Understanding key differences among the current and emerging Alzheimer's clinical trials in Down syndrome

FEBRUARY 2025

People with Down syndrome face a heightened risk of developing Alzheimer's disease (AD) due to their unique genetic makeup. That makes them more vulnerable to early-onset AD and significantly increases their likelihood of developing AD in their lifetime, compared to the general population. While researchers have made progress in understanding the biological mechanisms underlying Alzheimer's, much remains to be learned about how to intervene effectively to protect brain health in this community. Today, multiple research efforts are underway to identify effective therapeutic approaches for individuals with Down syndrome, each targeting the problem in a distinct and specialized way.

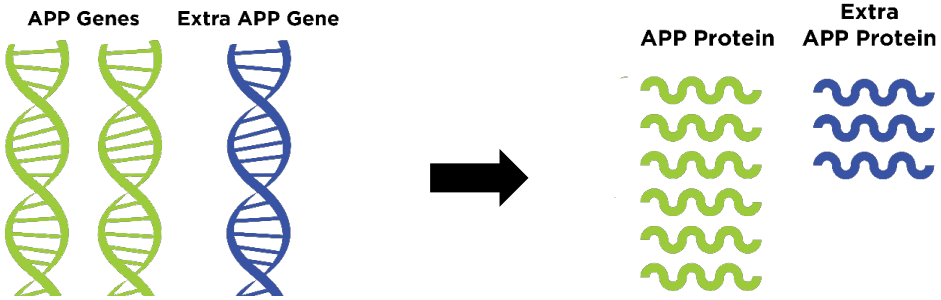
Understanding the differences among these new therapies is crucial—not only in terms of how they are meant to prevent or slow the progression of AD, but also in the drug delivery methods. Some therapies aim to address the problem at its source, while others focus on clearing existing damage. By exploring these nuances, caregivers and self-advocates can better appreciate the research underway and the steps scientists are taking to potentially improve outcomes for individuals with Down syndrome.

Why are adults with Down syndrome affected by Alzheimer's disease at such a high rate?

The answer can be found in the genetic makeup of most people with Down syndrome.

Every cell in the human body has a set of instructions ("genes") that tell cells how to make proteins—those tiny building blocks that help our bodies function properly. People with Down syndrome have an extra copy of a particular gene called the **APP gene** (illustrated by the blue helix below), which gives their bodies an extra set of instructions for making a protein called **amyloid precursor protein** (APP), a protein made in the brain that helps cells function normally.

Imagine a factory that typically handles two orders for APP, producing just enough to meet the body's needs. In people with Down syndrome, the factory gets three orders instead of two, causing it to overproduce APP—like an assembly line working overtime and creating a surplus of product (in blue in illustration below).



After APP is made, it naturally breaks down into smaller pieces. Some of those pieces are called amyloid beta (Aß, shown in red in the illustration).

In the brains of people without Down syndrome, extra or used Aß typically gets cleared away by the brain's natural cleanup systems. However, in the brains of people with Down syndrome, the overproduction of APP protein means that extra Aß is made starting at birth, which can overwhelm these brain cleanup systems.

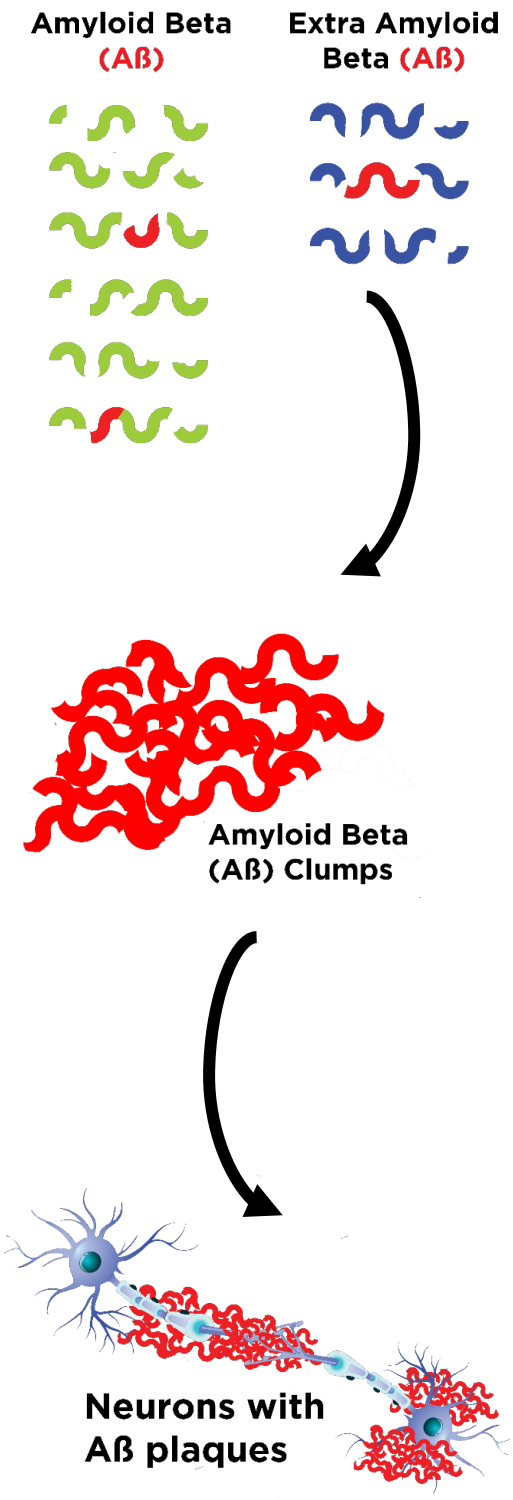
It's like the factory's assembly line is running so fast that too many parts pile up, and the janitors (the brain's cleanup system) can't keep up with the extra Aβ.

Some of these extra Aß pieces can misfold and begin to stick together into clumps (shown in red, at right). Once these clumps form, they act like sticky residue on the factory floor, making it harder for normal operations to continue.

The initial Aß clumps can grow into larger clumps that can eventually be seen by a microscope. The larger clumps are called Aß plaques (shown in red at right), which can start to build up around neurons, the cells in the brain that carry our thoughts and store our memories (shown in lavender at right).

When smaller clumps and plaques build up in the brain, they can start to interfere with memory and thinking, similar to how a factory with cluttered assembly lines and blocked pathways can't function effectively. This blockage can lead eventually to Alzheimer's disease.

People with Down syndrome are more prone to Aβ clumping, which is why they have a >90% lifetime risk of developing Alzheimer's dementia. As such, scientists are working hard to find ways to prevent these Aß clumps and plaques from forming or to remove them after they accumulate, in order to protect their brain health.



How do the different types of therapies intervene in the process of Ab clumping?

Researchers are currently investigating at least three types of therapies that address this buildup of Aß plaques. Each therapy seeks to intervene at different points in the plaque accumulation process, and each involves a different mechanism of intervention.

Antisense Oligonucleotides (ASOs)

Imagine a supervisor stepping in to slow down the factory's production line by cancelling the extra APP order. ASOs work at the genetic level to reduce the amount of APP protein produced, which is intended to lower the amount of Aß made. This subsequently may prevent excess Aß clumping and reduce plaque levels, which together may slow down disease progression.

To return to our analogy, the ASO helps ensure the factory doesn't generate an overwhelming surplus of components that could lead to assembly line clutter.

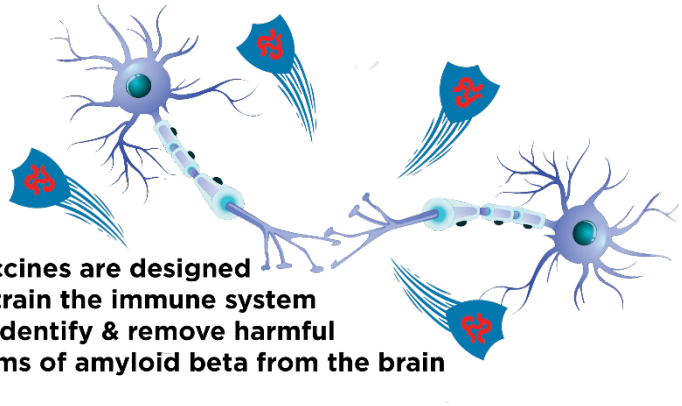
The HERO study, sponsored by Ionis Pharmaceuticals, is an active clinical trial studying the safety and tolerability of an ASO intervention. The mechanism Ionis is testing is administered into the spine (intrathecal), by lumbar puncture, which allows the ASO to be delivered directly to the brain via spinal fluid.

ASOs are designed to silence the extra gene that causes overproduction of APP

Vaccine Immunotherapies

Vaccines train the body's "security team" to patrol the factory floor, identifying and removing harmful Aß clumps and plaques. The security team inspects the assembly line for faulty parts and clears them out early, while also recognizing and breaking down larger blockages that have already formed. In this way, vaccines act as both preventative measures and cleanup crews.

The ABATE study, sponsored by AC Immune, is currently seeking to determine the safety, tolerability, immunogenicity, and effects of vaccine immunotherapy ACI-24.060 in adults



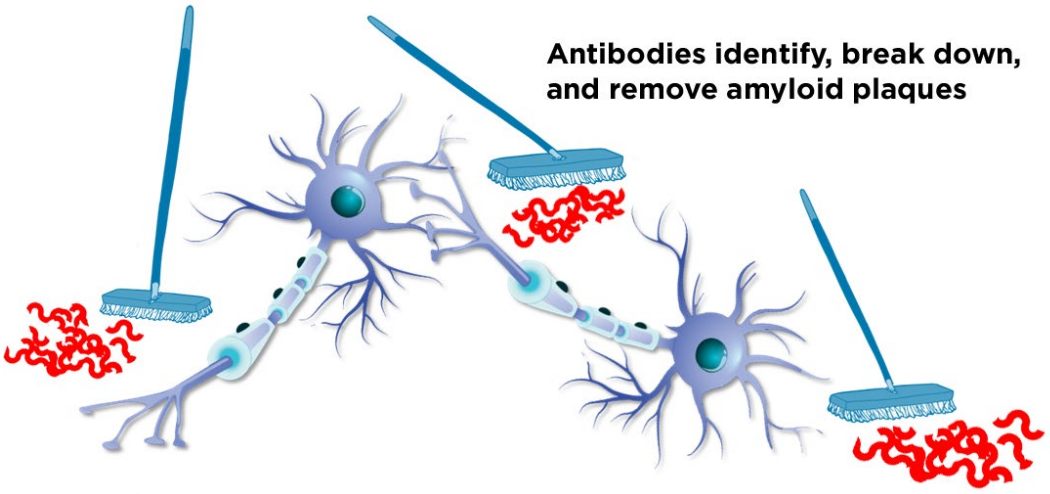
Vaccines are designed to train the immune system to identify & remove harmful forms of amyloid beta from the brain

with Down syndrome. This vaccine candidate is delivered, like any other vaccine, by injection into a muscle; the same way vaccines that protect against flu are administered.

Antibody Immunotherapies

Antibody treatments are like specialized “cleaning crews” that step in when harmful clumps of Aß plaques have already built up. These crews target the stubborn blockages, breaking them down and removing them from the factory floor, much like clearing a clogged assembly line to restore functionality.

Commercially known as Leqembi (sold by Eisai and Biogen) and Kisunla (sold by Lilly), anti-amyloid antibodies are currently approved by the FDA for use by neurotypical adults with early Alzheimer’s disease. The upcoming ALADDIN study will be the first investigation of the antibody Kisunla in a cohort of people with Down syndrome.



What’s next in the treatment of DS-AD?

These therapies are still being studied, and researchers are working to understand how effective and safe they are for people with Down syndrome-associated Alzheimer’s disease (DS-AD).

While the treatments show promise, it’s important to remember that the goal of these studies is to gather knowledge, not to promise immediate results or cures. Each study is a step toward better understanding how to support brain health in Down syndrome and prevent or delay Alzheimer's disease.

Families should always consult their loved one’s doctor when considering clinical research participation.

Next page: details on the current and anticipated clinical trials in DS-AD...

What are the differences in the current and upcoming clinical trials in Down syndrome-associated Alzheimer's disease?

	HERO Study	ABATE Study	ALADDIN Study
Study Sponsor	Ionis Pharmaceuticals	AC Immune	Alzheimer's Clinical Trials Consortium - Down Syndrome (ACTC-DS)
Therapy Being Investigated	ION269	ACI-24.060	Donanemab (Kisunla, by Lilly)
Type of Intervention	Antisense Oligonucleotide	Vaccine Immunotherapy	Antibody Immunotherapy
Aim of the Study	To evaluate the safety and tolerability of ION269 in adults with Down syndrome	To assess the safety, tolerability, immunogenicity, and pharmacodynamic effects of ACI-24.060 in adults with Down syndrome	To evaluate the safety, tolerability, and efficacy of Donanemab in adults with Down syndrome
Phase	Phase 1b	Phase 1b/2	Phase 4
Has this therapy been studied in Down syndrome previously?	No	No, but AC Immune conducted a Phase 1 study in Down syndrome with an earlier version of the vaccine	No, approved for treatment of early Alzheimer's disease but not tested in Down syndrome individuals yet
Is the study Placebo-Controlled?	No, not Placebo-Controlled	Yes, Placebo-Controlled	Yes, Placebo-Controlled
Method of Delivery	Lumbar Puncture	Intramuscular Injection	Intravenous Infusion
Enrollment Criteria	People with DS between ages of 35 and 55, who do not have dementia, have a study partner, and have evidence of amyloid pathology.	People with DS between ages of 35 and 50, who do not have dementia and have a study partner. Participants between ages 35 and 39 require evidence of amyloid pathology.	To be announced
Requires MRI/PET scans?	MRI + PET	MRI + PET	To be announced
Expected Enrollment	30	80	To be announced
Participation Duration	~1 year	2 years	To be announced
Active Locations	US, Spain	US, UK, Spain	To be announced
Date of Study Completion	2027	2026	To be announced
Clinicaltrials.gov link	https://clinicaltrials.gov/study/NCT06673069	https://clinicaltrials.gov/study/NCT05462106	To be announced

Overview of Investigational Therapy Types:

- **Antisense Oligonucleotides**: These investigational therapies aim to address the root cause of DS-AD by reducing the expression of the Amyloid Precursor Protein (APP) gene. People with Down syndrome are born with three copies of the APP gene, which produces a protein that can form harmful amyloid beta plaques. ASO is delivered by lumbar puncture.
- **Vaccine Immunotherapies:** These therapies train the immune system to identify and remove harmful forms of amyloid beta from the brain, similar to how a flu vaccine helps the body recognize and fight the flu virus. Vaccine immunotherapies are delivered by intramuscular injection.
- **Antibody Immunotherapies:** These therapies identify and bind to harmful forms of amyloid beta, signaling immune cells to help remove the plaques from the brain that are bound to the antibody. Antibody immunotherapies are delivered via IV infusion.

Overview of Methods of Delivery:

- **Lumbar Puncture:** A needle is inserted into the lower back to deliver the therapy directly into the cerebrospinal fluid surrounding the brain and spinal cord. This method, sometimes referred to as "intrathecal administration," is often used when the treatment needs direct access to the brain.
- **Intramuscular Injection**: A shot is administered into the muscle, similar to a flu vaccine. The medication is absorbed into the bloodstream from the muscle tissue.
- **Intravenous Infusion**: A therapy delivered directly into a vein through an IV drip, allowing immediate entry into the bloodstream.

Defining Study Phases:

- Phase 1 or Phase 1b: An early-stage study primarily focused on evaluating the safety and tolerability of a drug or treatment in a small group of participants. It often includes preliminary assessments of how the body processes the drug and potential side effects.
- Phase 1b/2: A combined phase continuing safety testing from Phase 1 while also beginning to assess the treatment's effectiveness like a Phase 2 study. This phase provides early insights into whether the treatment impacts the disease process the way it was intended.
- Phase 2: A mid-stage study designed to evaluate the effectiveness of a drug or treatment in a larger group of participants. It also continues to assess safety and aims to identify the optimal dosage and administration methods. Phase 2 provides critical data on whether the treatment is showing the desired effects and helps refine the design for larger trials before FDA approval (Phase 3).
- Phase 3: A late-stage study conducted with a much larger group of participants to confirm the drug or treatment's effectiveness and monitor side effects. Phase 3 trials provide the evidence that the FDA will consider when deciding whether or not to approve the new treatment for general use.
- Phase 4: Conducted after a drug or treatment has been approved for public use, focusing on long-term safety and effectiveness in a larger, real-world population. In some cases, such as with Down

syndrome, Phase 4 trials may be conducted if the drug was not specifically tested in this population during earlier phases.

Placebo Controlled:

- Non-Placebo Controlled: All participants receive the investigational drug treatment with no comparison to an inactive substance. This design is often used in early-phase trials (such as Phase 1) focused on safety.
- Placebo Controlled: Some participants receive the investigational treatment, while others receive a placebo (an inactive substance) to compare results. This design helps ensure any effects observed are due to the treatment itself rather than natural changes or psychological factors like the "placebo effect."

Randomization:

- Randomized Clinical Trial: Participants are assigned to different groups by chance (randomly), ensuring fairness and reducing bias. This helps researchers determine whether the treatment is truly effective.
- Non-Randomized Clinical Trial: Participants are assigned to groups based on specific criteria rather than by chance. While this approach may be necessary in some cases, it can introduce bias and make results less reliable, but is appropriate for observational studies like a Natural History Study.

Blinding:

- Blinded Clinical Trial: Participants (and sometimes researchers) do not know which treatment they are receiving. This helps prevent expectations or biases from influencing results. Blinding can be single-blind (only participants don't know) or double-blind (both participants and researchers don't know).
- Open-Label Clinical Trial: Everyone involved knows which treatment is being given. This design is often used when blinding isn't possible, such as when studying a drug with noticeable effects or long-term safety.

MRI/PET Scans:

- MRI Scans (Magnetic Resonance Imaging): MRI scans use magnets and radio waves to create detailed images of the brain. They help researchers monitor changes in brain size and define the brain structure to identify which parts of the brain are affected by Alzheimer's disease.
- PET Scans (Positron Emission Tomography): PET scans involve a safe, low-dose injection of a tracer that highlights amyloid plaques in brain images. These plaques are harmful proteins linked to Alzheimer's disease and help researchers assess the presence of disease-related changes in the brain.

Read on for additional terms

Biomarker

A biomarker is a biological marker to measure change. It's a reliable predictor and indicator of disease and disease progression. Examples of biomarkers include glucose for diabetes and cholesterol for heart disease. The biomarkers currently used for Alzheimer's disease are brain imaging known as PET scans. There are two FDA-approved types of PET scans: one that can detect amyloid plaques and one that can detect tau tangles. Biomarkers found in cerebrospinal fluid (CSF) are also FDA-approved. Blood biomarkers are not yet FDA-approved for use in clinical practice. However, blood, CSF, and PET imaging are all used frequently as a means of measuring change in clinical trials.

Biotechnology

Biotechnology (often shortened to "biotech") companies historically conduct research on the use of live organisms, such as bacteria, enzymes, and antibodies, to develop medicines. Over time, the term "biotechs" has evolved to refer to those companies as well as all smaller companies developing new medicines, typically at the earlier stages of development. Pharmaceutical companies refer to larger, more established companies. Both biotechnology and pharmaceutical companies are involved in Down syndrome research to tackle unmet medical needs facing children and adults in our community, including addressing the crisis of Alzheimer's disease.

Endpoint

An endpoint is measure used to prove the efficacy of a drug or treatment being tested in a clinical trial. Endpoints can be objective (e.g., increased survival rates of patients) or subjective (e.g., patient and/or caregivers offering a "symptom score" to measure their experience). Sometimes, trials will use a "surrogate" endpoint to show that although there is no provable causal relationship between their tested treatment and a traditional clinical endpoint, there is a demonstrable effect on a biomarker related to the condition/disease being treated. The sponsor of a clinical trial choses a "primary endpoint" that they need to meet in order to get their drug or treatment approved by the FDA.

Clinical Trial

The U.S. National Institutes of Health (NIH) define a clinical trial as a research study in which one or more human research subjects are prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of those interventions on health-related biomedical or behavioral outcomes. Interventions may be medical products, such as drugs or devices; procedures; or changes to participants' behavior, for example by testing a new diet.

FDA

The U.S. Food and Drug Administration (FDA) is responsible for protecting the public health by ensuring the safety, efficacy, and security of human and veterinary drugs and the U.S. food supply. After conducting research on the efficacy of a drug, biotech and pharmaceutical companies need to send their results to the FDA showing that it is safe, effective, and meets regulatory standards.

Immunogenicity

Some drugs or treatments use the immune system to attack a disease like Alzheimer's disease. Immunogenicity is the ability of a foreign/external substance to cause the body to make an immune response against that substance. There are different ways to make that happen, for example through a vaccine or by infusing or injecting very specific antibodies against that foreign/external substance. In

Alzheimer's such treatments target an internal substance, which are the different forms of amyloid beta (such as fibrils and plaque) that accumulate in the brain.

IRB

An Institutional Review Board (IRB) is defined by the FDA as a group that has been formally designated to review and monitor biomedical research involving human subjects. An IRB has the authority to approve, require modifications in (to secure approval), or disapprove research and any corresponding materials (such as marketing/advertising content). FDA regulations require that IRBs have at least five members and take into consideration race, gender, and cultural background to build a diverse membership. Typically, each hospital and academic institution has an IRB.

Natural History Study

A natural history study collects information over time about the natural history of a condition in the absence of an intervention, typically from the condition's onset until either its resolution or the individual's death. Researchers observe participants as they are by recording medical, physical, and behavioral data points, like: height, weight, blood/ plasma samples, key behaviors, sleeping patterns, and blood pressure. Researchers use the information collected from all study participants to better understand the clinical profile of a given condition and help sponsors to best design future clinical trials. LIFE-DSR, ABC-DS, DABNI, LonDowns, Horizon 21 Cohort, and DS-4C are examples of natural history studies in the Down syndrome field.

Pharmacodynamics

Pharmacodynamics is the study of the biochemical and physiologic effects a drug has on the body, in other words what effect the drug has on the body. The effects could be measured by biomarkers or clinical assessment measures.

Pharmacokinetics

Pharmacokinetics is the measurement and observation of the ways the body affects a specific substance after administration. What the body does to influence the drug.

PI

The principal investigator (PI) is the researcher leading a clinical trial or scientific research project. The principal investigator prepares and carries out the plan for the research. Once the initial research has been conducted, the PI analyzes the data and reports the results.

Placebo Effect

A placebo is a fake treatment with no known clinical benefit given to one group of a clinical trial, while the other group (the "control group") receives the actual treatment being tested. The placebo effect is a beneficial health outcome resulting from a member of the placebo group's anticipation that the tested treatment will help.

Preclinical Research

Before clinical trials for potential new treatments can begin on humans, they must go through preclinical research that proves they are safe enough to be tested that way. Preclinical studies take place in two ways: in vitro (Latin for "within the glass"), in which the treatment is tested with cell cultures in a Petri dish or test tube; and in vivo (Latin for "within the living"), in which the treatment is tested on animal subjects.

Sponsor

In the context of a clinical trial, a sponsor is a person, company, institution, group, or organization that oversees or pays for the trial. The sponsor is responsible for oversight of the trial and communication with the FDA. The longer term "trial sponsor" also refers to this same idea.

Translational Research

Translational research is conducted with the goal of solving a particular problem; for example, reducing the risk of Alzheimer's disease in adults with Down syndrome. It's the process of transforming research discoveries from the laboratory into practical medical or therapeutic protocols, policies, approaches, and treatments.

About LuMind IDSC:

Founded in 2004 by families seeking better research and more meaningful connections, today LuMind IDSC envisions a world where every person with Down syndrome thrives with improved health, independence, and opportunities to reach their fullest potential. LuMind IDSC is a national Down syndrome research advocacy organization that serves as the bridge between researchers and the Down syndrome community. LuMind IDSC programs accelerate research for people with Down syndrome and empower families with connections, resources and support.

For more information, please visit: www.LuMindIDSC.org to learn about other co-occurring conditions in Down syndrome, policy issues that impact our community, ways to connect, and opportunities to participate in Down syndrome research.