anticipated in early Q2 2026 and planned BLA submission via accelerated approval pathway mid-2026. (10)
- **Avidity (del-zota):** Phase 1/2 EXPLORE44 trial showing consistent improvements across biomarkers with favorable safety profile, BLA submission planned by end of 2025 for potential late 2026 launch. (11)
- **Solid Biosciences (SGT-003):** INSPIRE DUCHENNE trial dosed 40 participants without new serious safety signals as of March 2026, with Phase III IMPACT DUCHENNE trial planned for early 2026. (12)
- **Entrada (ENTR-601-44):** ELEVATE-44-201 trial authorized entry into Cohort 2 at 12mg/kg dose escalation, with Cohort 1 data expected next quarter and expansion cohort planned to support accelerated approval. (13)

#### Enrollment & Protocol Challenges

- DMD trials face protracted timelines due to limited patient availability (estimated 16,000 persons in US, reduced to ~2,000 for specific age ranges), with growing competition for enrollment across multiple drug candidates. (14)
- Recruitment challenges include comorbid conditions, stringent eligibility criteria, and logistical difficulties enrolling across multiple sites. (15)
- FDA has not established definitive clinical outcome measurements for DMD studies, creating risk of inappropriate endpoint selection and potential trial redesigns. (16)

#### ▼ Opus

I'll research the current clinical trial landscape for Duchenne Muscular Dystrophy (DMD), focusing on enrollment challenges, protocol amendments, and operational risks. Now let me search for the Sarepta ESSENCE trial and Edgewise/Avidity updates to complete the picture. Now I have enough data to build a comprehensive operational fragility analysis. Let me create a detailed visualization. Here's the synthesis of what's happening across the DMD pipeline:

### DMD clinical trial operational fragility dashboard showing enrollment status, protocol stability, and risk signals for 10 active programs as of April 2026

Active programs tracked

**10**

Gene therapy, exon skip, cell, small mol

High fragility signals

**3**

Sarepta PMOs, Elevidys non-amb, Edgewise DMD

On track / accelerating

**4**

REGENXBIO, Dyne, Wave, Avidity

Key PDUFA / BLA dates

**5**

Multiple filings expected H1-H2 2026

High fragility Moderate risk On track Regulatory review

**Slipping — operationally fragile assets**

Program	Phase	Enrollment	Status	Key risk signals
<b>Sarepta — Elevidys</b> Non-ambulatory (Cohort 8)	Ph 1b	~15%	<b>High fragility</b>	3 patient deaths (2 non-amb DMD + 1 LGMD) triggered label restriction, FDA requested distribution halt (Sarepta declined). Protocol amended to add sirolimus immunosuppression. Non-amb indication commercially paused. Enrollment just started Mar 2026 for ~25 pts; primary data H2 2026. CEO retiring. 36% workforce cut (~500 jobs).
<b>Sarepta — ESSENCE</b> Vyondys 53 / Amondys 45	Ph 3 (done)	Complete	<b>High fragility</b>	Confirmatory trial missed primary endpoint (p=0.309). COVID-era missed doses cited as confound. Post-hoc COVID-adjusted analysis reached only p=0.050. sNDA filing for traditional approval by end of Apr 2026 using real-world evidence. FDA conversion to traditional approval uncertain — accelerated approval at risk.
<b>Edgewise — sevasemten</b> LYNX / FOX (DMD-specific)	Ph 2	~55%	<b>High fragility</b>	DMD Ph 3 not yet initiated — still finalizing design (H2 2026 target). Dose selected (10mg) from Ph 2 but BMD-first strategy delays DMD timelines. GRAND CANYON (BMD) topline Q4 2026. No pivotal DMD data until 2028+. FDA meeting on Ph 3 design was Q4 2025 — outcome not yet disclosed.

#### Moderate risk — watch closely

Program	Phase	Enrollment	Status	Key risk signals
<b>Solid Bio — SGT-003</b> INSPIRE DUCHENNE	Ph 1/2	33/~43 pts	<b>Moderate risk</b>	Microdystrophin expression of 110% reported (first 3 pts). But early-stage with 5-cohort design — later cohorts (12-18y) contingent on earlier safety data. Trial runs through ~May 2027. Rolling BLA "perfect storm" end of 2026. AAV safety overhang from Elevidys deaths creates recruitment headwind.
<b>Capricor — deramioce</b> HOPE-3 / BLA	BLA under review	106 pts (done)	<b>Moderate risk</b>	FDA issued CRL in Jul 2025 (insufficient evidence + CMC). CRL lifted Mar 2026 after HOPE-3 data submission. New PDUFA Aug 22, 2026. Primary endpoint (PUL v2.0) met, but FDA refused to switch primary to LVEF. Seeking broader DMD/skeletal label beyond cardiomyopathy — uncertain.
<b>Sarepta — Elevidys</b> Ambulatory (EMBARK/EXPEDITION)	Ph 3 LTF	52/64 in LTF	<b>Moderate risk</b>	3-yr data positive (73% slowing TTR, 70% slowing 10MWR). 12 pts dropped from 64 in long-term follow-up. Boxed warning added for hepatotoxicity. LGMD gene therapy death + platform designation revoked creates general AAV confidence drag. Japan launch proceeding.

#### On track — executing well

Program	Phase	Enrollment	Status	Key signals
<b>REGENXBIO — RGX-202</b> AFFINITY DUCHENNE	Ph 1/2 → Pivotal	~85%	<b>On track</b>	Pivotal enrollment completed. Ph 3 first patient dosed Feb 2026. Confirmatory trial (~30 pts) enrolling. Zero SAEs or liver injury signals across 13 pts (up to 24 mos). Topline pivotal data early Q2 2026. BLA filing planned mid-2026. Clean safety differentiation vs Elevidys.
<b>Dyne — DYNE-251 (z-rostudirsen)</b> DELIVER	Ph 1/2 → BLA	Fully enrolled	<b>On track</b>	Registrational expansion (32 pts) fully enrolled. Breakthrough Therapy designation granted Aug 2025. Dystrophin expression 8.7% (best-in-class exon 51). BLA submission targeted early-to-mid 2026. Redosable therapy — key differentiator vs

Program	Phase	Enrollment	Status	Key signals
				one-shot gene therapies. 54 pts enrolled total; clean safety profile.
<b>Wave — WVE-N531FORWARD-53</b>	Ph 2 → NDA	11 pts (done)	<b>On track</b>	48-wk data met all endpoints. First-ever improvement in muscle health with exon skipping. 7.8% mean dystrophin (sustained). TTR improvement of 3.8 sec vs natural history (p<0.05). NDA filing planned 2026. Small sample (n=11) may draw scrutiny. Confirmatory trial planned.
<b>Avidity — del-zotaEXPLORE44 → BLA</b>	Ph 1/2 → BLA	Complete + OLE	<b>On track</b>	25% dystrophin of normal — best exon skipping data ever. CK reduced >80% to near-normal. BLA filing planned 2026 (accelerated approval). Managed Access Program launched. Acquired by Novartis (2025's 2nd-largest buyout). Only exon 44 therapy in development (~900 US pts addressable).

#### The three most operationally fragile assets:

**Sarepta's Elevidys (non-ambulatory)** is the biggest red flag. Two non-ambulatory patients died of liver complications in 2025, prompting the FDA to revoke the conditional authorization for non-ambulant patients. A third death — a 51-year-old with LGMD in a separate Sarepta gene therapy trial — led the FDA to request a full distribution halt, which Sarepta declined. Enrollment in ENDEAVOR Cohort 8 (testing a sirolimus immunosuppression regimen) just began in March 2026 for roughly 25 participants, meaning primary data won't arrive until H2 2026 at the earliest. Meanwhile, the company has cut 36% of its workforce (~500 employees) and its CEO is retiring.

**Sarepta's ESSENCE trial** (Vyondys 53 / Amondys 45) is an acute regulatory risk. The confirmatory Phase 3 study failed to reach statistical significance on its primary endpoint, and the company attributes the miss partly to COVID-era missed doses, with 57 participants missing treatment during the shutdown. Sarepta plans to submit sNDAs by end of April 2026 seeking traditional approval conversion, but the data package relies heavily on post-hoc adjustments and real-world evidence — a gamble with the FDA.

**Edgewise's DMD program** (sevasemten/LYNX) is structurally delayed. LYNX Phase 2 data identified a 10mg dose for Phase 3, but the pivotal DMD trial design is still being finalized with the Phase 3 start targeted for H2 2026, meaning pivotal DMD data is likely 2028+.

#### On the other side — programs executing well:

REGENXBIO's RGX-202 has the cleanest operational profile, with zero serious adverse events or liver injury signals across 13 patients up to 24 months, and expects topline pivotal data in early Q2 2026 with a pre-BLA meeting planned for mid-2026.

Dyne's DYNE-251 has fully enrolled its 32-patient registrational expansion cohort and received Breakthrough Therapy Designation, putting it on track for a BLA submission in early-to-mid 2026 — protocol stability has been excellent.

Avidity's del-zota is filing its BLA this quarter after being acquired by Novartis, and Capricor's deramiocel BLA is back under active FDA review with a PDUFA date of August 22, 2026 after overcoming its CRL.

The big structural takeaway: the AAV gene therapy safety overhang from Elevidys deaths is creating a recruitment headwind for all AAV programs while simultaneously accelerating the competitive window for redosable platforms like Dyne, Wave, and Avidity. The small patient pool (~20,000 new DMD diagnoses/year globally) means enrollment competition is a zero-sum game, and the growing number of drugs in development makes it increasingly difficult to recruit enough participants.

▼ AXL

## DMD Operational Fragility Map: Slipping vs. On Track

### Executive Summary

The active DMD trial landscape is characterized by pervasive operational stress. Of 48 total DMD trials in the database, 44 carry risk signals, and 16 are rated Critical (the highest stress tier). The median cumulative primary completion delay across trials with this signal is **979 days** — nearly three years of timeline slippage embedded in the baseline. Against this backdrop, half of all active DMD trials (50%) are flagged as dormant (no registry updates in extended periods), and 56.2% show modified eligibility criteria — the highest frequency signal in the indication. This is not a field with isolated trouble spots; it is a field with structural execution difficulty. The key analytical task is separating the truly fragile from the merely noisy.

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## The DMD Asset Map

**48 total trials** | 17 Recruiting | 17 Active/Not Recruiting | 4 Not Yet Recruiting | 41 active

**By phase:** Phase 2 dominates (48%), followed by Phase 1 (27%), Phase 3 (19%), Phase 4 (4%)

**Phase 3 Enrollment Gap:** The most important enrollment signal in the entire dataset. Phase 3 trials are budgeted for a mean of 194 patients but achieving a mean actual enrollment of only 124 patients — a **36% structural shortfall**. Phase 4 is worse: 80 anticipated vs. 9 actual (89% shortfall). This is not trial-specific noise; it is a systemic DMD enrollment challenge driven by the small eligible patient population, competing studies competing for the same patients, and the geographic concentration of neuromuscular disease specialists.

**Top modalities in conflict:** Gene therapy (AAV-based, primarily Dystrophin target) accounts for the largest enrollment ambition. Exon-skipping ASOs (Exon 51, 44, 53 targets) form a crowded second tier with overlapping patient populations.

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## Historical Base Rate: What Operational Distress Predicts

From 50 historical DMD trials, the termination rate is **38%** (19 terminated, 2 withdrawn). Among the 4 trials with confirmed endpoint data:

- **1 of 4 met primary endpoint** (25% success rate on extractable data)
- Confirmed Phase 3 failures include Sarepta's ESSENCE (missed 4-step ascend velocity at 96 weeks,  $p=0.309$ ), both Kyntra/FibroGen LELANTOS studies for pamrevlumab (PUL 2.0 at 52 weeks), and PepGen's PGN-EDO51 (insufficient dystrophin restoration + safety signal)

The pattern in failures: functional endpoint misses in ambulatory and non-ambulatory patients are the dominant failure mode, with dystrophin-level surrogacy questioned as a reliable bridge to function. This is the scientific risk layered on top of the operational risk.

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## Operational Fragility Ranking

### TIER 1 — Maximum Fragility (Multiple compounding distress signals + dormancy)

**NCT04626674 | Sarepta | Delandistrogene Moxeparvovec | Phase 1** The single most chaotic trial in the DMD space. Risk score: 100/Critical. Nine distinct operational signals: primary completion date changed **9 times** with a cumulative delay of **2,535 days** (nearly 7 years of slippage since original timeline), enrollment target changed **7 times**, eligibility criteria modified **6 times**, and the trial has re-entered recruiting from Active status. The whipsaw signal — delay followed by a 130-day pull-in with a new completion date within 60 days of the change — suggests schedule management under duress rather than genuine operational recovery. Protocol stability label from registry: **Unstable** (16 total change events, highest in Sarepta's DMD portfolio, 3.33 changes/year). This is the gene therapy platform trial; its volatility partially reflects the complexity of AAV manufacturing and the anti-AAV antibody problem Sarepta has been managing (the imlifidase and plasmapheresis sub-studies, NCT06241950 and NCT06597656, were both terminated).

**NCT04906460 | Wave Life Sciences | WVE-N531 (FORWARD-53) | Phase 1/2** Risk score: 100/Critical. Nine signals: primary completion date changed **4 times**, cumulative delay of **1,395 days**, enrollment target swung from 15 → 11 (26% cut) → 26 (136% increase) — the enrollment cut followed by a doubling is a behavioral fingerprint of early failure that was subsequently masked by scope expansion. Eligibility criteria modified **5 times**, re-entered recruiting. Registry stability: **Moderate** (6 events, 1.89/year) — but this understates the directionality of the changes. This trial is nearing

completion (Jun 2026 primary completion), but the magnitude of cumulative delay means the readout has been deferred repeatedly.

**NCT05126758 | Capricor | Deramioceol (CAP-1002) | Phase 3** Risk score: 100/Critical. Ten signals: the most signal-dense Phase 3 in the DMD landscape. Primary completion date changed 3 times with cumulative 885-day delay, enrollment target raised 50% (68 → 102), start date changed 3 times, study completion changed 4 times. The whipsaw signal — a 166-day pull-in with a new completion date within 60 days — occurred after extended delays, consistent with a sponsor compressing timelines to force a readout on remaining enrolled patients rather than achieving the original enrollment target. Protocol stability: **Moderate** (6 events, 1.68/year). Status is Active/Not Recruiting, meaning enrollment is closed — the 102-patient enrollment bar is either met or abandoned. For investors: this is the Phase 3 cell therapy readout closest to completion in DMD, but the operational history suggests enrollment was managed under duress.

**NCT03362502 | Pfizer | Fordadistrogene Movaparvovec | Phase 1** Risk score: 100/Critical. Twelve signals: primary completion date changed **7 times**, cumulative delay 1,294 days, enrollment cut 34% (35 → 23), eligibility criteria modified 4 times, re-entered recruiting, **dormant for 565 days**. Protocol stability at Pfizer's DMD trial level: **Unstable** (17 change events on the Phase 3 sibling NCT04281485, 3.46/year). The dormancy signal here is particularly notable — 565 days without a registry update on an active Phase 1 is inconsistent with normal execution. Combined with the context that Pfizer terminated its Phase 3 fordadistrogene program (NCT05689164, terminated with 7 enrolled), this dormancy likely reflects program wind-down activity rather than active execution.

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## TIER 2 — Elevated Fragility (Significant signals, active execution concern)

**NCT05524883 | Dyne Therapeutics | DYNE-251 | Phase 1** Risk score: 100/Critical. Six signals: cumulative primary completion delay of **1,096 days** (3 years), enrollment target raised 83% (48 → 88), eligibility criteria modified 3 times, **dormant for 237 days**. Protocol stability: **Moderate** (4 events, 1.93/year). The 237-day dormancy combined with an 83% enrollment expansion that didn't resolve the delay is the key behavioral read. Dyne is in a competitive squeeze with Sarepta's approved eteplirsen and the exon-51 field crowding.

**NCT06244082 | Avidity Biosciences | AOC 1044 | Phase 2** Risk score: 100/Critical. Seven signals: cumulative delay 485 days, enrollment target raised 46% (24 → 35), re-entered recruiting from Enrolling by Invitation (a meaningful status downgrade — it means the initial invitation-only cohort didn't fill), **dormant 328 days**. The transition from closed/invitation to open recruiting is a rescue behavior. Avidity has positive Phase 1/2 data from NCT05670730 (EXPLORE44, completed) with functional improvements reported, so the scientific thesis appears intact — but the Phase 2 execution is showing clear enrollment pressure.

**NCT05540860 | Edgewise Therapeutics | Sevasemten (LYNX) | Phase 2** Risk score: 100/Critical. Eight signals: cumulative delay **944 days**, enrollment target changed **4 times** in successive upward steps (27 → 45 → 54 → 72 — a 167% total increase), eligibility criteria modified 3 times. Protocol stability: **Moderate** (6 events, 2.92/year for the LYNX trial). The stair-step enrollment expansion is notable — each successive increase suggests the trial is adding scope to keep recruitment numbers moving rather than filling the original target. The gene therapy context matters: LYNX is studying sevasemten in DMD patients **who previously received gene therapy**, a rapidly emerging but still small patient population, which directly explains the enrollment pressure.

**NCT06100887 | Edgewise Therapeutics | Sevasemten | Phase 2 (post-gene therapy cohort)** Risk score: 100/Critical. Six signals: cumulative delay 638 days, enrollment target doubled (24 → 48), eligibility modified 3 times. Protocol stability: **Unstable** (4 events, 3.54/year). Same post-gene therapy patient population pressure as LYNX above, but a separate study. Both Edgewise DMD trials share the enrollment challenge of a patient pool that barely exists yet at scale.

**NCT03992430 | Sarepta | Eteplirsen (MIS510N) | Phase 3** Risk score: 100/Critical. Nine signals: primary completion date changed 4 times with cumulative delay 1,215 days, whipsaw pattern (delay + 455-day pull-in), re-entered recruiting, eligibility modified 3 times. Primary completion listed as Oct 2026. The 455-day pull-in after years of delays — combined with re-entering recruitment — is consistent with a sponsor accelerating toward a forced readout. Protocol stability: **Moderate** (6 events, 1.53/year). This is the high-dose eteplirsen confirmatory study; the parent program (casimersen/golodirsen ESSENCE) failed its primary endpoint in Nov 2025, which raises significant questions about what MIS510N will produce.

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### TIER 3 — Moderate Fragility (Single-domain stress, manageable)

**[NCT03373968](#) | Italfarmaco | Givinostat | Phase 2 (long-term safety)** Risk score: 100/Critical but important context: cumulative delay 2,192 days across a long-term follow-up study (started ~2017). Enrollment target changed 5 times, raised 51% (100 → 151), eligibility modified twice, re-entered recruiting. However, this is an open-label long-term safety study — enrollment expansions in OLE/long-term studies are more commonly explained by additional patients from completed studies being added than by enrollment shortfall per se. The HDAC inhibitor program remains active; Italfarmaco's Phase 3 non-ambulatory study ([NCT05933057](#)) shows protocol stability of **Stable** (1 event, 1.0/year). Bifurcated risk: long-term safety study shows noise, pivotal study shows stability.

**[NCT04687020](#) | NS Pharma | Viltolarsen (VILT-502) | Phase 4** Risk score: 100/Critical. Four signals: cumulative delay 305 days, enrollment cut 44% (16 → 9), enrollment underperformance (43.8% below target), **dormant 1,266 days**. With 1,266 days of dormancy, this trial is effectively abandoned. NS Pharma's other active studies ([NCT05996003](#) – Brogirdirsen Phase 2, nearing completion Sep 2026) appear to be the active focus.

### ON TRACK — Low Operational Stress

**[NCT05933057](#) | Italfarmaco | Givinostat | Phase 3 (non-ambulatory)** Protocol stability: Stable. Single primary completion date change. This is the most operationally clean late-stage DMD asset. Completion Feb 2028 provides runway.

**[NCT05881408](#) | Sarepta | Delandistrogene Moxeparvovec | Phase 3 (non-ambulatory/ambulatory)** Protocol stability: Stable (1 event, 1.0/year). Completion May 2027. This is the commercial post-approval extension study — low operational noise expected, and the data confirms it.

**[NCT07160634](#) | Solid Biosciences | SGT-003 | Phase 3 (INSPIRE DUCHENNE)** Newly registered Phase 3 (completion Jan 2029). Protocol stability: Unstable on the Phase 1 INSPIRE predecessor (565-day dormancy, 616% enrollment expansion from 6 → 43). The Phase 3 itself is too new to have accumulated meaningful operational signal — but the Phase 1's behavioral history warrants close monitoring of registry updates on the Phase 3 as enrollment opens.

**[NCT05996003](#) | NS Pharma | Brogirdirsen | Phase 2** Nearing completion (Sep 2026). Limited operational signals visible in the risk data; not flagged in the high-risk cohort.

### Landscape Context: Why DMD Is Hard to Execute In

The Dystrophin target-indication pair shows a **field decline** signal: 21 older trials vs. only 2 recent trials (recent ratio 0.087), indicating the field peaked in earlier years and new registrations have slowed. This is consistent with the 2017-2022 wave of exon-skipping ASO approvals creating a crowded post-approval follow-on study environment. The termination rate for Dystrophin/DMD pairs is **40%** (4 of 10 companies who entered have had failures), and the median enrollment timeline for this target-indication pair is **697 days** (P25: 493 days, P75: 1,132 days).

Phase 3 structural dynamics are particularly punishing: mean anticipated enrollment of 194 patients vs. mean actual of 124 (36% shortfall), against a total DMD prevalence of approximately 1 in 3,500-5,000 male births. Every Phase 3 in this space is competing for the same ~300-500 potentially eligible patients in any given enrollment window.

### Signal Summary Table

Trial	Sponsor	Drug	Phase	Operational Risk Score	Cumulative Delay	Enrollment Change	Dormant
<a href="#">NCT04626674</a>	Sarepta	Delandistrogene	Ph 1	100/Critical	2,535 days	7 changes	No
<a href="#">NCT04906460</a>	Wave Life Sci.	WVE-N531	Ph 1/2	100/Critical	1,395 days	Cut then doubled	No
<a href="#">NCT05126758</a>	Capricor	Deramiocecel	Ph 3	100/Critical	885 days	+50%	No (ANR)
<a href="#">NCT03362502</a>	Pfizer	Fordadistrogene	Ph 1	100/Critical	1,294 days	-34%	565 day:
<a href="#">NCT05524883</a>	Dyne Therapeutics	DYNE-251	Ph 1	100/Critical	1,096 days	+83%	237 day:
<a href="#">NCT06244082</a>	Avidity	AOC 1044	Ph 2	100/Critical	485 days	+46%	328 day:

Trial	Sponsor	Drug	Phase	Operational Risk Score	Cumulative Delay	Enrollment Change	Dormant
<a href="#">NCT05540860</a>	Edgewise	Sevasemten (LYNX)	Ph 2	100/Critical	944 days	+167% (4 steps)	No
<a href="#">NCT06100887</a>	Edgewise	Sevasemten	Ph 2	100/Critical	638 days	+100%	No
<a href="#">NCT03992430</a>	Sarepta	Eteplirsen (MIS51ON)	Ph 3	100/Critical	1,215 days	Multiple	No
<a href="#">NCT03373968</a>	Italfarmaco	Givinostat LTS	Ph 2	100/Critical	2,192 days	+51%	No
<a href="#">NCT05933057</a>	Italfarmaco	Givinostat	Ph 3	Stable	Minimal	None	No
<a href="#">NCT05881408</a>	Sarepta	Delandistrogene	Ph 3	Stable	Minimal	None	No

- Long-term safety/OLE study with context-appropriate enrollment expansion

## Key Implications

**For Investors:** The Capricor deramiocecel Phase 3 ([NCT05126758](#)) is the highest-stakes near-term binary catalyst in the fragility cohort — it's the most signal-dense Phase 3 in the indication, currently Active/Not Recruiting, with a June 2025 primary completion date that has already passed. A data readout is imminent or overdue; the operational history (50% enrollment expansion, whipsaw scheduling) warrants caution on interpreting any announcement. The MIS51ON eteplirsen Phase 3 ([NCT03992430](#)) carries the additional weight of the ESSENCE failure — the same exon-skipping mechanism at higher dose, competing against the backdrop of a failed confirmatory study.

**For Competitors and R&D teams:** The Edgewise sevasemten program's enrollment pressure in post-gene therapy DMD patients is a structural signal worth tracking — it defines the real-world sizing of the post-gene-therapy treatment population, which multiple sponsors are now targeting. If enrollment remains difficult, it implies the commercial opportunity is smaller than the patient advocacy narrative suggests.

**For CROs:** Dormant trials (24 of 48 DMD trials, averaging 737 days since last update) represent rescue or wind-down opportunities. The Pfizer fordadistrogene Phase 1 ([NCT03362502](#), 565 days dormant) and Solid Biosciences SGT-001 ([NCT03368742](#), 565 days dormant) are the highest-priority dormancy cases for business development targeting.

▼ ChatGPT

## Operational Fragility Report

### Duchenne Muscular Dystrophy (DMD) Clinical-Stage Assets

**Focus:** Enrollment trajectory × protocol stability

**Objective:** Surface which programs appear operationally fragile vs. on track

### Executive Summary

Operational fragility in DMD programs is primarily driven by:

1. **Enrollment pressure** (small addressable populations, mutation-specific cohorts, global site dispersion)
2. **Protocol instability** (dose changes, endpoint revisions, age-window shifts, regulatory-driven amendments)
3. **Manufacturing/logistics complexity** (gene therapy vector production, exon-skipping supply continuity)

#### Most Operationally Fragile (High Risk of Slippage):

- Sarepta Therapeutics – SRP-9001 confirmatory studies
- Pfizer – fordadistrogene movaparvovec program
- REGENXBIO – RGX-202
- Solid Biosciences – SGT-003

**Moderate Fragility (Execution Dependent):**

- Italfarmaco – givinostat
- Wave Life Sciences – exon skipping platform

**Relatively On Track (Operationally Stable):**

- NS Pharma – viltolarsen lifecycle expansion
  - Roche – discontinued DMD gene therapy exposure (low current fragility)
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## Asset-by-Asset Operational Assessment

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### 1. Sarepta Therapeutics – SRP-9001 (Elevidys)

**Modality:** AAV micro-dystrophin gene therapy

**Stage:** Commercial + confirmatory Phase 3

#### Operational Signals

**Enrollment Risk**

- Competing for global ambulatory and non-ambulatory boys
- Heavy U.S. site concentration
- Increasing competition for younger patients

**Protocol Stability**

- Multiple protocol amendments historically
- Endpoint tension between functional measures (NSAA) and biomarker endpoints
- Regulatory-driven confirmatory burden

**Fragility Score: HIGH**

**Why:**

Confirmatory data pressure + endpoint scrutiny + prior heterogeneity in functional outcomes = elevated execution risk. Any enrollment slowdown directly pressures regulatory durability.

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### 2. Pfizer – Fordadistrogene Movaparvovec

**Modality:** AAV gene therapy

**Stage:** Phase 3

#### Operational Signals

**Enrollment Risk**

- Global sites across US/EU/Asia
- Competition with Sarepta for similar patient pools
- Prior pauses impact site momentum

**Protocol Stability**

- Historical dose adjustments
- Trial pauses for safety signal review
- Endpoint interpretation scrutiny

**Fragility Score: HIGH**

**Why:**

Safety monitoring history + enrollment competition + prior operational resets create compounded fragility.

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### 3. REGENXBIO – RGX-202

**Modality:** Next-gen AAV micro-dystrophin

**Stage:** Early-to-mid stage

#### Operational Signals

##### Enrollment Risk

- Smaller company footprint
- Fewer activated sites relative to large pharma
- Competing against approved therapy narrative

##### Protocol Stability

- Evolving dose cohorts
- Vector optimization strategy
- Potential design pivots depending on biomarker readouts

**Fragility Score: HIGH-MODERATE**

**Why:**

Smaller operational infrastructure + dose-escalation learning curve = enrollment sensitivity.

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### 4. Solid Biosciences – SGT-003

**Modality:** Next-gen capsid gene therapy

**Stage:** Early clinical

#### Operational Signals

##### Enrollment Risk

- Small cohorts
- Sentinel dosing design slows cadence
- Competing against established players

##### Protocol Stability

- New capsid platform
- Immune monitoring heavy
- Adaptive learning design

**Fragility Score: HIGH**

**Why:**

Early-stage gene therapy + complex immune monitoring + capital constraints elevate operational fragility.

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### 5. Italfarmaco – Givinostat

**Modality:** HDAC inhibitor (small molecule)

**Stage:** Late-stage / regulatory

## Operational Signals

### Enrollment Risk

- Broad genotype eligibility
- Oral therapy = easier recruitment
- Non-gene therapy positioning reduces competition

### Protocol Stability

- Conventional endpoints (NSAA)
- Fewer adaptive design changes
- Standardized global trial design

**Fragility Score: MODERATE-LOW**

### Why:

Traditional drug development pathway lowers manufacturing and dosing variability risk.

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## 6. Wave Life Sciences – Exon Skipping Platform

**Modality:** Stereopure antisense oligonucleotides

**Stage:** Mid-stage

## Operational Signals

### Enrollment Risk

- Mutation-specific cohorts
- Smaller addressable population per program
- U.S.-heavy site base

### Protocol Stability

- Biomarker-heavy early endpoints
- Platform learning curve

**Fragility Score: MODERATE**

### Why:

Mutation segmentation constrains enrollment velocity, but operational design more stable than gene therapy programs.

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## 7. NS Pharma – Viltolarsen Lifecycle Expansion

**Modality:** Exon skipping (exon 53)

**Stage:** Approved + expansion

## Operational Signals

### Enrollment Risk

- Narrow mutation group
- But lifecycle studies easier to enroll

### Protocol Stability

- Established dosing
- Known safety profile
- Standard endpoints

## Cross-Program Fragility Drivers

### 1. Mutation Fragmentation

- Exon-specific programs inherently face enrollment friction.
- Broad micro-dystrophin programs compete for overlapping ambulatory boys.

### 2. Endpoint Volatility

- NSAA variability remains high.
- Increasing biomarker reliance (dystrophin expression) introduces regulatory interpretation risk.

### 3. Manufacturing Complexity

- AAV vector scale-up remains a chokepoint.
- Batch release timelines impact dosing cadence.

### 4. Regulatory Overhang

- Accelerated approvals now require confirmatory rigor.
  - Functional endpoint disagreements create downstream protocol amendments.
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## Fragility Ranking (Operational Execution Risk)

### Tier 1 – Most Fragile

1. Solid Biosciences – SGT-003
2. Pfizer – Fordadistrogene movaparvovec
3. Sarepta – SRP-9001 confirmatory

### Tier 2 – Moderate Fragility

4. REGENXBIO – RGX-202
5. Wave Life Sciences – exon skipping platform

### Tier 3 – More Stable

6. Italfarmaco – givinostat
  7. NS Pharma – viltolarsen lifecycle
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## Bottom Line

The DMD field shows a clear operational bifurcation:

- **Gene therapies = highest fragility** (complex manufacturing + safety monitoring + enrollment competition)
- **Small molecules and approved exon-skipping agents = more operationally durable**
- **Confirmatory gene therapy trials represent the single biggest slippage risk in the space**

If helpful, I can next layer in:

- Estimated probability of primary endpoint success
- Capital runway overlay

- Upcoming data catalysts ranked by operational risk
- Or a visual fragility matrix (Enrollment Velocity × Protocol Amendment Density)

▼ Perplexity

## Operationally Fragile DMD Assets: Enrollment & Protocol Stability Assessment

The DMD clinical trial landscape reveals several operationally fragile assets characterized by protocol instability, enrollment challenges, and efficacy failures. Here's the cross-reference analysis of programs slipping versus on track:

### Fragile Assets — Discontinued or Stalled

**Taiho Pharmaceutical (TAS-205/pizuglanstat)** — Discontinued Phase 3. The REACH-DMD trial enrolled only 82 patients across ambulatory and non-ambulatory cohorts and failed its primary endpoint for time-to-rise-from-floor over 52 weeks. Both cohorts were terminated, indicating enrollment couldn't be justified post-failure and protocol stability was compromised by lack of efficacy signal.

**Sarepta's ESSENCE Trial (AMONDYS 45 & VYONDYS 53)** — Failed confirmatory Phase 3. This nine-year trial enrolled 225 patients aged 6-13 but achieved only a 0.05 steps/second difference versus placebo—statistically non-significant despite numerical trends. COVID-19 disrupted enrollment and confounded protocol stability, though the study technically completed. These assets face approval uncertainty despite real-world evidence arguments.

**Sarepta's Elevidys (delandistrogene moxeparvovec)** — Gene therapy with FDA safety holds. Two patient deaths from liver failure triggered multiple trial pauses and a black box label, creating severe protocol fragility across the portfolio.

### Operationally Stable Programs — Progressing

**Precision BioSciences (PBGENE-DMD/FUNCTION-DMD)** — Phase 1/2, on track. Received FDA "Study May Proceed" notification in February 2026 with planned first site activation in H1 2026. This gene excision approach for exons 45-55 incorporates immune modulation, showing protocol robustness with specialized DMD centre infrastructure designed upfront.

**SGT-003 Gene Therapy** — Early phase with early safety/efficacy signals. Multiple sites operational (UC Davis, UCSD with multi-cohort enrollment). Enrollment progresses through age-stratified cohorts (0 to <18 years), with gating mechanisms for later cohorts, indicating deliberate protocol design protecting enrollment stability.

**UC Davis and UCLA Programs** — Active 2026 enrollment for SRP-9001 (Delandistrogene) and other investigational therapies, showing ongoing site activation despite historical setbacks in the broader gene therapy space.

### Cross-Referenced Fragility Indicators

Asset	Enrollment Scale	Protocol Modifications	Efficacy Status	Operational Stability
TAS-205	82 patients (low)	Both cohorts discontinued	Failed primary endpoint	<b>High risk</b> — discontinued
ESSENCE (Sarepta)	225 patients (moderate)	COVID-delayed 9 years	Statistically insignificant	<b>Medium risk</b> — approval uncertain
Elevidys (Sarepta)	Paused across trials	Multiple FDA holds; black box added	Safety signals	<b>Critical</b> — portfolio fragility
PBGENE-DMD	Ramping (newly activated)	Immune modulation protocol built-in	Early-phase safe	<b>Stable</b> — deliberate design
SGT-003	Multi-site, multi-cohort	Age-stratified gating mechanism	Early promise	<b>Stable</b> — staged enrollment

The fragile assets share common patterns: insufficient enrollment relative to attrition risk (TAS-205), external disruption confounding statistical power (ESSENCE), and safety signals destabilizing entire programs (Elevidys). Stable programs demonstrate pre-planned protocol safeguards and deliberate enrollment architecture rather than reactive modifications.

#### What does the KRAS competitive landscape look like?

## ▼ BB

### KRAS Competitive Landscape

The KRAS inhibitor market is evolving with multiple companies advancing therapies targeting different KRAS mutations, particularly in oncology.

#### Key Developments

- Astellas Pharma is advancing setidegrasib, a KRAS-targeting cancer drug, toward Phase 3 studies as part of its pipeline acceleration strategy. (1)
- Astellas Pharma's Phase 1 trial evaluating ASP3082 in adults with advanced solid tumors with KRAS G12D mutations has experienced a significant delay, with the anticipated primary completion date now set for December 31, 2028. (2)
- Silexion secured regulatory approval on March 24, 2026, to launch Phase 2/3 trials of SIL204, an RNAi therapy targeting KRAS-driven pancreatic cancer, featuring an innovative integrated systemic treatment delivery approach. (3)

## ▼ Opus

The KRAS inhibitor landscape is one of the most dynamic and competitive spaces in oncology right now. Here's a breakdown of the key dimensions:

### Approved Therapies

Three KRAS-targeted therapies have reached the market so far:

- **Sotorasib (Lumakras) — Amgen:** The first FDA-approved KRAS G12C inhibitor, approved in May 2021 for pretreated KRAS G12C-mutated NSCLC. [Barchart](#) It also received a new FDA approval in 2025 as part of a combination regimen with panitumumab for KRAS G12C-mutated colorectal cancer. [DelveInsight](#)
- **Adagrasib (Krazati) — Bristol Myers Squibb** (acquired via Mirati): Another approved KRAS G12C inhibitor for pretreated NSCLC, with multiple Phase III trials underway. BMS anticipates Phase III readouts from KRYSTAL-10 for second-line CRC by 2026, KRYSTAL-7 for first-line NSCLC by 2028, and KRYSTAL-4 by 2029. [Barchart](#)
- **Avutometinib + Defactinib (AVMAPKI + FAKZYNJA) — Verastem Oncology:** Approved in May 2025 under accelerated approval for KRAS-mutated recurrent low-grade serous ovarian cancer — the first and only approved therapy for that indication. [DelveInsight](#)

### The G12C Space: Crowded and Evolving

KRAS G12C is the most advanced and crowded space, with two FDA-approved drugs and over 23 additional programs in clinical development. [ScienceDirect](#) First-generation G12C inhibitors have shown limited durability due to resistance, so next-generation candidates are a major focus:

- **Divarasib — Roche/Genentech:** A next-generation G12C inhibitor with 5- to 20-fold higher potency than sotorasib/adagrasib in vitro. In Phase I, it showed a 55.6% response rate and median PFS of 13.8 months in NSCLC. [Cancer Cell](#) The Phase III KRASCENDO-1 trial comparing it head-to-head with sotorasib or adagrasib has a primary completion expected in 2026. [Cancer Cell](#)
- **Olomorasib — Eli Lilly:** A second-generation G12C inhibitor in Phase III for first-line NSCLC. In September 2025, the FDA granted Breakthrough Therapy designation to olomorasib in combination with pembrolizumab for first-line KRAS G12C NSCLC with PD-L1 ≥50%. [Yahoo Finance](#)
- **Other next-gen G12C candidates** include glecirasib, IBI351, garsorasib, and others in early-to-mid-stage trials, many originating from Chinese biotech companies.

### Beyond G12C: The Next Frontier

The biggest strategic shift is the expansion beyond G12C to other KRAS mutations, especially G12D and G12V, which collectively affect far more patients (particularly in pancreatic and colorectal cancers).

**Revolution Medicines** stands out as the most aggressive player here with a multi-pronged RAS(ON) inhibitor pipeline:

- **Daraxonrasib (RMC-6236)**: A pan-RAS (multi-selective) inhibitor. In April 2026, Revolution began dosing patients in RASolute 303, a Phase 3 trial for first-line metastatic pancreatic cancer. [Revolution Medicines](#) In earlier Phase 1 data for first-line pancreatic cancer, daraxonrasib monotherapy showed a 47% response rate and 89% disease control rate. [Revolution Medicines](#) It also received an FDA Priority Voucher and Breakthrough Therapy designation.
- **Zoldonrasib (RMC-9805)**: A G12D-selective inhibitor. In January 2026, it received Breakthrough Therapy designation for pretreated KRAS G12D NSCLC — the first such designation ever granted for a drug specifically targeting the G12D mutation. [Revolution Medicines](#)
- **Elironrasib (RMC-6291)**: Their G12C-selective next-gen competitor, also with Breakthrough Therapy designation.
- **RMC-5127**: A G12V-selective inhibitor. In January 2026, Revolution dosed the first patient in its first-in-human trial, targeting the second most common RAS mutation. [Revolution Medicines](#)
- The company also has earlier-stage programs targeting Q61H (RMC-0708) and G13C (RMC-8839).

## Pan-KRAS and Emerging Approaches

Several companies are pursuing pan-KRAS inhibitors that can target multiple mutation types, including Cardiff Oncology (onvansertib), Immuneering Corporation (IMM-1-104), Jacobio Pharma, and Eli Lilly. [DelveInsight](#) Other modalities under development include molecular glues, degraders, vaccines, and cell-based immunotherapies targeting RAS neoantigens.

**MK-1084 (Merck/Taiho/Astex)** is another notable pipeline asset in the G12C space, along with **ELI-002 (Elicio Therapeutics)**, which takes an immunotherapy approach to KRAS-mutated cancers.

## Key Themes and Takeaways

The landscape is characterized by a few overarching dynamics. First, **combination strategies** are becoming central — pairing KRAS inhibitors with checkpoint inhibitors, SOS1 inhibitors, SHP2 inhibitors, or chemotherapy to combat resistance. Second, there's a clear **race to expand beyond G12C** into G12D, G12V, and pan-RAS approaches, which would dramatically expand the addressable patient population across NSCLC, pancreatic cancer, and colorectal cancer. Third, the U.S. dominates the market, capturing roughly 70% of global market share as of 2024. [Barchart](#) Finally, resistance remains the core challenge — first-generation G12C inhibitors show limited durability, and novel mechanisms of action are needed to extend clinical benefit. [Cancer Cell](#)

It's a space moving very fast, with several Phase III readouts expected in 2026 that could meaningfully reshape the competitive picture.

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# KRAS Competitive Landscape: Full Analysis (April 2026)

## Executive Summary

KRAS has crossed from a "frontier" target to an established but still rapidly evolving oncology competitive space. With 177 active or recently active trials, 24 Phase 3 programs, and a momentum score of 0.715 (labeled "accelerating"), the field is both crowded and dynamic. The pivot point was the approval of sotorasib (2021) and adagrasib (2022) — both KRAS G12C inhibitors — which validated the target class and triggered an arms race now spanning G12C second-generation approaches, G12D, G12V, pan-KRAS, and novel modalities like protein degraders. NSCLC remains the dominant indication, but the next competitive wave centers on pancreatic cancer and colorectal cancer, where KRAS G12D programs are generating the most excitement.

The most critical near-term inflection point: Amgen's Codebrea202 ↴ (sotorasib Phase 3 1L NSCLC, [NCT05920356](#)) has a primary completion of June 2026 — the only trial nearing completion in the near-term catalyst window, with an OS primary endpoint.

## Landscape Overview — Trial Volume, Phase Distribution & Status

The KRAS space currently comprises:

- 83 trials recruiting, 44 active not recruiting — 137 active industry trials combined
- 10 trials not yet recruiting — a significant wave of new programs starting
- Total enrolled/anticipated enrollment across 50 sampled trials: ~19,500 patients
- Phase distribution: Phase 1 = 56% (99 trials), Phase 2 = 31% (54 trials), Phase 3 = 14% (24 trials)

The Phase 3 count of 24 is notable — this is a mature number for a target that was essentially undruggable until 5 years ago. The Phase 1 dominance (56%) still reflects continued early-stage investment, particularly in next-generation and mutation-specific approaches beyond G12C.

The trial enrollment infrastructure is large: Phase 3 trials average 617 anticipated patients; median trial duration is 2,181 days (~6 years), reflecting the long follow-up requirements of registrational oncology studies.

Landscape risk scores sit at a median of 31/100 (moderate) and mean of 37/100. Approximately 21% of trials carry "challenging" landscape scores; 42% sit in the favorable "smooth sailing" quadrant. This suggests the field is not uniformly crowded — mutation-specific programs in less-competed subtypes still have structural headwinds.

## Trend Analysis — Is KRAS Investment Accelerating?

The field trend data shows a recent-to-older trial ratio of 0.475 — meaning roughly half as many new trials in the recent window as in the prior window. However, the momentum score of 0.715 ("accelerating") is driven by strong innovation scores (1.0 — maximum) and phase progression (0.70), reflecting that while raw registration rates may be moderating, the depth and late-stage composition of the pipeline is still expanding.

Registration trends from May 2025 to April 2026 show consistent monthly registrations with a spike in March 2026 (5 new trials). The 10 trials listed as "not yet recruiting" reinforce that a new cohort of programs is staged for launch.

The interpretation: the KRAS field is not declining — it is transitioning from a registration surge to a maturation phase where capital is concentrating around registration-directed programs and the frontier has shifted from "can you drug KRAS" to "can you beat the approved agents" and "can you address non-G12C mutations."

## Top Sponsors & Competitive Positioning

The top 10 sponsors by active KRAS trial count, with enrollment scale:

Sponsor	Active Trials	Enrollment (Target)	Key Drug(s)
Amgen	10	~3,976	Sotorasib
Merck (MSD)	10	~3,461	Calderasib (MK-1084)
Eli Lilly	9	~4,063	Olomorasib (LY3537982)
Mirati (BMS)	8	~3,541	Adagrasib
Verastem	7	~1,084	Avutometinib
Hoffmann-La Roche	6	~3,720	Divarasib
Allist Pharmaceuticals	6	~1,187	(Chinese G12C programs)
Novartis	6	~753	Opnurasib
Revolution Medicines	4	~1,934	Daraxonrasib, Zoldonrasib
Genentech	4	~1,072	Divarasib (shared)

The four large-enrollment sponsors — Lilly, Amgen, Mirati/BMS, and Roche/Genentech — each have 3,500–4,000+ anticipated patients, signaling heavy Phase 3 investment. Merck is the fastest-growing presence: calderasib launched a Phase 3 (KANDLELIT-007, [NCT07190248](#)) in 1L NSCLC in January 2026, targeting 675 patients, and added a Phase 3 adjuvant NSCLC trial (KANDLELIT-013) in February 2026. Merck's KRAS expansion is the most aggressive new commitment in the space.

Revolution Medicines stands out strategically: despite just 4 trials, they have 1,934 anticipated patients concentrated in registrational-intent programs, received FDA Breakthrough Therapy Designation for zoldonrasib (KRAS G12D) in NSCLC in January 2026, and dosed the first patient in their KRAS G12V program (RMC-5127, [NCT07349537](#)) in January 2026. RevMed is building the broadest multi-mutation coverage of any single sponsor.

From the commitment credibility scorecard, Amgen leads on outcome success rate (100% of resolved outcomes succeeded) despite a mediocre 25% on-time rate. Mirati/BMS shows similar pattern: 100% on-time rate and 100% success rate on resolved commitments. Verastem has the largest commitment footprint (26) but only 38% credibility score and 50% on-time rate — behavioral signals consistent with the operational stress visible in their registry data.

## Indication Breakdown — Where Is KRAS Being Tested?

By trial count, the indication distribution is:

Indication	Trials
Non-Small Cell Lung Cancer	51
Solid Tumor (broad/agnostic)	39
Solid Tumors (variant labeling)	34
Colorectal Cancer	19
Pancreatic Ductal Adenocarcinoma	10

NSCLC is the dominant indication by trial count (51 trials), primarily driven by KRAS G12C prevalence (~13% of NSCLC patients carry the mutation). It is also the only indication with an approved KRAS inhibitor and thus carries the highest competitive density — new entrants face approved benchmarks.

Colorectal cancer (CRC) is the second most active specific indication: Amgen has an active Phase 3 (CodeBreak 301, [NCT06252649](#)) combining sotorasib + panitumumab + FOLFIRI vs. chemotherapy. CRC presents a distinct challenge — the co-occurring RAS pathway activation historically limits single-agent KRAS G12C benefit, making combination strategies central.

Pancreatic ductal adenocarcinoma (PDAC) is arguably the highest-unmet-need indication — KRAS is mutated in ~93% of PDAC cases, predominantly G12D — and represents the frontier where the next major clinical breakthrough could occur. Most PDAC programs are still Phase 1/2, but GenFleet's GFH375 showed encouraging Phase 1/2 data (ORR 41%, DCR 97% in PDAC at RP2D, as of October 2025), and VS-7375 (Verastem) cleared 900mg QD with no DLTs in 23 patients. PDAC catalyst commitments show a 0% on-time rate — consistent with the biological complexity and slow enrollment of this indication.

## Target Subtypes — The Mutation Hierarchy

The target breakdown reveals a clear stratification:

Target	Trials
KRAS G12C	65
KRAS G12D	25
KRAS (pan/broad)	23
PD-1 (combination)	16
EGFR (combination)	11

KRAS G12C is the established battleground with two approved drugs and 65 trials — a crowded space where competitive differentiation requires either superior efficacy (beating sotorasib/adagrasib head-to-head) or new indications/combinations. The Phase 3 head-to-head is already underway: Roche's [NCT06497556](#) compares divarasilab vs. sotorasib or adagrasib in previously treated KRAS G12C NSCLC.

KRAS G12D is the fastest-growing subtype (25 trials), driven by its prevalence in PDAC and NSCLC, and the January 2026 Breakthrough Therapy Designation for zoldonrasib in NSCLC validates clinical progress. The Arvinas KRAS G12D

degrader (ARV-806, [NCT07023731](#)) adds a novel modality dimension — protein degraders targeting KRAS G12D have near-zero landscape stress scores (risk score 5) given the novelty.

Pan-KRAS approaches (23 trials) represent an attempt to address resistance heterogeneity and multi-mutation patient populations, with BBOT's BBO-11818 ([NCT06917079](#)) the most prominent early-stage example (576 patients anticipated; showed a confirmed PR in PDAC at 56% tumor reduction).

## Key Drugs — The Leading Compounds

The most-studied drugs by trial volume and enrollment:

Drug	Trials	Enrollment	Sponsor	Mutation
Adagrasib	10	3,626	Mirati/BMS	G12C
Divarasib	8	4,317	Roche	G12C
Sotorasib	8	3,042	Amgen	G12C
Olomorasib	8	2,743	Eli Lilly	G12C
Calderasib	6	1,603	Merck	G12C
Avutometinib	6	789	Verastem	MEK/RAF

Divarasib leads by enrollment scale (4,317 patients) despite being in fewer trials than adagrasib — reflecting larger registrational trials. Calderasib (Merck's MK-1084) is the fastest-growing enrollment footprint with its new Phase 3 programs.

## Operational Risk — Where Are the Behavioral Signals?

Across the 50 sampled KRAS trials, 33 carry risk signals:

- 36% show cumulative primary completion delays, with average delay of 944 days among those affected
- 32% show significant enrollment target changes (average magnitude: 77%)
- 54% show eligibility criteria modifications — the highest-prevalence signal in this cohort
- 8 trials carry "critical" operational stress scores (100/100), including: Mirati's KRYSTAL-7 ([NCT04613596](#), 2,193 cumulative delay days), Roche's Phase 1 NSCLC divarasib trial ([NCT05789082](#), 2,312 cumulative delay days), Merck's Phase 1 solid tumor calderasib study ([NCT05067283](#), 1,482 cumulative delay days), and Amgen's MTAPESTRY 104 ([NCT06333951](#), 986 days).

The pattern across the highest-risk trials is consistent: these are early Phase 1 basket trials that expanded scope significantly as the programs evolved — the delays reflect design evolution rather than pure operational failure. Contextually, this is more signal of scientific learning than trial distress for the large-cap sponsors.

The highest-concern operational signals by indication: PDAC commitments show 0% on-time delivery historically, consistent with the biological and enrollment challenges in pancreatic cancer. NSCLC commitments show 100% on-time rate and 100% success rate — the most operationally reliable segment.

## Recent Outcomes — What Has Worked and What Hasn't

Key completed/recent data readouts:

### KRAS G12C (NSCLC) — Established efficacy, now refining:

- BBO-8520 (BBOT/ONKORAS-101, [NCT06343402](#)): Interim Phase 1 — ORR 65% (11/17) with 6-month PFS 66%. Encouraging but small N, immature. Spin detected. FDA Fast Track Designation granted November 2025.
- RAMP 203 (Verastem, avutometinib + sotorasib ± defactinib, [NCT05074810](#)): Interim Phase 1/2 — treatment-naive doublet ORR 40%, mPFS 11.1 months; previously-treated ORR 9.5%, mPFS 3.7 months. Mixed data; no spin detected. Trial carries critical operational stress (913 days cumulative delay).

### KRAS G12D — The emerging frontier:

- GFH375 (GenFleet, [NCT06500676](#)): PDAC ORR 41%, DCR 97%; NSCLC ORR 69% (11/16). Granted Breakthrough Therapy Designation in China for G12D NSCLC in March 2026. Enrollment expanding (34.5% increase from 290 to 390).
- VS-7375 (Verastem, [NCT07020221](#)): Phase 1/2 cleared 900mg QD, no DLTs in 23 patients. Protocol being amended to add disease-specific Phase 2 cohorts in PDAC, NSCLC, CRC. 153% enrollment target increase signals aggressive scope expansion.
- Zoldonrasib (Revolution Medicines, RMC-9805): Breakthrough Therapy Designation granted by FDA January 8, 2026 for G12D NSCLC (post-PD-1/platinum therapy). Primary completion due April 2026 with 243 days of cumulative delays already registered — watch for results.

**Pan-KRAS (novel approaches):**

- BBO-11818 (BBOT, [NCT06917079](#)): Confirmed PR in PDAC with 56% tumor reduction (n=13). Early but scientifically notable — pan-KRAS approach covering multiple mutations.

**LGSOC (adjacent — KRAS-mutant enriched):**

- RAMP 201J (Verastem Japan, [NCT06682572](#)): ORR 57% (4/7) in KRAS-mutated patients, DCR 100%. Sponsor spin detected; small N (n=16) but Phase 3 RAMP 301 is the confirmation vehicle.

## Upcoming Catalysts — Near-Term Inflection Points

**Immediate (April 2026):**

- RAMP 201 long-term analysis — late-breaking oral presentation at SGO Annual Meeting, April 10, 2026 ([NCT04625270](#)). This feeds the Phase 3 RAMP 301 narrative.

**H2 2026 (multiple readouts):**

- BBO-11818 (BBOT, pan-KRAS, [NCT06917079](#)): Additional monotherapy + combination data planned H2 2026
- BBO-8520 (BBOT, G12C NSCLC, [NCT06343402](#)): Pembrolizumab combination data, H2 2026. Note: this trial carries an 80/100 operational stress score with 1,339 days of cumulative delay — treat the timing with appropriate skepticism
- ERAS-4001 (Erasca, BOREALIS-1, [NCT07021898](#)): Initial Phase 1 monotherapy data, H2 2026
- VS-7375/GFH375 (Verastem/GenFleet, G12D): Additional efficacy data, H2 2026
- ARV-806 (Arvinas, KRAS G12D degrader, [NCT07023731](#)): "Important clinical data readout" H2 2026 — the protein degrader angle makes this a high scientific interest event

**Q2 2027:**

- RAMP 301 Phase 3 topline readout (Verastem, [NCT06072781](#)) — primary endpoint (PFS) expected mid-2027. This is a registrational trial. Operational stress is stable (20/100), but 4 start date changes registered. This is the most significant binary event in the adjacent KRAS pathway space.

**Phase 3 completions (registrational):**

- CodeBreak 202 (Amgen sotorasib 1L NSCLC, [NCT05920356](#)): Primary completion June 2026, OS endpoint. Risk score 70, 208 cumulative delay days — operationally stressed but closing in.
- Roche divarasib Phase 3 NSCLC ([NCT06497556](#)): Primary completion September 2027
- Lilly olomorasib Phase 3 NSCLC ([NCT06119581](#)): Primary completion November 2027 — carries 95/100 operational stress with 396 days of cumulative delay and 24% enrollment expansion

## Gaps & Strategic Observations

**G12C is played out as a monotherapy story.** Two approved drugs, 65 trials, multiple Phase 3 head-to-heads underway. Differentiation now requires combination strategies (G12C inhibitor + PD-1, + MEK/RAF, + EGFR), new indications (CRC, PDAC), and demonstrating superiority vs. benchmarks — not first-in-class status.

**G12D is the prize.** KRAS G12D drives PDAC (93% mutation rate) and is present in ~12% of NSCLC. No approved drug yet. Two Breakthrough Therapy Designations in 2026 alone (RevMed's zoldonrasib, GenFleet's GFH375). Arvinas is the only protein degrader approach in the clinic — a genuine modality gap relative to small molecule competitors.

**G12V is wide open.** Revolution Medicines dosed the first patient in RMC-5127 (KRAS G12V) in January 2026 — this is a first-in-class program with zero competition registered in the tracker. G12V is present in ~7% of NSCLC and ~5% of PDAC.

**Pan-KRAS approaches are nascent but strategically logical** for resistance management. BBO-11818 and ERAS-4001 represent genuine differentiation from mutation-specific inhibitors, though the safety/specificity trade-off remains to be defined.

**PDAC as an indication is behaviorally the hardest.** 0% on-time commitment rate, long trial durations (median 1,377 days to enroll for KRAS/solid tumor pairs), and no approved KRAS-directed PDAC therapy yet. Programs here should be evaluated with more conservative timeline assumptions — typically 2x the sponsor's stated schedule.

**China-based sponsors are increasingly relevant.** Allist Pharmaceuticals (6 trials), GenFleet, Abbisko Therapeutics (G12D Phase 2 just registered) and Jemincare (Phase 3 NSCLC, [NCT07242274](#) completion Dec 2027) represent a competitive cohort that is often underweighted in Western competitive analysis but carries meaningful trial activity, especially in China-first indications.

**The combination imperative.** PD-1 and EGFR appear in the top 5 co-targets alongside KRAS — the field has moved decisively toward combinations. Programs without a combination strategy for at least one cohort are strategic outliers.

▼ ChatGPT

The **KRAS competitive landscape** in oncology is evolving rapidly. After decades of KRAS being considered “undruggable,” scientific breakthroughs—especially targeting specific KRAS mutations—have created a crowded and strategically complex field spanning approved drugs, late-stage programs, early innovative platforms, and combination strategies. The competition now centers not just on *who gets to market first* but on *which mutations and mechanisms are effectively addressed* and *how to overcome resistance*.



## 1. Established KRAS Inhibitors (Approved Therapies)

These pioneers validated KRAS as a drug target and set commercial benchmarks:

- **Sotorasib (Lumakras / Lumykras) – Amgen**  
First approved KRAS G12C inhibitor (FDA 2021; China/NMPA 2022). Targets the inactive GDP-bound KRAS G12C.
- **Adagrasib (Krazati) – Bristol Myers Squibb / Mirati**  
Second approved G12C inhibitor (FDA 2022; NMPA 2023). Similar mechanism, widely used in NSCLC and combinations with other agents.
- **Fulzerasib (IBI351) – Innovent Biologics**  
Approved in China (NMPA 2024) targeting G12C.
- **Sosimerasib – Zhejiang Hangyu**  
NMPA approval in China by 2026 targeting KRAS G12C.

**Key dynamic:** These approvals have created a crowded G12C segment where differentiation comes from clinical positioning (e.g., CNS penetration, combination benefit) rather than fundamental mechanism differences.



## 2. Late-Stage & Emerging KRAS G12C Competitors

A number of next-generation and incremental improvements over existing G12C therapies are progressing:

- **Divarasib (Roche / Genentech) – Phase 3**
- **Calderasib (MK-1084; MSD R&D China) – Phase 3 with Breakthrough designation**
- **Olomorasib (Eli Lilly) – Phase 3 candidate**
- **MK-1084 (Merck / Taiho / Astex) – Phase development**

- Others active internationally, including China-based programs.

These tend to retain the same covalent, inactive-state targeting approach but aim for improved efficacy, safety, or specific indications (e.g., first-line NSCLC).

### 3. KRAS G12D / Non-G12C Specific Inhibitors

Targeting **non-G12C KRAS mutations** (especially G12D, the most common in pancreatic and many colorectal cancers) is a major frontier:

- **GFH-375 (Genfleet Therapeutics)** – Phase 2, Breakthrough designation
- **MRTX1133 (BMS / Mirati)** – Phase 2
- **RMC-9805 (Revolution Medicines)** – Phase 1/2 tri-complex SOS1-KRAS agent
- **HRS-4642 (Hengrui Medicine)** – Phase 1
- Ongoing academic and industry efforts targeting other alleles (e.g., G12V, Q61).

**Why this matters:** G12D/G12V mutations account for a much larger patient population (e.g., pancreatic ductal adenocarcinoma) but currently lack approved therapies, making this a major growth and innovation area.

### 4. Pan-KRAS & Alternative Mechanisms

Beyond allele-specific inhibitors, several approaches broaden coverage or alter mechanism:

#### Pan-KRAS / Active-State Inhibitors

- Targets multiple KRAS mutations, including active (GTP-bound) forms.
- Examples include **daraxonrasib (Revolution Medicines)** and research programs aiming at broad RAS engagement.

#### Indirect Modulators & Combinations

Rather than directly binding KRAS, these enhance blocking of RAS signaling or resistance pathways:

- **SHP2 inhibitors** – block upstream reactivation
- **SOS1 inhibitors** – prevent KRAS activation
- **MEK/ERK modulators** – downstream pathway suppression
- Combinations with **PD-1/L1 immunotherapy** or **EGFR inhibition** (especially in CRC) to tackle adaptive resistance.

### 5. Strategic Landscape & Competitive Factors

#### Mutation Coverage

- G12C: crowded with multiple approved and late-stage candidates.
- G12D/G12V/etc.: rapidly emerging, with high unmet need.

#### Combination Therapies

Secondary strategies are increasingly important to enhance response rates and overcome resistance.

#### Global Pipeline & Markets

- China has approved several local candidates and is a major competitive region.
- The U.S. remains dominant in KRAS R&D and commercial uptake.

#### Differentiation Beyond Potency

Focal points include:

- Tumor type (NSCLC vs CRC vs pancreatic)
- CNS penetration
- Combination efficacy
- Biomarkers predicting response or resistance.

## Summary: Competitive Landscape Snapshot

Segment	Status	Competition
Approved G12C Drugs	Market	Amgen, BMS/Mirati, Innovent, Hangyu
Next-Gen G12C	Phase 3/2	Roche, Merck, Lilly, others
Non-G12C Specific	Phase 1-2	Genfleet, BMS/Mirati, Revolution, Hengrui
Pan-KRAS / Novel MOA	Early stage	Revolution Medicines, academic programs
Indirect / Combo Strategies	Active	Multiple biotech + Big Pharma programs

## Outlook

The KRAS landscape remains one of the most dynamic areas in oncology:

- A shift from single-mutation targeting to broader mutation coverage.
- Post-monotherapy era emphasizes **combinations** and resistance management.
- Competitive advantage increasingly hinges on *clinical differentiation and strategic positioning* rather than *first-to-market alone*.

### ▼ Perplexity

The KRAS competitive landscape is rapidly evolving with significant market expansion expected and an increasingly crowded pipeline of next-generation therapeutics targeting multiple mutation subtypes.

## Current Market Size and Growth

The KRAS inhibitor market was valued at approximately \$526 million in 2025 and is projected to reach \$7.8 billion by 2034, representing a compound annual growth rate of 35%. This explosive growth is driven by recent regulatory approvals, expanding clinical applications beyond lung cancer, and the promise of next-generation pan-KRAS inhibitors.

## Approved Therapies and Dominant Players

Two KRAS G12C inhibitors currently dominate the market: Lumakras (sotorasib) developed by Amgen and Krazati (adagrasib) from Mirati Therapeutics. Both are approved for non-small cell lung cancer treatment, with adagrasib undergoing Phase 3 trials for combination therapy approaches. These agents have established proof-of-concept for RAS-directed therapies but face combination toxicity challenges with immunotherapy agents.

## Next-Generation Pipeline and Pan-KRAS Expansion

The competitive landscape is shifting toward pan-KRAS inhibitors targeting multiple mutation subtypes beyond G12C. Leading candidates include:

- **Divarasib** (Roche) — targeting multiple mutation variants
- **Daraxonrasib/RMC-6236** (Revolution Medicines) — RAS(ON) inhibitor in Phase 3 trials for pancreatic cancer
- **Olomorasib** and **MK-1084** — next-generation G12C inhibitors undergoing clinical evaluation
- **JDQ443** (Novartis) and **LY3537982** (Eli Lilly) — late-stage development candidates
- **RMC-5127** (Revolution Medicines) — selective G12V inhibitor in Phase I/Ib trials

Additional pan-KRAS candidates include programs from Cardiff Oncology, Immuneering Corporation, Jacobio Pharma, and Eli Lilly.

## Therapeutic Strategies and Differentiation

The market is characterized by divergent approaches to KRAS inhibition. Revolution Medicines differentiates by targeting the active "on" state of KRAS proteins, contrasting with the "off"-state approach of Lumakras and Krazati. Combination strategies are becoming central to competitive positioning, with trials exploring KRAS inhibitors plus chemotherapy, immunotherapy (PD-L1 inhibitors), EGFR inhibitors, and SOS1 pan-KRAS inhibitors.

## Emerging Indications and Geographic Leadership

Beyond NSCLC, KRAS inhibitors are expanding into pancreatic cancer and colorectal cancer, representing major growth opportunities. North America is expected to lead revenue generation in the market.

Is your interest in the KRAS landscape focused on a particular mutation subtype (G12C, G12D, G12V), indication (NSCLC, pancreatic, colorectal), or competitive positioning of specific companies?

### Will Intellia meet endpoints in its upcoming readout?

#### ▼ BB

#### Intellia Therapeutics — Upcoming Readout Expectations

##### HAELO Trial for Hereditary Angioedema (HAE)

- Top-line data for the HAELO study is expected mid-year, with anticipated results including attack rate reductions and attack-free intervals, as well as safety information. (1)
- Intellia expects its data to be competitive with or better than existing treatments, aiming for attack rate reductions comparable to or exceeding the market leader's approximately 45% reduction. (2)
- Additional data from the Phase 1/2 HAE study presented at AAI 2026 supports durable efficacy for lonvo-z, with a one-time 50 mg dose resulting in a 96% mean reduction in attacks and 97% of patients being attack- and LTP-free as of the data cutoff. (3)
- Three-year data from the Phase 1 trial of lonvo-z in adults with HAE showed a 98% mean reduction in the monthly HAE attack rate in all 10 patients, with all patients being attack-free and treatment-free for a median of 23 months. (4)
- Lonvo-z approval and launch are likely with a 75% probability, and pricing is expected to reflect multi-year efficacy supported by durability data. (5)

##### ATTR Program Status

- On March 27, 2026, Intellia re-opened enrollment for its Phase 3 trial evaluating NTLA-2001 in patients with transthyretin amyloidosis with cardiomyopathy (ATTR-CM), after previously being listed as active but not recruiting. (6)
- The FDA has lifted clinical holds on Intellia's ATTR trials, endorsing their safety framework, with protocol modifications not expected to change the overall trial design, statistical analysis plan, or enrollment target. (7)
- Long-term data from the Phase 1 study of nex-z in ATTR-PN was impressive, showing a mean serum TTR reduction of over 90% with up to 36 months of follow-up, and 72% of patients had improvements in mNIS+7 exceeding a clinically meaningful threshold. (8)
- KOLs see nex-z's ability to demonstrate efficacy in the current Phase III MAGNITUDE study as a "near-guarantee" given TTR silencer data, and view the event-driven study endpoint favorably. (9)

#### ▼ Opus

Nobody can predict with certainty whether Intellia will meet its endpoints, but here's what we know heading into the readout:

## The Key Upcoming Readout: Lonvo-z (HAELO Phase 3)

Intellia expects to report HAELO Phase 3 topline data for lonvo-z in hereditary angioedema (HAE) by mid-2026 [Intelliatx](#), making this the most imminent catalyst. The trial enrolled 80 patients in a randomized, double-blind, placebo-controlled design, with participants allocated 2:1 to a single 50 mg infusion of lonvo-z or placebo. The key endpoints are the number of HAE attacks and the proportion of patients achieving attack-free status from week 5 through week 28. [Intelliatx](#)

#### **What's encouraging:**

The Phase 1/2 data have been remarkably strong. In pooled Phase 1/2 data with up to three years of follow-up, the vast majority of patients who received a one-time 50 mg dose were both attack-free and free of long-term prophylaxis at the data cutoff. [Intelliatx](#) Deep, stable, and durable reductions in plasma kallikrein of about 89% on average were observed at month 24. [Intelliatx](#) Specifically, 31 out of 32 patients (97%) who received the 50 mg dose showed deep, stable, and durable kallikrein reductions. [GlobeNewswire](#)

#### **What introduces uncertainty:**

- Phase 3 trials sometimes don't replicate Phase 1/2 results at the same magnitude, especially with a larger, more diverse patient population and a placebo-controlled design.
- Regulatory expectations may scrutinize whether a 28-week primary endpoint window is sufficient for a first-in-class gene-editing prophylaxis, and manufacturing scalability could also be a gating factor even with positive efficacy data. [Clinicaltrials.gov](#)
- The company's other program (nex-z for ATTR amyloidosis) has had safety issues — the FDA placed clinical holds on the MAGNITUDE trials after a serious Grade 4 liver adverse event that required hospitalization. [BioPharma Dive](#) While lonvo-z targets a different gene (KLKB1 vs. TTR), both use the same LNP-CRISPR delivery platform, so any safety signals will be closely watched.

## **Bottom Line**

The Phase 1/2 data for lonvo-z in HAE are among the most impressive in the gene editing space, with near-complete attack suppression. Most analysts view this as a relatively high-probability readout for efficacy, though nothing is guaranteed. The bigger question marks are around safety (particularly liver-related signals given the nex-z experience), the durability window captured by the Phase 3 design, and manufacturing readiness.

Analysts have described this as a binary risk story — success could unlock multi-billion-dollar markets, while setbacks could significantly impact the company's valuation. [Seeking Alpha](#)

I'm not a financial advisor, so if you're considering this from an investment perspective, it's worth consulting a professional who can factor in your specific situation.

▼ AXL

## **Intellia's Upcoming Readout: HAELO (lonvo-z in HAE)**

Before answering the endpoint question directly: behavioral analytics cannot predict whether a trial will meet its endpoint — that depends on scientific validity and clinical effect size, which registry data cannot reveal. What they can assess is operational health, confidence signals, and historical context. On those dimensions, HAELO looks notably clean. Here is the full picture.

### **The Imminent Catalyst: HAELO Phase 3**

The closest readout in Intellia's portfolio is the HAELO Phase 3 study ([NCT06634420](#)) evaluating lonvo-z (NTLA-2002), a single-dose CRISPR-based therapy targeting plasma kallikrein in hereditary angioedema. Intellia has guided to a topline readout by **mid-2026**. The registry primary completion date is April 1, 2026, and Intellia's conditional BLA filing plan targets H2-2026 if results are supportive.

### **Operational Health: Minimal Distress Signals**

HAELO is operationally clean by every behavioral measure:

- **Operational risk score: 5/100 (stable)** — the single signal is one minor eligibility criteria modification, severity rated low. No enrollment changes, no date delays, no site volatility.
- **Enrollment trajectory: Linear and on target.** The trial enrolled at least 60 participants (target met), with screening completion announced in June 2025 and full enrollment confirmed by September 18, 2025. The registry shows exactly one status event — the transition from Recruiting to Active, not recruiting in June 2025 — with zero enrollment modifications and zero date modifications. That is the behavioral signature of a trial that ran according to plan.
- **Landscape risk: 50/100 (challenging).** The trial sits in the "Smooth so far, but landscape is treacherous" quadrant — operationally clean, but faces structural competition from a crowded HAE field.
- **Enrollment timeline:** HAE Phase 3 trials have a median enrollment period of ~505 days. HAELO enrolled approximately 60 patients in roughly 5 months (January to June 2025), which is aggressive and on-plan.

A confident sponsor operating a well-executing trial looks exactly like this: a registry that barely moves.

### Phase 1/2 Scientific Context: Strong Mechanistic Signal

The supporting Phase 1/2 data for lonvo-z is among the most consistent early-stage readouts in the HAE space:

- **June 2025 (EAACI):** Phase 1 cohort (n=10) showed 98% mean reduction in monthly HAE attack rate; all 10 patients attack-free for median ~23 months; no treatment-emergent SAEs.
- **November 2025 (ACAAI):** Pooled 50mg Phase 1/2 cohort (n=32) — 97% (31/32) attack-free and long-term prophylaxis-free at data cutoff; mean 89% plasma kallikrein reduction at month 24; safety described as well-tolerated over 3 years with one SAE (pulmonary embolism) and one Grade 2 AST elevation.

The numbers are compelling and consistent across multiple data cuts. That said, both presentations flag red flags: post-hoc emphasis and small-n in certain arms. Sponsor spin detected in both readouts — language like "dramatic reductions" without upfront numerics is a spin signal. The actual underlying data does not appear spun, but communications framing warrants scrutiny.

### Historical Base Rate in HAE Phase 3: Favorable

Of 48 Phase 3 HAE trials in the database, the structured outcome data shows **4 of 4 trials with extractable results met their primary endpoint** (100% observed success rate in trials with data). Zero documented failures in the indication at Phase 3. Critically, the terminated trial in this cohort ([NCT02670720](#), avoralstat) was stopped with only 6 patients — a small early termination, not an efficacy failure. The HAE indication has been a high-success field: lanadelumab, donidalorsen, berotralstat, sebetralstat (KONFIDENT), and deucricitibant (RAPIDe-3) all cleared Phase 3. The base rate here is favorable.

### Intellia's Sponsor Credibility: Mixed

Intellia's commitment scorecard across its HAE program shows an **on-time rate of 50% and a credibility score of 0.40** (scale 0–1). Across all indications, the company-wide credibility score is 0.45. These are below-average figures driven largely by timeline slippage in the ATTR programs. However, HAELO itself has shown no timeline deviations — so the HAE-specific track record for this particular study is clean.

### The Nex-z Shadow: Material but Separate

The larger context for Intellia involves significant turbulence in its nex-z (NTLA-2001 / nexiguran ziclumeran) ATTR programs:

- **October 29, 2025:** FDA placed clinical holds on both MAGNITUDE (ATTR-CM, [NCT06128629](#), >650 enrolled) and MAGNITUDE-2 (ATTRv-PN, [NCT06672237](#)) after Grade 4 liver transaminase elevations in MAGNITUDE, including one patient death.
- **January/March 2026:** Both holds lifted, with enhanced liver safety monitoring protocols. MAGNITUDE re-entered recruiting on March 27, 2026 with enrollment target raised 56.9% (765 to 1,200 patients) — a major protocol change consistent with FDA-required design modifications. That trial carries an elevated operational risk score of 80/100.

- **MAGNITUDE BLA timeline pushed to 2028.**

This safety history is for nex-z, not lonvo-z. The two molecules are distinct CRISPR-based therapies targeting different proteins via different mechanisms. However, investors should be aware that the liver toxicity signal in nex-z (hepatocellular injury) is not a target-specific concern — it relates to delivery or off-target editing. Whether FDA will require any additional lonvo-z liver monitoring disclosures in the BLA review is a regulatory risk that behavioral data cannot assess.

## Probability Assessment

**What the data supports:** HAELO is operationally healthy, enrolled on time without modification, its primary completion date has not moved, and the underlying Phase 1/2 data is mechanistically strong with consistent attack-rate suppression across multiple cohorts. The HAE indication has a historically favorable Phase 3 success rate.

**What the data cannot assess:** Whether the Phase 3 effect size will reproduce the Phase 1/2 data across a broader, more heterogeneous population; whether the HAELO endpoint (HAE attack rate reduction) was appropriately powered; and whether the liver toxicity signal from nex-z creates any regulatory overlay that affects the lonvo-z review.

**The behavioral read:** No operational distress detected in HAELO. Intellia's behavior in the registry is consistent with a sponsor that has confidence in this trial — they enrolled it quickly, haven't touched the design, and are publicly committing to a BLA in H2-2026 conditional on positive data. Conditional BLA guidance this specific, this close to primary completion, is a meaningful behavioral signal of internal confidence.

**What to watch:** The mid-2026 topline readout date. If Intellia misses that window without a press release explaining why, that lag is the signal.

## Intellia Portfolio Summary

Trial	Indication	Status	Operational Risk	Landscape Risk
HAELO ( <a href="#">NCT06634420</a> )	HAE (lonvo-z)	Active, not recruiting	5/100 — stable	50/100 — challenging
MAGNITUDE ( <a href="#">NCT06128629</a> )	ATTR-CM (nex-z)	Recruiting (hold lifted)	80/100 — elevated	Not assessed
MAGNITUDE-2 ( <a href="#">NCT06672237</a> )	ATTRv-PN (nex-z)	Active, not recruiting	0/100 — low	31/100 — moderate

### ▼ ChatGPT

Here's a balanced, **fact-based view on whether Intellia Therapeutics may meet endpoints in its upcoming clinical readouts (primarily HAELO Phase 3 and ATTR MAGNITUDE trials):**

#### 1. HAELO Phase 3 (NTLA-2002) — Most Immediate and Material Readout

- Intellia completed enrollment in its Phase 3 **HAELO** trial of **NTLA-2002 / lonvoguran ziclumeran** for **hereditary angioedema (HAE)** in late 2025 and expects **topline topline results in H1 2026**.
- This trial's **primary endpoints** are **reduction in HAE attacks and the proportion of patients who are attack-free from week 5 through week 28** versus placebo.
- **Why this matters:** Earlier Phase 1/2 data showed very large reductions in attack rates and many patients attack-free with a single dose — suggesting **strong biological activity and clear signal** that could translate into meeting these endpoints in Phase 3.
- **Risk factors:** Phase 3 is placebo-controlled and larger; real-world variability and longer follow-up can sometimes temper effect sizes. But the preponderance of Phase 1/2 signals is positive.

**Bottom line on HAELO:** Given the strong early signals and clearly defined endpoints, the probability of **meeting those endpoints in HAELO is generally viewed as favorable by many analysts (though not guaranteed)**.

#### 2. MAGNITUDE / MAGNITUDE-2 (ATTR Amyloidosis) — Longer Term and More Uncertain

- Intellia's flagship **nexiguran ziclumeran (nex-z)** Phase 3 MAGNITUDE trials in **transthyretin (ATTR) amyloidosis** are complicated by a **clinical hold that was lifted by the FDA in early 2026** after safety concerns.

- The **MAGNITUDE primary endpoint** is a composite of **cardiovascular mortality/events** in patients with cardiomyopathy — a tough, long-term clinical outcome to achieve in pivotal trials.
- The ATTRv-PN study (MAGNITUDE-2) also has co-primary endpoints including change in neuropathy score and TTR levels.
- **Uncertainty:** Regulatory holds, safety concerns, and the complexity of the endpoints introduce **significant uncertainty** around timeline and likelihood of success.

**Bottom line on MAGNITUDE:** Because of the hold and the challenging nature of the composite cardiovascular endpoints, **predicting success there is much more speculative at this stage.**

## Overall Expectations

Here's a practical way to think about the upcoming readouts:

### ♦ HAELO (NTLA-2002)

- **Likely well-powered and readout in 1H 2026 with clear endpoints** (attack count/free patients).
- **Data from earlier phases strongly supportive scientifically.**

### ♦ ATTR Trials (NTLA-2001 nex-z)

- **More complex endpoints and regulatory overhang.**
- Might not read out in the near term depending on how protocol amendments proceed.
- Outcome will hinge not just on efficacy signals but safety interpretation by regulators.

## Key Takeaways

- **Meeting endpoints in HAELO** is possible and arguably supported by the strong Phase 1/2 efficacy signal, but Phase 3 still needs to confirm it.
- **ATTR endpoint success is less certain** due to safety complications and the nature of the clinical endpoints being harder to hit.
- Investors and clinicians will likely view HAELO topline as the *first major proof-point* of the company's CRISPR platform's therapeutic potential.

If you want, I can summarize the specific statistical power and historical effect sizes from the earlier data to estimate the statistical likelihood of meeting the HAELO endpoints.

### ▼ Perplexity

Intellia Therapeutics' most imminent readout is from the Phase 3 HAELO trial of lonvo-z (NTLA-2002) for hereditary angioedema (HAE), with topline data expected by mid-2026. No results are available yet, as enrollment completed in September 2025 and primary endpoints (HAE attack frequency and attack-free status from weeks 5-28) remain pending analysis.

## HAELO Trial Details

The randomized, double-blind, placebo-controlled study enrolled ~80 patients (2:1 lonvo-z:placebo), including adolescents ≥16 years old with Type I/II HAE. Phase 1/2 data showed strong efficacy, with single doses reducing attacks and enabling prophylaxis-free status, supporting optimism for Phase 3 success. Analysts highlight this as a key catalyst, with BLA planned for H2 2026 if positive.

## ATTR Programs Status

Nex-z (nexiguran ziclumeran) Phase 3 trials (MAGNITUDE for ATTR-CM, MAGNITUDE-2 for ATTRv-PN) resumed dosing after FDA holds lifted in Jan/Mar 2026 following a Grade 4 liver event. Enrollment completion is slated for H2 2026, so no near-term readouts; primary endpoints are neuropathy scores, TTR reduction, and CV events. Early Phase 1 data indicated deep, durable TTR knockdown.

## Likelihood Assessment

Meeting endpoints is uncertain without data, but prior trials met primary/secondary goals, and HAELO's rapid enrollment signals execution strength. Safety concerns from nex-z could impact ATTR odds, though mitigations are in place. Positive HAELO readout could drive BLA and 2027 launch. For predictions, Phase 1/2 durability (Q4 2025) offers interim clues.

### What is the read-through if the first PROTAC approval gets a CRL?

#### ▼ BB

I was unable to find specific information about the first PROTAC approval or the implications of a potential Complete Response Letter (CRL) for this drug class in the available sources.

#### ▼ Opus

This is a really important question for biotech investors. Here's the setup and the read-through:

## The Key Event

Vepdegestrant (ARV-471), developed by Arvinas and Pfizer, has a PDUFA date of June 5, 2026. [Arvinas](#) This would be the first-ever PROTAC protein degrader approved in oncology [Clinicaltrialvanguard](#), making it a bellwether event for the entire targeted protein degradation field.

## What a CRL Would Mean — The Read-Through

A Complete Response Letter for vepdegestrant would have cascading implications across several dimensions:

### 1. Platform De-Risking Goes Into Reverse

The entire PROTAC thesis depends on proving that this modality can clear the regulatory bar. Vepdegestrant is the furthest-along PROTAC, and its approval would validate ~25 years of science going back to the original Crews/Deshaies work. A CRL would raise fundamental questions about whether PROTACs as a drug class face unique regulatory hurdles — around degradation kinetics, selectivity, or long-term safety — that investors hadn't priced in. Pipelines are full of diverse PROTACs for oncology and immunology [Drug Hunter](#), and all of those programs would face intensified skepticism.

### 2. Sector-Wide Damage

More than two dozen biotech developers of PROTACs, molecular glues, and other protein-degrading drugs have emerged over the past two decades. [BioPharma Dive](#) A CRL would likely trigger a broad selloff across the targeted protein degradation space — companies like Nurix, C4 Therapeutics, Kymera, and others would take sympathetic hits even if their molecules and targets are entirely different. The market tends to treat first-in-class regulatory failures as modality-level signals.

### 3. Arvinas-Specific Impact

ARVN stock is currently around \$10.29 [Stocktitan](#), already well off highs, reflecting some market caution. A CRL can send biotech stocks down 40% to 80%. [BioPharmaWatch](#) Arvinas does have mitigating factors — \$685M in cash with runway into the second half of 2028 [Stock Titan](#), plus a diversifying pipeline including ARV-102 (LRRK2 for Parkinson's/PSP), ARV-806 (KRAS G12D), and ARV-393 (BCL6). But the stock's identity is deeply tied to PROTAC platform validation, and a CRL would crush that narrative.

### 4. The Nature of the CRL Matters Enormously

This is critical context. Not all CRLs are equal:

- A **manufacturing/CMC CRL** (like what sometimes happens) would be relatively benign for the broader sector — it would say nothing about whether PROTACs work, just that there was a process issue. The stock would drop but could recover.
- A CRL citing **insufficient efficacy evidence** would be far more damaging. The VERITAC-2 data showed a 2.9-month PFS improvement over fulvestrant (5.0 vs 2.1 months) — statistically significant but modest in absolute terms. [ACS Publications](#) If the FDA questioned whether this benefit was clinically meaningful enough, it would call into question the commercial viability of the drug and potentially signal a higher bar for the modality.

- A CRL raising **safety or mechanistic concerns specific to protein degradation** (e.g., off-target degradation, E3 ligase-related toxicities) would be the worst-case scenario — that would be read as a modality-level red flag and would devastate the entire space.

## 5. The Pfizer Factor

In September 2025, Arvinas and Pfizer announced their plan to jointly select a third party for commercialization of vepdegestrant. [Stock Titan](#) The fact that Pfizer is already distancing from direct commercialization suggests limited Big Pharma conviction in the commercial opportunity. A CRL would likely accelerate Pfizer's pullback and raise broader questions about whether large pharma partners will continue investing heavily in PROTAC programs.

## 6. M&A and Financing Implications

The regulatory climate in the U.S. remains unpredictable, leaving some companies with surprise rejections and delays that make risky biotech investments even riskier. [BioPharma Dive](#) A CRL on the first-ever PROTAC would likely chill M&A appetite for protein degradation companies and make it harder for earlier-stage PROTAC companies to raise capital or command attractive deal terms.

## Bottom Line

The read-through of a vepdegestrant CRL depends heavily on the *reason* for rejection, but in any scenario it would be a significant negative event extending well beyond Arvinas. At minimum, it delays the modality's validation by years and forces investors to re-underwrite every PROTAC program at a higher discount rate. The worst case — a CRL on mechanistic or efficacy grounds — could set the entire targeted protein degradation field back meaningfully and trigger a repricing across 20+ public and private companies. It would essentially be the "PROTAC winter" scenario.

▼ AXL

## The PROTAC CRL Read-Through: A Live Event, Not a Hypothetical

Before mapping the read-through, a critical framing correction: **this is not hypothetical**. Vepdegestrant (ARV-471), developed by Arvinas/Pfizer, has a PDUFA date of **June 5, 2026** — less than two months away. The NDA was accepted by the FDA in August 2025. This would be the first PROTAC/protein degrader to receive FDA approval (or rejection). The data below reflects a live, actively monitored event.

There is also a meaningful analytical wrinkle in the underlying trial data: **VERITAC-2 (NCT05654623) showed mixed results**. It met the ESR1-mutant subgroup endpoint (HR 0.57; median PFS 5.0 vs 2.1 months) but **failed the ITT population** (HR 0.83; p=0.07). Multiple read flags are present in the catalyst data: "multiple\_primary\_one\_met," "subgroup\_only," and sponsor spin detected. OS data remains immature at less than a quarter of required events. The NDA was submitted and accepted on the strength of the ESR1-mutant result — which means the FDA approval, if it comes, will be a biomarker-restricted label. A CRL is therefore a credible, non-trivial scenario despite the sponsor's optimistic framing.

## The Lead Candidate: Regulatory Status & Timeline

**Vepdegestrant (ARV-471 / PF-07850327)** — VERITAC-2 ([NCT05654623](#))

- Sponsor: Arvinas + Pfizer (co-development and commercialization)
- Enrollment: 624 actual patients, Phase 3, registrational
- Indication for NDA: ESR1-mutated ER+/HER2- advanced/metastatic breast cancer, 2L+
- NDA submitted: June 2025; FDA accepted: August 2025
- Fast Track designation: confirmed
- PDUFA: June 5, 2026
- Primary data: Statistically significant PFS benefit in ESR1-mutant subgroup only; ITT did not achieve significance

Vepdegestrant is classified mechanistically as an "Estrogen Receptor Degradator" (PROTAC-based) — the first of its mechanism class to reach FDA decision. The ESR1 field shows strong deceleration: 682 older trials vs. only 52 recent (ratio 0.07), confirming this is a mature but still active competitive space.

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## CRL Scenario Analysis: What Reason Determines the Magnitude

The read-through severity depends entirely on **why** the FDA issues a CRL.

### Scenario A — Efficacy CRL (FDA declines ESR1-mutant label as insufficient or requires ITT benefit)

This is the most contained scenario for the PROTAC platform itself. A pure efficacy rejection would mean the ESR1-mutant PFS benefit (5.0 vs 2.1 months, HR 0.57) wasn't deemed clinically meaningful enough, or that FDA required ITT-level evidence. The platform mechanism is not implicated. Impact is severe for Arvinas/Pfizer but limited for degrader competitors. Giredestrant and imlunestrant — both non-PROTAC oral SERDs targeting ESR1 — would benefit from competitive relief in the ER+ breast cancer space, not suffer from it. Arvinas's second VERITAC-3 Phase 3 ([NCT05909397](#), vepdegestrant + palbociclib vs letrozole + palbociclib, 1L) continues.

### Scenario B — Safety CRL (unexpected toxicity, novel safety signal)

This is the most damaging scenario for the degrader platform. PROTACs work by hijacking the ubiquitin-proteasome system — a mechanism shared across all PROTAC-class drugs regardless of their target. A class-level safety signal (e.g., off-target degradation, novel hepatotoxicity, or proteasome-related effects) would constitute a **platform-level read-through** affecting every PROTAC in development. This is the scenario that would cascade to Arvinas's KRAS G12D program (ARV-806, [NCT07023731](#)), BCL6 degrader (ARV-393, [NCT06393738](#)), and BMS's iberdomide program ([NCT05827016](#)). Investor sentiment toward degrader platform companies (Kymera, C4 Therapeutics, Nurix) would take a severe hit regardless of their target and indication differences.

### Scenario C — Manufacturing/CMC CRL (chemistry, manufacturing, controls)

The most platform-agnostic scenario. PROTACs are notoriously complex heterobifunctional molecules (they must bind the target protein, recruit an E3 ligase, and maintain appropriate linker geometry). CMC issues are endemic to novel modalities. A manufacturing CRL would cause a ~12-month delay for vepdegestrant, would not implicate the science, and would have minimal read-through to competitors. The 2L+ ER+ breast cancer space would remain status quo.

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## Direct Read-Through: Tier 1 — Same Target/Indication

The immediate read-through targets are the competing ESR1-degrader programs in ER+ breast cancer:

### Giredestrant (Genentech/Roche) — evERA Breast Cancer ([NCT05306340](#), Phase 3)

- Registrational, ESR1-targeted oral SERD, 373 actual patients, 2L+
- Currently "Active, not recruiting" — primary completion due July 2025
- Critical operational stress score (100/100): cumulative 806-day delay, then dramatic 456-day pull-in, enrollment expanded 42.9%
- A vepdegestrant CRL would likely validate FDA's willingness to scrutinize ESR1-mutant-only evidence — directly relevant to giredestrant's regulatory pathway
- Paradoxically a beneficiary if CRL is efficacy-based (reduces competition), but faces same regulatory uncertainty if FDA raises the evidentiary bar

### Imlunestrant (Eli Lilly) — EMBER-3 ([NCT04975308](#), Phase 3)

- Registrational, ESR1/ER $\alpha$ , 2L+ ER+ breast cancer
- This trial has already reported and is further along; an efficacy CRL for vepdegestrant could complicate Lilly's own submission strategy if FDA signals concern about ESR1-mutant subgroup labeling approaches

### Camizestrant (AstraZeneca, AZD9833) — SERENA-1 ([NCT03616587](#)) and SERENA-4

- Also an oral SERD targeting ESR1; critical risk score with 1,333 cumulative days of delay across 12 completion date changes
- Also enrolled Phase 3 programs (SERENA-4, SERENA-6) that would face the same regulatory precedent questions

**Fulvestrant (intramuscular SERD, standard of care)** — the CONFIRM trial ([NCT00099437](#), AstraZeneca) served as the comparator in VERITAC-2. A CRL that validates fulvestrant's adequacy as standard of care strengthens AstraZeneca's existing franchise while next-gen SERDs remain in regulatory limbo.

## Tier 2 — Broader PROTAC Platform Programs

These programs share the PROTAC mechanism but target different proteins and indications. A **safety CRL** would hit all of them; an efficacy or manufacturing CRL would have minimal direct impact.

Trial	Sponsor	Drug	Target	Indication	Phase	Risk
<a href="#">NCT07023731</a>	Arvinas	ARV-806	KRAS G12D	Pancreatic/Solid Tumor	Ph 1/2	Stable (5/100)
<a href="#">NCT06393738</a>	Arvinas	ARV-393	BCL6	Non-Hodgkin Lymphoma	Ph 1	Elevated (70/100)
<a href="#">NCT05827016</a>	BMS	Iberdomide	Cereblon/IKZF1/3	Multiple Myeloma	Ph 3	Low (40/100)

Note: Iberdomide (BMS) is technically a CELMoD (cereblon E3 ligase modulator) rather than a classical PROTAC — its mechanism involves the same E3 ligase hijacking logic but without the bifunctional linker architecture. A PROTAC-class safety signal could affect it secondarily, but the distinction matters scientifically.

ARV-806 (KRAS G12D) is a notable watch: it completed once-weekly dose escalation ahead of schedule, has a Phase 1/2 data readout planned for H2 2026, and carries essentially no operational stress. Arvinas has strategically positioned this as the platform's next major catalyst. A safety CRL for vepdegestrant would shadow this readout regardless of the data.

## Most Exposed Sponsors & Programs

**Arvinas (most exposed by far):** The company's entire commercial thesis rests on vepdegestrant being the first approved PROTAC. A CRL of any type destroys the near-term revenue narrative, potentially threatens the Pfizer collaboration economics, and forces reassessment of the pipeline timing. ARV-393 already shows 821 cumulative days of primary completion delay and a status regression. The credibility scorecard shows only 14% of Arvinas's commitments have been resolved on time (1/7). A CRL extends the period during which Arvinas is a revenue-free development company.

**Pfizer (moderately exposed):** Pfizer co-sponsors the pivotal VERITAC-2 and an additional Phase 3 ([NCT05909397](#), vepdegestrant + palbociclib). The second Phase 3 shows an extreme enrollment underperformance — enrollment target fell 95% from 1,180 to 59 — suggesting this program was significantly scaled back even before the CRL decision. Pfizer also has ongoing combination studies across the TACTIVE-U umbrella with enrollment shortfalls of 43–84% across sub-studies. The operational picture across the entire vepdegestrant portfolio is poor.

**Genentech/Roche (moderately exposed):** Giredestrant in evERA Breast Cancer carries a critical risk score (100/100) with the highest operational stress in the ESR1 competitive set — 806-day cumulative delay, enrollment expanded 42.9%, and a dramatic whipsaw completion date pattern. A vepdegestrant CRL that raises the regulatory bar for ESR1-mutant labeling would add structural headwind to a trial already struggling operationally.

## Potential Beneficiaries of a CRL

**AstraZeneca (fulvestrant franchise):** Immediate beneficiary if vepdegestrant's 2L+ label never materializes. AZ maintains long-term OS data for fulvestrant as the standard of care.

**CDK4/6 inhibitor combinations:** Programs building on CDK4/6 + endocrine combinations (Lilly's MONARCH suite, Pfizer's palbociclib combinations in other indications) do not depend on PROTAC approval and could capture share in a market where oral SERDs fail to displace fulvestrant.

**Non-PROTAC oral SERDs with cleaner ITT data:** If imlunestrant or camizestrant have achieved ITT-level significance in their pivotal trials (not just ESR1-mutant subgroup benefit), they are strategically advantaged by any FDA CRL that implies ITT evidence is required. This is the most important competitive read-through for Lilly and AstraZeneca.

**Alternative degrader modalities:** Molecular glue degraders (not PROTAC bifunctional, but cereblon-dependent) and lysosome-targeting chimeras (LYTACs) are earlier but would benefit from differentiation narratives if PROTAC platform encounters safety headwinds specifically.

## Key Signals to Watch Before June 5, 2026

1. **Advisory Committee meeting convening:** FDA has not announced an adcom for vepdegestrant. If FDA schedules one, particularly focused on the ITT vs. ESR1-mutant endpoint controversy, it would be a yellow flag for approval.
2. **Arvinas/Pfizer pre-PDUFA press:** Any press release in the weeks before June 5 not mentioning NDA or PDUFA date is a concern. Confident sponsors go quiet before approval; anxious ones front-run with pipeline noise.
3. **Complete Response Letter language (if CRL issued):** The specific CMC, clinical, or statistical deficiency cited will determine the cascade magnitude. Watch for Class 1 (minor, ~6 months) vs. Class 2 (major, ~12 months) CRL designations.
4. **OS maturity timing:** Pfizer/Arvinas acknowledged OS data is "less than a quarter of required events." FDA may require OS maturity before full approval or grant accelerated approval with a post-marketing OS commitment — a middle scenario that is neither clean approval nor CRL.
5. **Giredestrant data readout:** evERA Breast Cancer ([NCT05306340](#)) primary completion was July 2025 — results should be emerging soon. If giredestrant also shows ESR1-mutant subgroup benefit without ITT benefit, it creates a pattern that could strengthen or complicate the regulatory precedent.
6. **Arvinas ARV-806 enrollment velocity:** ARV-806 enrolled ahead of schedule in its Phase 1. Any slowdown post-CRL would signal that a PROTAC-class perception problem is affecting site-level enthusiasm beyond the ER+ indication.

### ▼ ChatGPT

If the **first PROTAC to reach the FDA gets a Complete Response Letter (CRL)**, the read-through would depend heavily on *why* it received the CRL. In platform stories like PROTACs, regulators don't just evaluate the molecule — they implicitly validate (or challenge) the modality.

Below is a structured breakdown of likely scenarios and cross-asset impact.

## 1 If the CRL Is CMC / Manufacturing Related

**Most common for first-in-class modalities.**

### Implication

- Platform risk remains intact.
- Seen as "execution" rather than "mechanism failure."

### Read-through

- Mild-to-moderate sector pullback.
- Companies with similar linker chemistry or manufacturing processes may see temporary pressure.
- Large-cap pharma partners unlikely to exit.

### Historical analogs

- Zolgensma (gene therapy CMC scrutiny)
- Luxturna (AAV manufacturing learning curve)

**Net effect:** 3–6 month delay narrative, not existential.

## 2 If the CRL Is Safety Related (Off-target degradation, hepatotoxicity, immunogenicity)

This is where platform read-through becomes material.

### Implication

- Raises concerns about:
  - Proteasome overload

- Off-target protein knockdown
- Class-wide liver signals

#### Read-through

- Broad derisking of:
  - Early-stage PROTAC oncology programs
  - CNS-targeted degraders
- Increased FDA conservatism on dose-escalation ceilings.
- Potential requirement for longer safety databases.

#### Who feels it most

- Smaller biotechs with single-asset exposure.
- Companies using the same E3 ligase (e.g., cereblon-heavy portfolios).

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### 3 If the CRL Is Efficacy / Marginal Benefit

This would be the most damaging read-through.

#### Implication

- Questions core thesis:

┆ “Does degradation produce meaningfully better outcomes than inhibition?”

If the first approval candidate (likely in oncology) fails to demonstrate superiority over existing inhibitors, investors may reprice:

- The “degradation premium”
- Valuations based on undruggable target expansion

#### Read-through

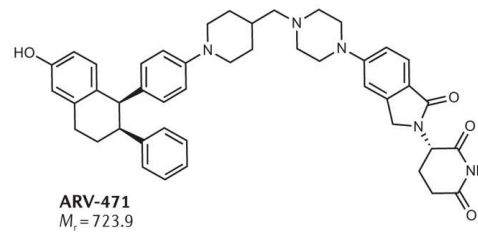
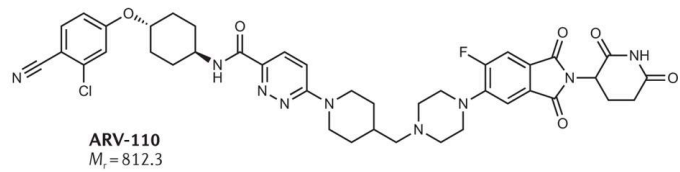
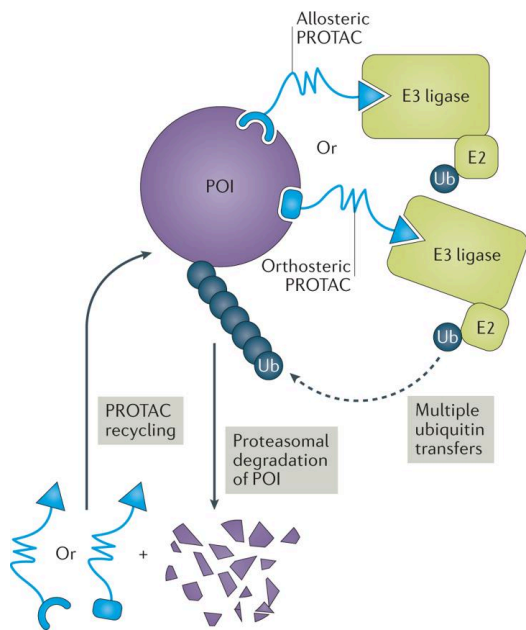
- Multi-quarter sector reset.
- Shift toward:
  - Earlier-line combinations
  - Novel E3 ligases
  - Tissue-restricted degradation strategies



## Public PROTAC Leaders Most Sensitive to Read-Through

### Arvinas

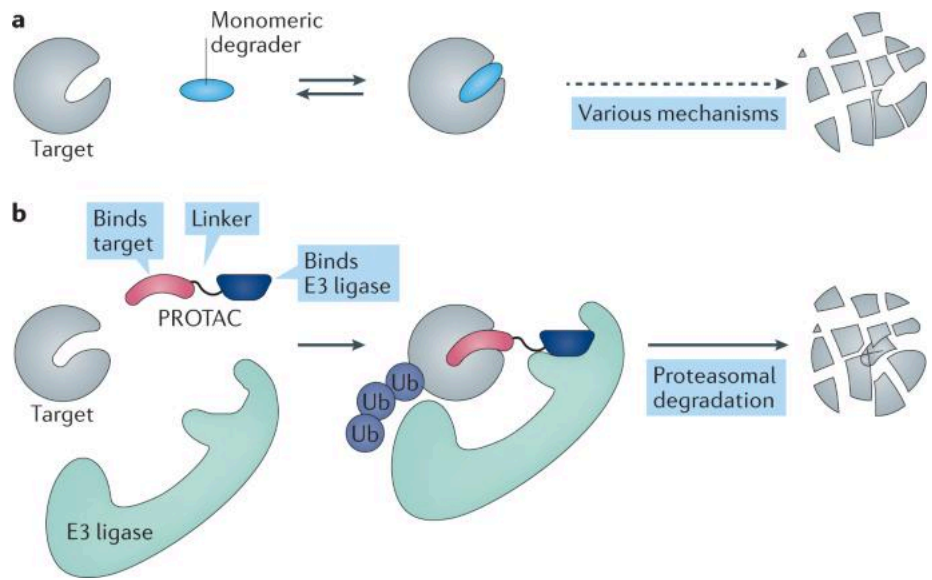




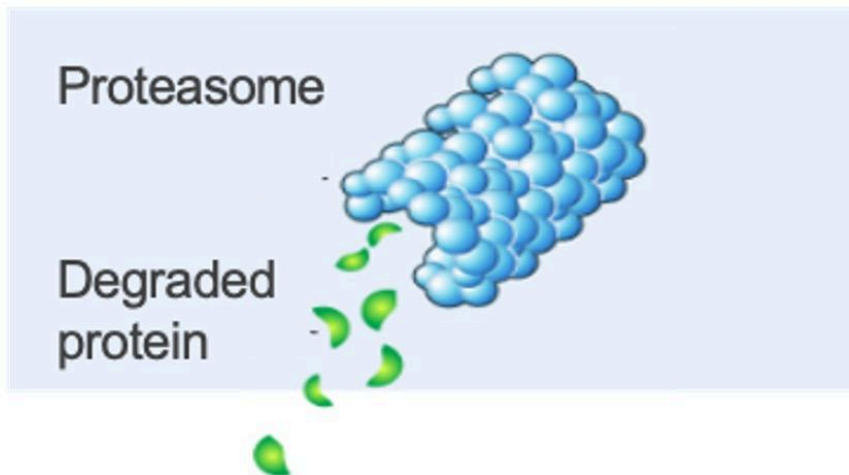
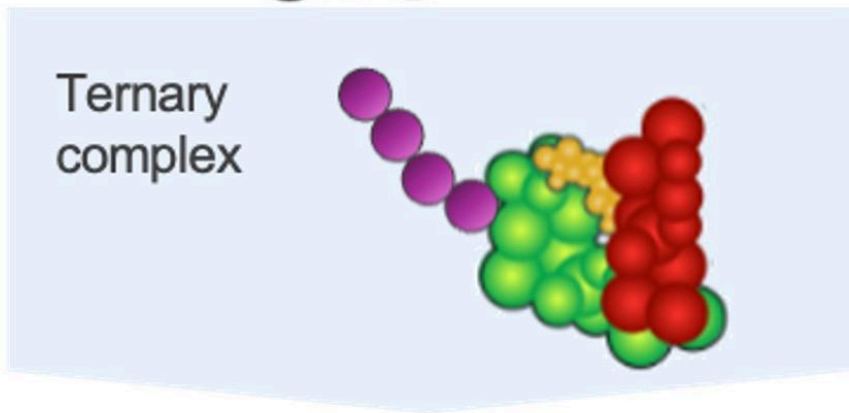
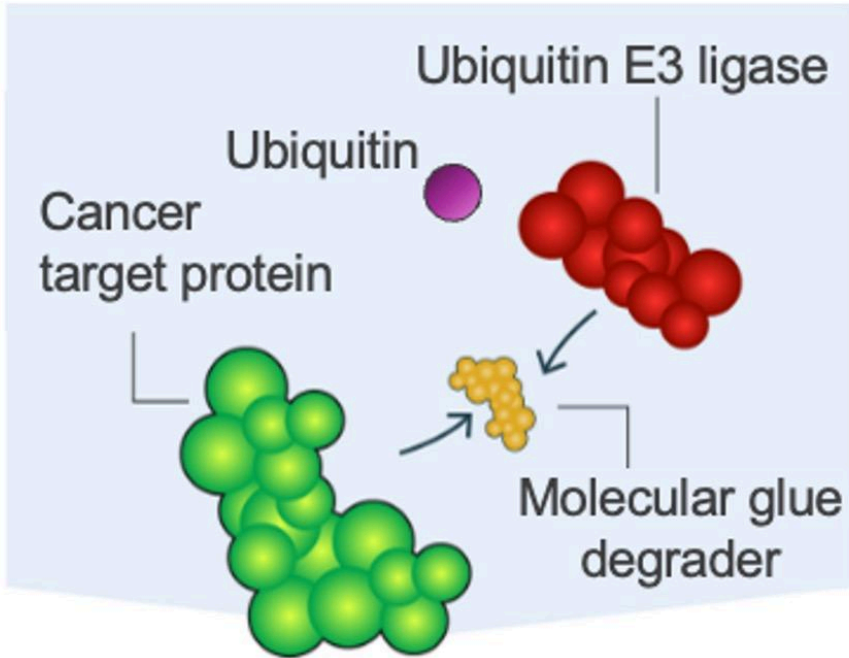
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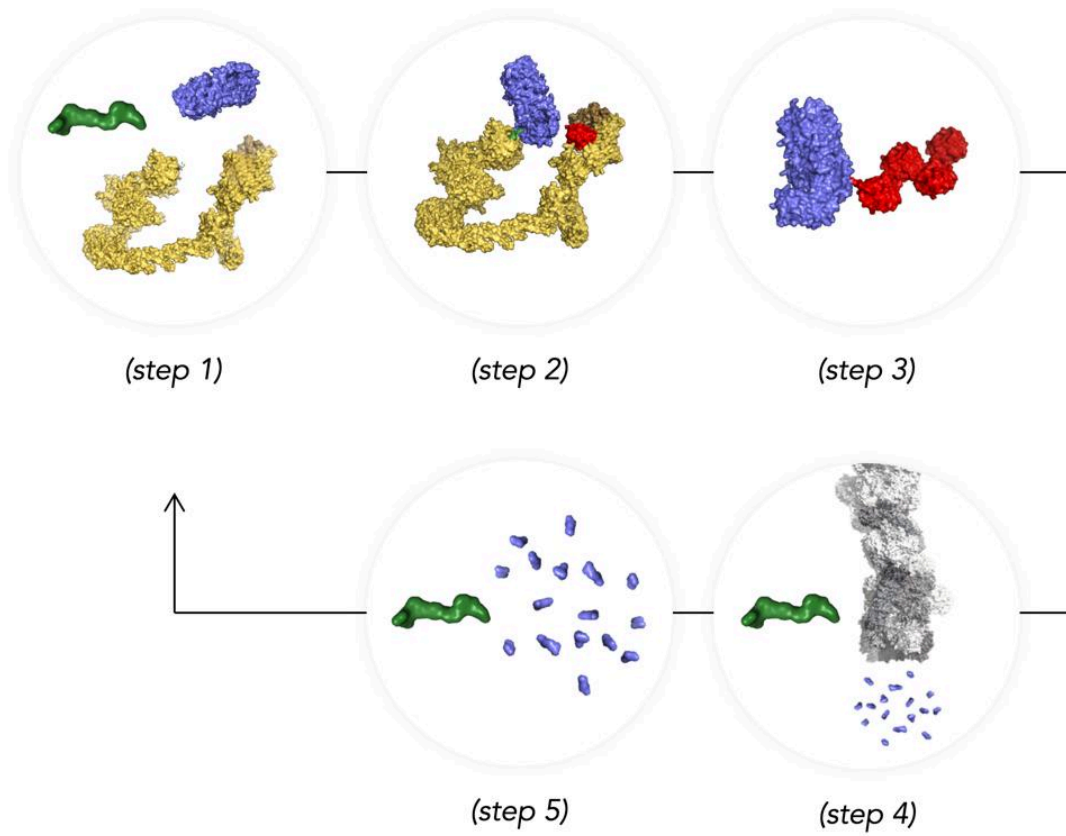
- Platform pioneer
- Heavy cereblon reliance
- Most direct sentiment impact

## C4 Therapeutics



# Molecular mechanism of targeted protein degradation





5

- Oncology-focused degraders
- Early-stage valuation sensitivity

## Kymera Therapeutics





5

- Immunology angle
- More diversified E3 strategy

### What Actually Matters Most

The market will ask three diagnostic questions:

1. **Is this molecule-specific or modality-specific?**
2. **Is the issue fixable within 12 months?**
3. **Did the FDA signal structural skepticism about degradation as a mechanism?**

If the CRL language includes:

- "Class safety concerns"
- "Limited clinical differentiation from inhibitors"
- "Insufficient understanding of degradation pharmacodynamics"

→ That's sector-wide.

If it says:

- "Facility inspection deficiencies"
- "Additional CMC validation required"

→ Contained impact.



## Estimated Sector Impact (Directional)

CRL Type	Sector Selloff	Recovery Time
CMC	-10–20%	1–2 quarters
Safety (manageable)	-20–35%	2–4 quarters
Mechanistic efficacy doubt	-35–60%	Multi-year reset

## Bottom Line

The first PROTAC approval is a **modality referendum**.

A CRL:

- **CMC** → **speed bump**
- **Safety** → **class volatility**
- **Efficacy** → **thesis compression**

The real risk isn't delay — it's whether the FDA implicitly questions whether protein degradation offers a clinically meaningful step-change over inhibition.

If you'd like, I can also:

- Map which upcoming readouts are most exposed to negative read-through
- Or run a scenario tree with probability-weighted sector impact

### ▼ Perplexity

A Complete Response Letter (CRL) from the FDA for the first PROTAC approval would signal fixable issues rather than fundamental flaws in the modality. Vepdegestrant (ARV-471), the leading PROTAC candidate from Arvinas/Pfizer, has its NDA under review with a PDUFA date of June 5, 2026, and no CRL issued as of April 2026.

## Hypothesized Impact

A CRL typically cites manufacturing, labeling, or additional data needs, not outright rejection. For a novel modality like PROTACs, it would likely delay approval by 6-18 months for resubmission but validate the platform if addressed, boosting investor confidence in follow-ons like ARV-110.

## Read-Through to Pipeline

- Minimal negative spillover: Other PROTACs (e.g., ARV-102 in Phase 1) target distinct proteins/diseases, so company-specific fixes wouldn't halt them.

- Positive precedent: CRLs for first-in-class drugs (e.g., gene therapies) often precede approval after iteration, enhancing perceived de-risking.
- Stock/market reaction: Arvinas shares might drop 10-30% short-term, but rebound on clear remediation path, similar to oncology CRLs.

## Broader Modality Outlook

PROTACs remain promising for "undruggable" targets, with vepdegestrant's Phase 3 PFS data (5.0 vs 2.1 months) supporting efficacy. A CRL wouldn't undermine the tech's validation from 10+ clinical programs. What specific PROTAC program or issue (e.g., CMC, efficacy) are you modeling this for?

### What endpoints did successful obesity trials use and how does VK2735 compare?

#### ▼ BB

#### Obesity Trial Endpoints and VK2735 Performance

##### Standard Obesity Trial Endpoints

- The primary endpoint for Viking Therapeutics' Phase 3 VANQUISH trials is the percent change in body weight from baseline after 78 weeks of treatment. (1)
- Secondary endpoints include the percentage of patients achieving specific weight loss milestones of at least 5%, 10%, 15%, and 20% body weight reduction. (2)
- Novo Nordisk's high-dose Wegovy (7.2 mg) demonstrated a 20.7% mean weight loss in the STEP-UP trial and a 14.1% mean weight loss in the STEP UP T2D trial. (3)
- Eli Lilly's retatrutide met primary and secondary endpoints in the TRANSCEND-T2D-1 Phase 3 trial, achieving up to an average of 16.8% body weight loss at 40 weeks. (4)

##### VK2735 Phase 2 Efficacy Results

- The Phase 2 VENTURE study demonstrated statistically significant reductions in mean body weight from baseline, ranging up to 14.7% after 13 weekly doses. (5)
- The oral tablet formulation of VK2735 achieved its primary and secondary endpoints, with participants demonstrating statistically significant reductions in mean body weight after 13 weeks, ranging up to 12.2% from baseline. (6)
- In the Phase 2 VENTURE-Oral trial, the 120mg dose showed 12.2% weight loss from baseline (-10.9% placebo adjusted) after 13 weeks, comparable to Lilly's Orforglipron which showed 12.4% weight loss at 72 weeks. (7)
- Viking's VK2735 Phase 2 data demonstrated up to 13.1% placebo-adjusted weight loss at 13 weeks, with efficacy surpassing that of Lilly's retatrutide in its midstage study. (8)

##### Safety and Tolerability Profile

- Gastrointestinal adverse events were mostly mild or moderate, with discontinuation rates in the low to mid-teens, consistent with other Phase 2 studies for the class. (9)
- The discontinuation rate due to treatment was 38% for the 120mg oral dose compared to 18% for placebo, primarily driven by gastrointestinal adverse events like nausea. (10)

#### ▼ Opus

Here's a comprehensive overview of the endpoints used in successful obesity trials and how VK2735 stacks up.

## Endpoints in Successful Obesity Trials

**Primary endpoints** across the major programs have converged on a common structure. The standard primary endpoint is percentage of total body weight loss (TBWL%) from baseline at the end of the study period. [Nature](#) Most pivotal trials use a co-primary design: the mean percent change in body weight from baseline, and the proportion of participants achieving at least 5% weight loss versus placebo. For example, the OASIS 4 trial for oral semaglutide used co-primary

endpoints of mean percent change in body weight and the percentage of patients achieving  $\geq 5\%$  weight loss from baseline to week 64. [Gastroenterology Advisor](#)

**Key secondary and responder endpoints** typically include the proportion of patients reaching higher weight-loss thresholds —  $\geq 10\%$ ,  $\geq 15\%$ , and  $\geq 20\%$  body weight reduction. The 2025 FDA guidance now accounts for results from recent trials demonstrating  $>10\%$ ,  $15\%$ , and  $20\%$  weight loss; while long-term weight loss  $\geq 5\%$  remains a clinically meaningful outcome, the recommendation to use it as a categorical primary efficacy endpoint has been removed in favor of responder analyses at higher thresholds. [Medpace](#) The FDA's updated benchmark is a statistically significant difference between drug and placebo groups of  $5\%$  sustained weight loss after one year of treatment. [Patient Care Online](#)

**Beyond-weight endpoints** are increasingly important. Secondary endpoints now commonly include lipid profile, blood pressure, hemoglobin A1c, fasting plasma glucose, mental health, serious adverse events, quality of life, cardiovascular morbidity and mortality, and remission of obesity-related comorbidities. [Nature](#) The landmark SELECT trial, for example, established semaglutide as the first obesity medication to demonstrate a  $20\%$  reduction in major adverse cardiovascular events, a benefit that occurred independently of weight loss. [NCBI](#) Lilly's retatrutide TRIUMPH-4 trial used co-primary endpoints of weight reduction and pain reduction in knee osteoarthritis at 68 weeks. [Eli Lilly and Company](#)

**Estimand frameworks** have also become standard. Most recent trials report two estimands: an "efficacy estimand" (results assuming all participants stayed on treatment) and a "treatment-regimen estimand" (results regardless of adherence or dropout), giving regulators and clinicians both an efficacy ceiling and a real-world estimate.

## How VK2735 Compares

VK2735 is Viking Therapeutics' dual GLP-1/GIP receptor agonist, being developed in both subcutaneous and oral formulations. Here's how it lines up:

**Endpoint alignment.** The Phase 2 VENTURE-Oral trial used percent change in body weight from baseline after 13 weeks as its primary endpoint, with secondary and exploratory endpoints evaluating additional safety and efficacy measures. [Vikingtherapeutics](#) The Phase 3 VANQUISH-1 trial uses percent change in body weight from baseline at 78 weeks as its primary endpoint, with secondary endpoints including the percentage of patients achieving  $\geq 5\%$ ,  $\geq 10\%$ ,  $\geq 15\%$ , and  $\geq 20\%$  body weight reduction. [PR Newswire](#) This structure closely mirrors the tirzepatide (SURMOUNT) and semaglutide (STEP/OASIS) programs and aligns with the 2025 FDA guidance.

**Phase 2 efficacy signals.** In the subcutaneous Phase 2 VENTURE trial, patients receiving weekly VK2735 demonstrated weight reductions of up to  $14.7\%$  from baseline after just 13 weeks, with no plateau observed. [Viking Therapeutics](#) On the key secondary endpoint,  $88\%$  of patients achieved  $\geq 10\%$  weight loss, compared to  $4\%$  on placebo. [PharmExec](#) The oral tablet formulation showed up to  $12.2\%$  mean weight loss at 13 weeks, with up to  $97\%$  of treated participants achieving  $\geq 5\%$  weight loss and up to  $80\%$  achieving  $\geq 10\%$  weight loss. [Applied Clinical Trials Online](#)

**How the numbers compare at cross-trial level** (acknowledging differences in duration, dose, and population):

Program	Duration	Max Mean Weight Loss
Semaglutide SC (STEP 1)	68 weeks	$\sim 15\%$
Oral semaglutide 25 mg (OASIS 4)	64 weeks	$\sim 16.6\%$ (efficacy estimand)
Tirzepatide (SURMOUNT-1)	72 weeks	$\sim 20.9\%$
Retatrutide (TRIUMPH-4)	68 weeks	$\sim 28.7\%$
VK2735 SC (VENTURE Ph2)	13 weeks	$\sim 14.7\%$ (no plateau)
VK2735 oral (VENTURE-Oral Ph2)	13 weeks	$\sim 12.2\%$ (no plateau)
Orforglipron (ATTAIN-1)	72 weeks	$\sim 12.4\%$

The VK2735 13-week data are notable because weight loss curves were still progressing without plateau, suggesting the 78-week Phase 3 results could be substantially higher. That said, the Phase 3 data don't exist yet — VANQUISH-1 enrollment completed in November 2025 [PR Newswire](#) and VANQUISH-2 enrollment completed in March 2026. [PR Newswire](#)

**Key differentiators and open questions for VK2735:**

The oral formulation's 12.2% weight loss at 13 weeks is rapid, but the 28% dropout rate among patients receiving VK2735 in the oral Phase 2 trial raised investor concern. [Ddw-online](#) Viking has framed an oral-to-oral maintenance dose-reduction strategy as a potential advantage, and an exploratory maintenance arm in the oral Phase 2 showed positive proof of concept. [Vikingtherapeutics](#) VK2735 does not yet have cardiovascular outcomes data, MASH data, or comorbidity-specific endpoints (sleep apnea, osteoarthritis) the way the more mature semaglutide, tirzepatide, and retatrutide programs do. Those additional endpoints are increasingly what differentiate drugs in the regulatory and commercial landscape.

In short, VK2735's Phase 2 weight-loss velocity is competitive with or ahead of where the leading programs were at equivalent timepoints, and its Phase 3 endpoint design is well-aligned with current FDA expectations. The key unknowns are long-duration efficacy, tolerability at scale, and whether Viking will pursue the beyond-weight-loss endpoints (cardiovascular, metabolic) that have become differentiators for the established players.

▼ AXL

## VK2735 vs. Proven Obesity Trial Endpoint Standards

### Endpoint Patterns in Successful Obesity Trials

The obesity field has converged on a remarkably consistent primary endpoint standard: **percent change in body weight from baseline** measured at a fixed timepoint. This applies across nearly all late-phase programs that have generated successful results. What varies is the timepoint (13 weeks in Phase 2, 52–84+ weeks in Phase 3) and secondary endpoint breadth.

The high-profile successful readouts in the dataset illustrate the pattern clearly:

**Orforglipron (Eli Lilly, [NCT05872620](#) — Phase 3, [ATTAIN-2](#)):** Primary endpoint was percent change in body weight at 72 weeks. Met with orforglipron 36mg producing -10.5% vs. -2.2% placebo. Secondary endpoints included A1C reductions and cardiometabolic markers. The trial then followed up with a maintenance study ([NCT06584916](#), [ATTAIN-MAINTAIN](#)) where the primary endpoint shifted to *maintenance* of body weight reduction at 52 weeks — a newer endpoint structure designed to differentiate drugs in a crowded market.

**Bivamelagon (Rhythm Pharmaceuticals, [NCT06046443](#) — Phase 2, [hypothalamic obesity](#)):** Primary endpoint was mean percent BMI reduction at Week 14. Achieved -9.3% at 600mg vs. +2.2% on placebo.

**VTX3232 (Ventyx/Zomagen, [NCT06771115](#) — Phase 2, [obesity + CV risk](#)):** Primary endpoint was a *safety* endpoint (AEs comparable to placebo) — a different design philosophy suited to testing a novel mechanism with efficacy as exploratory. Statistically significant reductions in hsCRP (~80%) and IL-6 were secondary signals.

**Key failure for comparison — TERN-601 (Terns, [NCT06854952](#)):** Primary endpoint was percent change in body weight at 12 weeks. Maximum placebo-adjusted weight loss of only 4.6% at the highest dose. Company halted development. Safety signals (12% discontinuation for AEs, three Grade 3 liver enzyme elevations) compounded the efficacy shortfall.

**CagriSema (Novo Nordisk, [NCT06131437](#) — Phase 3):** Primary endpoint was non-inferiority on percent weight change at 84 weeks vs. tirzepatide. Failed — a cautionary example of an ambitious non-inferiority design against a strong active comparator rather than placebo.

#### The standard pattern for regulatory success:

- Primary: Mean percent change in body weight from baseline (placebo-controlled)
- Secondary: Proportion achieving  $\geq 5\%$  weight loss; proportion achieving  $\geq 10\%$  weight loss; waist circumference; cardiometabolic parameters (BP, lipids, A1C if diabetic population)
- Duration: 52–72 weeks for Phase 3 (the FDA has consistently expected this timeframe for full weight loss assessment)

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### VK2735 Trial Design and Endpoints

Viking has three meaningful trials to evaluate:

**NCT06068946 — VENTURE (Phase 2, subcutaneous, completed)**

- Primary: Percent change from baseline in body weight at Week 13
- Enrollment: 176 (actual)
- Status: Completed
- Result: Met primary endpoint — up to 14.7% mean weight loss from baseline, up to 13.1% placebo-adjusted at Week 13. All secondary endpoints also met. Safety: mostly mild/moderate GI AEs, consistent with GLP-1/GIP dual agonist class.
- Note: The registry shows an enrollment target increase of 40.8% (125 → 176) during the trial — a signal that merited monitoring at the time, though the trial ultimately completed successfully.

**NCT06828055 — VENTURE-Oral (Phase 2, oral formulation, completed)**

- Primary: Percent change from baseline in body weight after 13 weeks
- Enrollment: 280 (actual)
- Status: Completed; data readout August 19, 2025
- Result: Met primary endpoint — up to 12.2% mean weight loss (vs. 1.3% placebo). Responder rates: ≥5% weight loss achieved by up to 97% of patients; ≥10% by up to 80%. Safety: favorable, mild/moderate GI AEs; note that one readout event flagged "high\_dropout" as a red flag — this warrants attention in Phase 3 design for the oral formulation.
- Viking held an End-of-Phase 2 FDA meeting and plans to initiate oral Phase 3 in 3Q26.

**NCT07104500 — VANQUISH-1 (Phase 3, subcutaneous, registrational, active not recruiting)**

- Acronym: VANQUISH-1
- Primary: Percentage change in body weight from baseline after **78 weeks** of treatment
- Enrollment target: 4,500 (anticipated)
- Sites: 137 (US only)
- Status: Active, not recruiting; primary completion target July 2027
- Operational risk: Low (score: 0); landscape risk: moderate (score: 46)
- Registrational: Yes

**Head-to-Head Comparison: VK2735 vs. Proven Endpoint Standards**

Dimension	Successful Precedents	VK2735 Phase 2	VK2735 Phase 3 (VANQUISH-1)
Primary endpoint	% body weight change from baseline	% body weight change from baseline	% body weight change from baseline
Timepoint (Ph2)	12–16 weeks	13 weeks	—
Timepoint (Ph3)	52–84 weeks	—	78 weeks
Responder endpoints	≥5%, ≥10% weight loss rates	Both reported (up to 97% / 80%)	Registry silent; likely pre-specified
Comparator	Placebo-controlled	Placebo-controlled	Placebo-controlled
Trial duration benchmark	~687 days median for GLP-1R obesity trials	~175 days	~760 days (on track)
Enrollment scale	~500–3,000+ in Phase 3	176 (Ph2 SQ) / 280 (Ph2 oral)	4,500 (ambitious)
Mechanism	GLP-1/GIP dual agonist predominates	GLP-1/GIP dual agonist	GLP-1/GIP dual agonist
Diabetics excluded	Tirzepatide programs included T2D separately	Yes (excluded)	Yes (excluded)

**VK2735's endpoint architecture is squarely aligned with the proven regulatory playbook.** The Phase 3 primary endpoint — percent body weight change at 78 weeks — closely mirrors Lilly's successful ATTAIN-2 structure (72 weeks) and falls within the FDA-accepted window. The choice of 78 weeks (vs. 52 or 84) is slightly longer than the minimum but shorter than the most ambitious Phase 3 timelines, suggesting a balanced approach.

The Phase 2 results are genuinely strong: 14.7% mean weight loss (SQ) and 12.2% (oral) at 13 weeks compare favorably against tirzepatide's Phase 2 data and semaglutide's Phase 2 benchmarks. The placebo-adjusted SQ figure of 13.1% is competitive with what ultimately drove tirzepatide's Phase 3 success.

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## Competitive and Regulatory Context

The GLP-1R / Obesity landscape has 96 active trials across 62 unique sponsors, with a 4% Phase 2 failure rate for the GLP-1 Receptor x Obesity pair — among the lowest in the space. VK2735 operates in genuinely favorable scientific territory by this measure. The field shows a declining activity ratio (recent vs. older trial ratio of 0.22), which is consistent with the market maturing around established leaders; this actually helps VK2735 if it can reach market before the window narrows further.

The primary competitive pressure is magnitude of weight loss. Tirzepatide achieved ~22% weight loss in its pivotal SURMOUNT-1 trial; retatrutide (triple agonist) showed up to 24% in Phase 2. VK2735's Phase 2 SQ data of 14.7% at 13 weeks is promising for a 13-week Phase 2, but the field's Phase 3 bar is now set by tirzepatide's 52-week results. Whether VK2735's weight loss magnitude can approach or exceed those benchmarks at 78 weeks is the central scientific question — one the registry data alone cannot answer.

The oral formulation is the more differentiated strategic asset. Orforglipron (Lilly) is now in Phase 3 with oral data (ATTAIN-2: -10.5% at 72 weeks), providing a direct comparator. VK2735 oral's Phase 2 result of -12.2% at 13 weeks is encouraging but comparisons across timepoints and study designs are imprecise.

**One operational flag to monitor:** The VENTURE Phase 2 SQ trial showed a 40.8% enrollment target increase (125 → 176) during execution. This was resolved without apparent consequence, but with VANQUISH-1 targeting 4,500 patients across 137 US-only sites, enrollment velocity will be a key watch variable. US-only site concentration is a constraint — most large obesity trials use multi-country sites to accelerate enrollment. The current registry shows the trial is "active, not recruiting," suggesting enrollment has already closed, which removes near-term enrollment risk for VANQUISH-1 specifically.

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## Key Takeaways and Risk Assessment

**Alignment with proven standards:** High. VK2735's endpoint design — percent body weight change from baseline at 78 weeks (Phase 3), placebo-controlled, GLP-1/GIP dual mechanism — follows the established regulatory template precisely. No novel endpoints, no non-inferiority designs against active comparators, no modified populations. This reduces regulatory execution risk.

**Phase 2 efficacy signal:** Strong. The 14.7% SQ weight loss and 12.2% oral weight loss at 13 weeks place VK2735 in the competitive tier, though the translation to 78-week Phase 3 weight loss magnitude remains the key unknown.

**Operational health (VANQUISH-1):** Low operational stress (score: 0). Enrollment appears complete. Primary completion July 2027. No behavioral distress signals in the registry.

**The oral program is the strategic differentiator:** Phase 3 initiation for oral VK2735 planned for 3Q26 per FDA end-of-Phase 2 feedback. If the oral formulation can replicate or exceed its Phase 2 signal at longer durations, it offers genuine differentiation from semaglutide in a market where patient preference increasingly favors oral dosing.

**Key risk:** The obesity Phase 3 market now has tirzepatide as the efficacy benchmark. VK2735 needs to demonstrate competitive weight loss magnitude — not just a clean endpoint design — to carve out commercial space. That is a scientific and clinical question the behavioral data cannot resolve in advance.

### ▼ ChatGPT

Here's a clear breakdown of the **endpoints used in successful obesity drug trials** (those that led to FDA approval or strong phase 3 success) and how **VK2735's endpoints/results compare** based on the available clinical data:

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## 1. Typical Endpoints in Successful Obesity Drug Trials

### A. Primary Endpoints

Most modern obesity drug trials are designed to demonstrate clinically meaningful weight loss. The primary endpoint commonly used is:

- **Percent change in body weight from baseline to a predefined time point**
  - Example: *Percent change in body weight at Week 72 for tirzepatide* in SURMOUNT-1/-3 trials.
  - Example: *Percent change in body weight at Week 68 for the cagrilintide + semaglutide combination* in phase 3 REDEFINE studies.

This measure captures the overall efficacy of the drug in reducing weight over long-term treatment.

### B. Key Secondary Endpoints

Secondary endpoints in successful obesity trials frequently include:

- **Proportion of participants achieving categorical weight loss thresholds, e.g.:**
  - $\geq 5\%$  weight loss
  - $\geq 10\%$  weight loss
  - $\geq 15\%$ ,  $\geq 20\%$ ,  $\geq 25\%$  weight loss

These thresholds are clinically relevant because larger percent losses are associated with greater improvements in cardiometabolic risk factors and clinical outcomes.

- **Waist circumference reduction** (a surrogate for central adiposity and metabolic risk)
- **Quality-of-life measures** and other metabolic parameters (glycemic control, blood pressure, lipids)

### C. Long-Term and Cardiometabolic Endpoints (Exploratory in Some Trials)

- Some trials also integrate *cardiovascular outcome measures* or risk reductions, particularly in diabetes populations (e.g., major adverse CV events).

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## 2. VK2735 Trial Endpoints

### Phase 2 VENTURE Study (Subcutaneous VK2735)

In the Phase 2 VENTURE obesity trial evaluating injectable VK2735:

#### Primary Endpoint

- **Percent change from baseline in body weight at Week 13** — standard efficacy measure for early obesity studies.

#### Key Secondary Endpoints

- **Proportion of participants achieving  $\geq 5\%$  weight loss at Week 13**
- **Proportion achieving  $\geq 10\%$  weight loss at Week 13**
  - These are exactly the categorical thresholds used in many registrational studies.

#### Exploratory Endpoints (reported in full publication)

- *Proportion achieving  $\geq 15\%$  weight loss*
- Cardiometabolic assessments (HbA1c/FPG, etc.).

### Phase 3 VANQUISH Program

Ongoing Phase 3 studies of VK2735 are using **longer treatment durations (78 weeks)** with similar endpoints to those in successful registrational trials:

#### Primary Endpoint

- **Percentage change in body weight from baseline at 78 weeks** — aligning with long-term efficacy standards for obesity drugs.

#### Key Secondary Endpoints

- Proportions achieving **≥5%, ≥10%, ≥15%, and ≥20% weight loss** — these mirror the categories used in trials like SURMOUNT and REDEFINE.

### 3. How VK2735's Results Compare to Successful Trials

#### A. Short-Term (Phase 2) Results

- In the 13-week VENTURE study, VK2735 achieved up to **~14.7% mean weight loss** at the highest dose vs ~1.7% with placebo.
- **≥5% and ≥10% weight loss:** very high proportions achieved these thresholds (e.g., ~93% hitting ≥5%).

#### Compared with other mid-stage candidates:

- These 13-week results are **impressive for a short-duration trial**; many approved drugs demonstrate similar or even greater percentages but over longer (52–72+ week) periods.

#### B. Phase 3 Expectations

- For reference, *tirzepatide* in major phase 3 trials yielded ~15–20%+ weight loss at ~72+ weeks, with high proportions achieving ≥10–15% and even ≥20%.
- *CagriSema (cagrilintide + semaglutide)* showed ~20% weight loss at 68 weeks.

VK2735 is now being evaluated over similar long-term endpoints, which will be crucial for ultimate regulatory comparison:

✓ VK2735's Phase 3 **primary endpoint** (78-week percent weight change) mirrors what has *worked* for currently successful programs.

✓ Its **secondary endpoints** (≥5–20% categories) align with established clinical relevance thresholds.

### Summary

Trial Type	Common Primary Endpoint	Common Secondary Endpoints
Successful obesity registrational trials (e.g., tirzepatide, semaglutide combos)	Percent change in body weight at long term (68–72+ weeks)	% ≥5%, ≥10%, ≥15%, ≥20% weight loss; waist circumference; metabolic outcomes
VK2735 Phase 2	% change in body weight at 13 weeks	% ≥5% and ≥10% at 13 weeks
VK2735 Phase 3	% change in body weight at 78 weeks	% achieving ≥5%, ≥10%, ≥15%, ≥20%

If you'd like, I can also outline how these endpoints relate to **clinically meaningful outcomes** (e.g., cardiometabolic risk reduction) or draft a comparison table with specific studies like *SURMOUNT* and *REDEFINE*.

#### ▼ Perplexity

Successful obesity trials used consistent primary endpoints centered on **percentage body weight reduction and categorical weight loss thresholds**. The FDA-approved standard involves measuring percent change in body weight from baseline at a defined timepoint (typically 72 weeks for phase 3 trials) and assessing the proportion of patients achieving clinically meaningful milestones like ≥5% and ≥10% weight loss.

### Standard Trial Endpoints

The benchmark trials for approved obesity drugs used these primary endpoints:

- **Percent change in body weight from baseline** at week 72 (co-primary)
- **Proportion achieving ≥5% weight reduction** (co-primary threshold)
- **Secondary outcomes:** ≥10% and ≥20% weight loss categories, waist circumference reduction, and improvements in metabolic markers

**Tirzepatide (SURMOUNT-1)** demonstrated: 15-21% mean body weight reduction, with 85-91% of patients achieving  $\geq 5\%$  loss and 30-57% achieving  $\geq 20\%$  loss.

**Semaglutide** showed 6.6-8.6% weight loss at 56 weeks in earlier trials (CONQUER/SEQUEL), with 62-70% of participants achieving  $\geq 5\%$  loss.

## VK2735 Endpoints and Comparative Performance

VK2735 used the same primary endpoint framework: **percent change in body weight at week 13** and **proportion achieving  $\geq 5\%$  and  $\geq 10\%$  weight loss**.

### VK2735 Phase 2 results (VENTURE-Oral):

- Mean weight loss: **up to 12.2%** at 13 weeks
- $\geq 5\%$  weight loss: **97%** of patients
- $\geq 10\%$  weight loss: **80%** of patients

**Key comparison:** VK2735's 12.2% weight loss at 13 weeks appears competitive on an annualized basis, but fell **below tirzepatide's 20.9% and semaglutide's established benchmarks** when considering tirzepatide achieved 20.9% over 72 weeks (roughly 20.7% annualized).

## Evolving Regulatory Landscape

Notably, obesity trial endpoints are shifting beyond weight alone. The FDA's January 2025 guidance now emphasizes **patient-reported outcomes (PROs) including quality of life, physical function, mental health, and even body composition (lean mass preservation)**—addressing concerns that GLP-1 agonists cause muscle loss. VK2735 trial data on these broader endpoints would strengthen its competitive positioning.