PORTFOLIO — DOOR 1

ADUHELM
(ADUCANUMAB)

Biogen/Eisai | Anti-Amyloid Monoclonal Antibody | Alzheimer's Disease
Phase III | EMERGE + ENGAGE | Accelerated Approval June 2021

Independence is not a ceremonial concept.
It is an active structural condition that must be continuously protected from human convergence.

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01. The Verdict

Independence is not a ceremonial concept. It is an active structural condition that must be continuously protected from human convergence.

That is the sentence this entire document rests on.

Not: the science was bad. Not: the people were corrupt. Not: Alzheimer's research is hopeless. The science was real. The people were not corrupt. None of that is the story.

The story is that a governance system, designed specifically to protect independent evidence evaluation, quietly allowed independence to become optional. And once it became optional, the system began producing something that looked like science and behaved like negotiation.

> *You might be wondering why this trial specifically.*

Because Aduhelm is the case study that reveals what happens when institutional pressure, emotional desperation, and governance ambiguity occupy the same room at the same time. The drug reduced amyloid plaques. But biological activity and meaningful clinical benefit are not automatically the same thing, and the moment that distinction became inconvenient, the governance structures designed to protect it began to bend.

> **A building can pass site inspection while its foundation is already compromised. The inspection measures what it was designed to measure. It does not measure what it was not designed to look for.**

My argument is not that the drug should have failed. My argument is that the system could not tell the difference between *evidence of benefit* and *evidence that benefit was still possible.* Those are not the same thing. And in Alzheimer's drug development, confusing them cost more than a trial.

02. What Happened

Aducanumab was designed to be the first disease-modifying therapy for Alzheimer's disease, not symptom management, but actual slowing of cognitive decline through amyloid-beta plaque clearance. The amyloid cascade hypothesis had dominated the field for two decades, surviving a trail of failed anti-amyloid drugs that should have prompted more structural doubt than they did.

Two Phase III trials launched simultaneously: EMERGE and ENGAGE. Identical design. Identical population, early Alzheimer's disease, mild cognitive impairment due to AD, mild AD dementia. Primary endpoint: change in Clinical Dementia Rating-Sum of Boxes (CDR-SB) at 18 months. The CDR-SB measures actual clinical and functional decline. Not a biomarker. Not a proxy. The thing itself.

Date	Event
March 2019	Independent DMC reviewed interim analysis. Both trials: <20% probability of success. Futility recommended. Biogen halted both trials.
October 2019	Biogen reversed. Claimed "analytical error." Revised EMERGE dataset showed high-dose subgroup benefit. ENGAGE showed no signal. DMC not reconvened.
Nov 2019 — Nov 2020	115+ meetings, calls, and email exchanges between FDA and Biogen over 12 months. 66 additional unrecorded exchanges identified by Congressional staff, not by FDA.
November 2020	FDA Advisory Committee: 11 members. 10 voted against approval. 1 uncertain. 0 in favour.
June 2021	FDA granted accelerated approval based on amyloid reduction surrogate endpoint not on the failed clinical endpoint.
Post-Approval	3 FDA committee members resigned. CMS restricted coverage to clinical trial participants only. Congressional investigation launched. DOJ investigation opened. EU application withdrawn.

Trial	Primary Endpoint	High-Dose Subgroup	Regulatory Use
EMERGE	Failed (CDR-SB)	"Positive" in post-hoc high-dose subgroup	Biogen submitted as primary evidence
ENGAGE	Failed (CDR-SB)	Failed in high-dose subgroup	Absent from approval narrative
Combined	No significant clinical benefit	Amyloid reduction consistent	Surrogate accepted for accelerated approval

You might be thinking: this sounds like corruption.

It was not corruption. That is what makes it more dangerous than corruption. Corruption has a solution: remove the corrupt actor. What happened here was structural, a governance architecture that could not protect its own principles under the weight of what was riding on the decision.

03. Where It Broke

> **This is where we stop reading the congressional report and start reading the collaboration architecture.**

The verdict is short: **the replacement of independent judgment with negotiated narrative.**

Not five separate scandals. One governance mode expressing itself five ways. Every crack below is that mode finding another surface to move through.

Crack One - The Post-Hoc Salvage as Governance Failure

Biogen's October 2019 reversal claimed an analytical error in the initial futility dataset. A larger dataset from EMERGE showed high-dose benefit the interim analysis had missed.

The structural question is not whether the data changed. The structural question is: *who verified it?*

The answer: nobody independent. The DMC that recommended futility was not reconvened. No third-party biostatistical review of the original and revised datasets was published or submitted. The high-dose subgroup emerged from sponsor-controlled data re-examination, not from pre-specified analysis. ENGAGE - the sister trial with identical design, showed no corresponding signal in any subgroup.

The governance system allowed a sponsor to self-correct a DMC decision without independent verification. The DMC's authority was advisory, not binding, and the sponsor treated it as optional.

> **Who independently verified this reinterpretation before momentum restarted? Nobody was assigned to look.**

> *You might be wondering: isn't sponsor re-analysis permitted under GCP?*

Exploratory re-analysis is permitted. Using it as the primary evidence base for a regulatory submission after the pre-specified analysis failed is something different. The system had no mechanism to distinguish between a genuine analytical correction and a search for a defensible result.

That distinction, between *finding a real signal* and *finding a signal that can still be defended*, is exactly where the crack formed. Because once a team stops asking "Is this true?" and starts asking "Can this still be defended?", the skeleton has already started cracking. The question just changed. Quietly. Without anyone deciding to change it.

Crack Two. The FDA-Biogen Collaboration as Firewall Collapse

115 meetings in 12 months. 66 unrecorded. Joint briefing documents drafted by FDA staff.

Institutions call this kind of closeness efficiency. The correct name for it is the systematic removal of productive friction. Sometimes friction is protective.

Standard regulatory interaction has a structure for a reason: sponsor submits data, FDA reviews independently, advisory committee provides external expert opinion, FDA decides. Each step preserves a layer of separation between the party seeking approval and the party granting it. That separation is not bureaucratic inconvenience. It is the structural guarantee that independent evidence evaluation is actually occurring.

The House Committee on Oversight and Reform's investigation, 18 months, 500,000 pages of internal FDA and Biogen documents, found something that should have been impossible to find: FDA admitted it could not reconstruct the full record of its interactions with Biogen because it lacked a clear record of informal interactions. A regulatory agency, whose entire institutional function is documentation integrity, did not document its own decision-making process.

> **The most dangerous breaches look like efficiency.**

By the time the advisory committee convened, the approval pathway had already been chosen. The committee's vote on clinical efficacy was rendered structurally irrelevant, not by ignoring their advice, but by designing a question they were not asked to answer. This is more than ignoring advice. It is making meaningful advice structurally impossible to give.

> *You might be wondering: is this a problem unique to Aduhelm?*

No. It is a problem unique to what happens when emotional desperation about an unmet need meets governance ambiguity about what independence actually requires. My concern is not the existence of pressure. My concern is that systems still behave as though human emotional distortion is removable rather than manageable.

> **Systems under emotional pressure should become more independently verified, not more collaboratively blended.**

Cracks Three, Four, and Five. The Pattern Completing Itself

Crack Three. FDA approved on amyloid reduction as a surrogate endpoint after the clinical endpoint (CDR-SB) failed. Decades of anti-amyloid drug failures had already raised serious doubts about whether amyloid reduction predicts cognitive benefit. The surrogate and clinical endpoints were divorced not correlated. The approval treated a biomarker as evidence in the same trial that tested and disconfirmed its predictive validity.

Crack Four. The advisory committee was not overruled. It was structurally disempowered. The approval pathway had been pre-constructed around amyloid reduction before the committee convened. Their vote on clinical efficacy, 10 against, 0 for, was advisory on a question the approval pathway again, did not require them to answer. Making meaningful advice structurally impossible to give.

Crack Five. The post-approval collapse was the system working. When internal governance cannot correct itself, external correction arrives, from payers, from clinicians, from the scientific community, from Congress. CMS, the resignations, the investigations, Biogen's EU withdrawal: not as failures but as the consequence of a governance failure that the approval structure was not designed to catch or absorb internally.

Five cracks. One foundation. One direction of failure.

04. What I Built

Where KEYNOTE-991 needed more patience, Aduhelm needed stronger restraint. Different trials. Different failures. Same root: structures that could not hold under human pressure.

My intervention does not redesign the FDA. It does not replace the DMC. It does not decide what constitutes sufficient evidence. It builds the structural conditions under which independent evidence evaluation can actually occur, and stay intact, under pressure.

The Independent Evidence Integrity Unit (IEIU)

The IEIU is a firewalled governance function, independent of sponsor, regulator, and DMC, responsible for protecting interpretive independence throughout the trial and approval process.

The IEIU Does	The IEIU Does Not
Triggers independent audits on sponsor-claimed analytical corrections	Does not replace the FDA
Enforces transparent documentation of all sponsor-regulator interactions	Does not override scientific conclusions
Preserves firewall conditions between sponsor and regulator staff	Does not make approval decisions
Protects DMC independence from unilateral sponsor override	Does not decide what constitutes sufficient evidence
Escalates interpretive conflict to advisory committee with full visibility	Does not eliminate human judgment

Its purpose is to protect the conditions under which truth can be evaluated without institutional convergence replacing it. It is the structural answer to one question Aduhelm left permanently open:

> **Who was assigned to look underneath?**

Intervention A - DMC Governance Lock

Owns Crack One

Element	Standard Design (Aduhelm)	Locked Design
DMC authority	Advisory — sponsor may override	Binding on futility — sponsor may not unilaterally resume after DMC halt
Post-hoc subgroup analysis	Permitted for exploratory claims	Prohibited as primary evidence — requires SAP pre-specification and independent review

Analytical error claims	Self-reported by sponsor	Mandated independent IEIU audit before any regulatory submission
DMC reconvening	Optional, sponsor-controlled	Mandatory — within 30 days of any sponsor request to revisit prior recommendation

DMC Charter Amendment:

> *"Following any recommendation for trial discontinuation due to futility, the sponsor shall not resume, amend, or reanalyze trial data without reconvening the original independent DMC within 30 days. Any claim of analytical error, dataset revision, or subgroup emergence shall be submitted to the Independent Evidence Integrity Unit for third-party biostatistical audit — firewalled from both sponsor and regulator — prior to any regulatory submission. The DMC's futility recommendation is binding unless overturned by the reconvened DMC itself, not by sponsor initiative. Post-hoc subgroup analyses shall not serve as primary evidence in regulatory submissions absent pre-specification in the Statistical Analysis Plan."*
>
> *Regulatory anchor: ICH E6(R2) §5.19 — DMC independence and charter requirements. ICH E9 Statistical Principles — pre-specification requirements for primary and subgroup analyses. FDA Adaptive Designs Guidance (2019) — post-hoc analysis limitations. 21 CFR 312.32 — IND safety reporting and DMC interaction requirements.*

Why this works: it removes the unilateral sponsor override that allowed Biogen to search for a different answer after the DMC said no. The third-party IEIU verification layer currently does not exist in GCP. This makes it mandatory, not assumed.

Intervention B - Sponsor-Regulator Interaction Audit Trail

Owns Crack Two

Element	Standard Design (Aduhelm)	Audited Design
Meeting documentation	Sponsor logs and regulator logs, optional	Unified mandatory log, all interactions in shared IEIU-audited system
Document authorship	Sponsor drafts, regulator reviews	Paragraph-level authorship attribution, visible to advisory committee before vote
Unrecorded meetings	Permitted for informal consultation	Prohibited — all substantive discussions on approval pathway or endpoint strategy must be recorded
Joint drafting	FDA staff may assist sponsor documents	Firewalled — regulator staff shall not draft sponsor submissions
Advisory committee transparency	Committee sees sponsor-submitted documents	Committee sees full interaction log and authorship chain, not less than 14 days before vote

Regulatory Compliance Protocol:

> *"All sponsor-regulator interactions on approval strategy, endpoint selection, or statistical methodology shall be documented in a unified electronic system with timestamp, participant list, and substantive summary. No substantive discussion shall occur outside this system. All briefing documents shall carry paragraph-level authorship attribution. The advisory committee shall receive the complete interaction log and authorship chain as part of its briefing materials, not less than 14 days before the scheduled vote. FDA staff shall not draft, revise, or approve sponsor-submitted documents; sponsor staff shall not draft, revise, or approve FDA internal briefing materials. The IEIU shall conduct quarterly compliance audits and report directly to the advisory committee chair. Violation is documented as a regulatory compliance deviation with mandatory disclosure."*
>
> *Regulatory anchor: ICH E6(R2) §5.18 — sponsor and investigator communication requirements. ICH E6(R2) §5.0 — quality management and oversight obligations. FDA Guidance: Formal Meetings Between FDA and Sponsors (2017) — meeting documentation standards. 21 CFR 314.102 — communications with FDA during review. PDUFA commitments on advisory committee transparency.*

Why this works: it makes the collaboration visible before the advisory committee votes, not after a congressional investigation. The 66 unrecorded meetings were found by Committee staff reviewing 500,000 documents eighteen months after approval. This protocol makes concealment structurally impossible rather than retrospectively discoverable.

05. Why I Am Confident

The strongest systems in the world already solved this problem.

Aviation, cybersecurity, nuclear operations, intelligence work, pharmacovigilance. Every high-stakes system that cannot afford interpretation failure operates under one assumption: humans will distort, fatigue, rationalise, and overcommit under pressure. Therefore they build redundancies, adversarial review, escalation triggers, independent oversight, distributed interpretation, and structured dissent.

Clinical trial governance does not yet operate under that assumption. It operates under the assumption that procedural compliance, having a DMC, holding advisory committee meetings, filing meeting minutes, is equivalent to structural independence. Aduhelm demonstrated that it is not.

I am not proposing innovation. I am proposing that clinical trial governance adopt an assumption that aviation adopted decades ago: humans inside high-pressure systems will converge toward shared narratives, and the system must be designed to resist that convergence rather than accommodate it.

The IEIU does not eliminate human judgment. It protects the conditions under which human judgment can be exercised without institutional momentum replacing it. My confidence is not in having invented something new. It is in following the logic of existing governance principles to their necessary operational conclusion.

06. A Final Word

You might be wondering why I did this.

To impress you? Maybe. Ego? Probably.

But there is something underneath that matters more than either of those.

This trial disturbed me in a way KEYNOTE-991 did not. KEYNOTE disturbed my analytical instincts. Aduhelm disturbed something closer to a moral instinct, the part of my cognition that cannot tolerate watching a question quietly change shape while everyone pretends it remained the same.

"Is this true?" becoming "Can this still be defended?", that shift happens in rooms I will one day sit in. It happens gradually, under pressure, with reasonable people who are not doing anything they would call dishonest. That is not a reason to despair about institutions. It is a reason to design them better.

The CRA who sits in that monitoring visit, who verifies the source data, who flags the protocol deviation, who maintains the audit trail, is one of the few people in that system whose job is to see what is actually there, not what the narrative requires to be there. That role matters more than it is credited for.

The instinct to look underneath is what I am building a career on.

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