White Paper

Advancing Alzheimer's Disease Therapies

How Biotech sponsors can accelerate clinical development of early stage interventions

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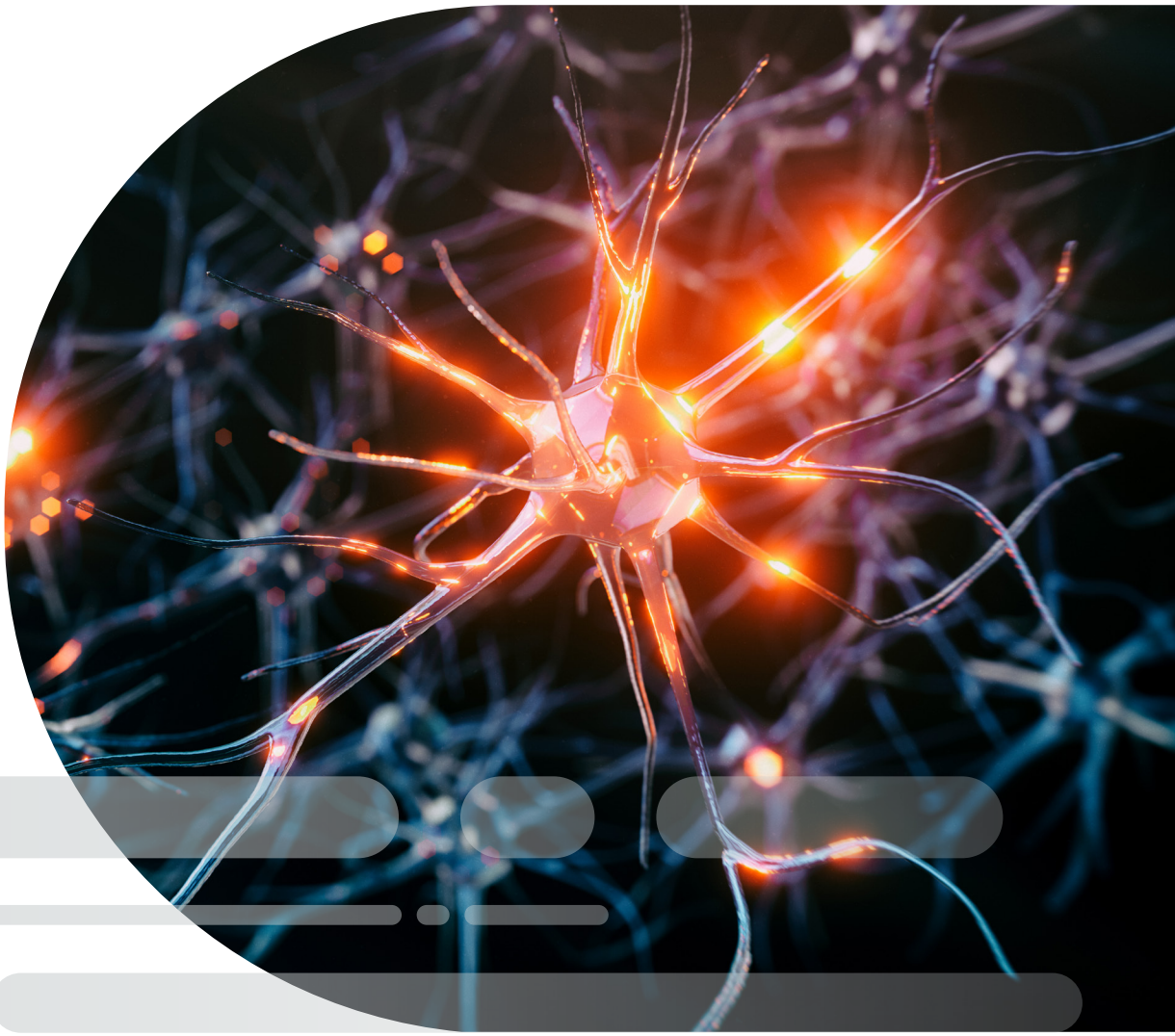


Introduction

As the global elderly population grows, the urgency to address unmet Alzheimer's disease (AD) treatment needs intensifies. Biotech and emerging biopharma companies are at the forefront of developing novel therapies aimed at disrupting AD pathology before extensive irreversible damage occurs. Biotech sponsors can optimize trials by leveraging, diagnostic advances — particularly newly characterized blood plasma biomarkers — and novel protocol designs. This white paper explores how collaborations with a clinical research organization with deep expertise in neurology and AD can unlock opportunities for sponsors to successfully operationalize AD clinical trials and bring transformative therapies to patients faster.

Understanding Alzheimer's disease

THE GROWING GLOBAL IMPACT

No single factor is known to cause AD. A hallmark is the abnormal accumulation of proteins within the brain. The neurofibrillary aggregation of tau proteins inside neurons leads to their dysfunction and death. The clumping of amyloid beta protein (Aß) into plaques between brain cells also is an AD biomarker, although elderly adults without dementia can develop Aß plaques.

One known genetic risk factor for AD is the apolipoprotein E ε4 allele (ApoE4), which about 40 percent of patients carry.[1] One copy of ApoE4 increases the risk of developing AD three- to seven-fold, while carrying two copies raises the risk 12-fold and may be a distinct genetic form of AD.[2] Personal health history, such as severe head injury, smoking, hypertension or atherosclerosis, all can modify a person's ApoE4-related risk.[1]

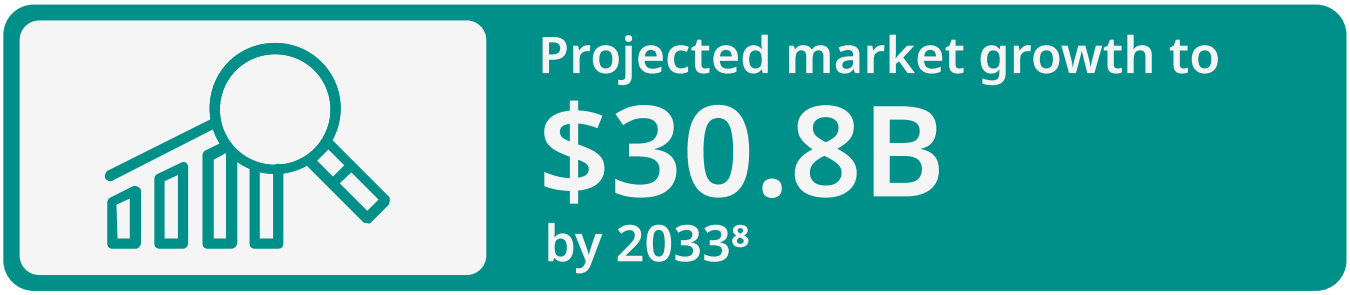
AD can take about 20 years to advance from the first evidence of amyloid pathology to dementia onset.[3] An estimated 22 percent of adults 65 or older and about half of those 90 and older have preclinical AD, functioning with normal cognition yet with evidence of AD pathology.[3] AD progressively worsens cognition, memory, behavior, language and movement. As severity increases, AD impacts a person's ability for self-care and to engage in daily living activities, with a higher likelihood of changes in personality and emotion.

In the U.S., more than 6.5 million adults older than 65 have AD.[4] Global projections for the number of people living with AD and other forms of dementia in 2050 range from 139 million to 152 million.[5]

The estimated costs associated with dementia are growing exponentially. Direct medical expenses, social care fees and unpaid informal care globally tallied more than US$1.3 trillion in 2021 and are expected to more than double by 2030 to an estimated US$2.8 trillion.[6] Notably, unpaid U.S. dementia care in 2022 reached nearly $340 billion, representing 18 billion hours provided by more than 11 million caregivers.[4]

MARKET GROWTH TO $30.8 BILLION BY 2033

Advancements in disease-modifying therapies (DMT), a growing aging population, and increased investment in AD research are expected to drive significant global AD market growth in the next decade. One estimate states the market could more than triple from about US$4.21 billion in 2022 to US$16 billion by 2030.[7] Another estimate projects a 2033 value of US$30.8 billion.[8]



Recent approvals by the U.S. Food and Drug Administration (FDA) are expanding the AD market. In 2023, the agency cleared Leqembi® (lecanemab-irmb) for mild cognitive impairment or mild dementia due to AD and Rexuliti® (brexpiprazole) for the treatment of agitation associated with dementia due to AD.

The FDA approvals of lecanemab, and aducanumab (Aduhelm) in 2021, sparked controversy because the EMA declined authorization for both due to risk/benefit concerns. Both drugs are DMTs that have some evidence suggesting they slow cognitive decline in patients with early AD.

An ocean-wide divide on Lecanemab

In a move that sharply illustrates contrasting regulatory perspectives on novel treatments for patients with AD, lecanemab met with rejection from the EMA last summer over safety concerns after having received FDA approval.

The FDA granted accelerated approval for lecanemab in January 2024, which it converted to a traditional approval in July, with an indication for patients with AD and mild cognitive impairment or mild dementia. At the time, the FDA noted the therapy represented an important advancement, as it was "the second of a new category of medications approved for Alzheimer's disease that target the fundamental pathophysiology of the disease."[9]

However, citing a risk-benefit balance, the EMA refused to grant lecanemab marketing authorization in July 2024. Specifically, it cited the therapy's side effects, which include serious adverse events such as brain swelling and bleeding referred to as amyloid-related imaging abnormalities (ARIA). The EMA Committee for Medicinal Products for Human Use expressed concern that people with two ApoE4 alleles (homozygotes) had a notably higher ARIA risk. However, in November 2024, CHMP issued a new opinion recommending approval of the drug for use in a restricted population of APOE4 non-carriers or those with one allele, indicating that APOE4 testing will likely need to become a standard for precision medicine.

Lecanemab is a monoclonal antibody, developed by Eisai and Biogen, designed to slow AD progression by targeting Aß proteins to clear plaques in the brain. The therapy has received marketing approval from Japan, China, South Korea, Hong Kong and Israel.

Innovating clinical development for AD

Biotech companies are developing innovative AD drugs with potential as DMTs or preventative treatments. For example, Tau Rx Pharmaceuticals Ltd received acceptance of its UK Marketing Authorisation Application for hydromethylthionine mesylate, designed to inhibit the aggregation of tau proteins in patients who have mild cognitive impairment or mild to moderate AD.

Also, AC Immune SA announced in September 2024 completion of prescreening of patients for a phase 2b trial of the first active immunotherapy used as a preclinical AD therapy: ACI-35.030. The FDA-Fast Tracked agent is designed to induce an antibody response targeted to phosphorylated tau (pTau) while sparing normal endogenous forms of tau.

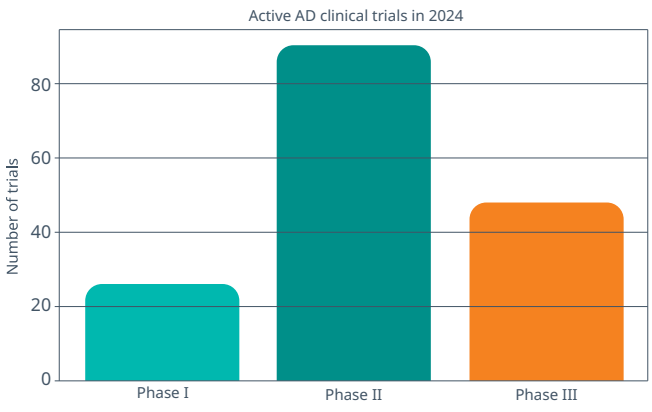
ROBUST CLINICAL TRIAL LANDSCAPE

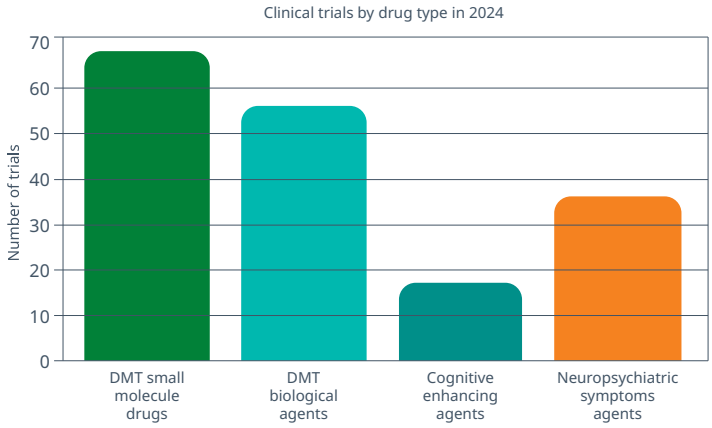
AD clinical trial starts globally surpassed 470 since 2019.[10] This volume illustrates the dedication of sponsors to find improved therapies for AD, a therapeutic area for which the failure rate of phase 2 and 3 trials is historically 98 percent.[11]

In January 2024, the AD pipeline included 127 drugs in 164 clinical trials.[12] These trials are active in more than two dozen countries. Among trials active in 2024 for which sites are available, 31 percent are global and 46 percent occur only in North America.

"New blood-based biomarkers could bring more AD testing into primary care settings"

Figure 1: Alzheimer's disease clinical trial activity in 2024.[12]





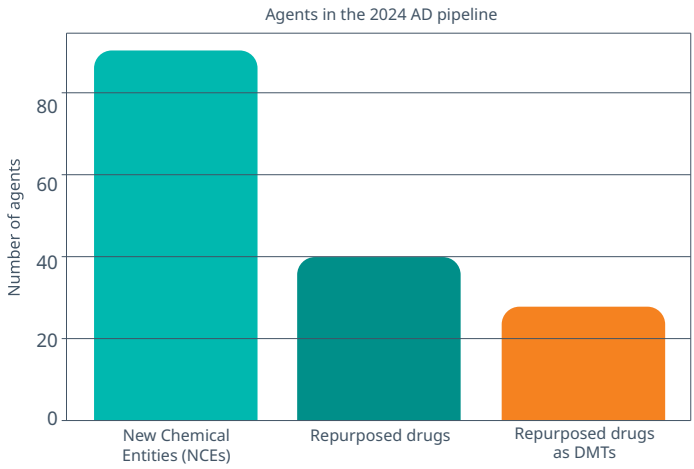
The pharmaceutical industry funds 60 percent of the 2024 AD pipeline clinical trials.[11] Many of these studies are supported via partnerships. Deals to develop neurology drugs, generally, represented 17 percent of pharmaceutical deal activity in 2023, second only to oncology among value for a single therapeutic area.[13]

The largest 2023 neurology deal, at $14 billion, was Bristol Myers Squibb's acquisition of Karuna Therapeutics, Inc., which included a first-in-class small molecule xanomeline and trospium chloride. The drug, which received FDA approval in September 2024 as the first new treatment in more than 30 years for adults with schizophrenia, is in three phase 3 trials for the treatment of psychosis in patients with AD.[12]

TESTING DMT AND OTHER AD THERAPIES

The 88 agents in the 2024 AD pipeline address 15 of the 18 molecular and physiological processes underlying AD as defined by CADRO.[11] Almost all these agents differ by mechanisms of action.

Figure 2: Summary of agents in the 2024 Alzheimer's disease clinical trial pipeline.[12]



Top five investigative AD therapies in trials:
1. Neurotransmitter receptors
2. Neuroinflammation
3. Aß processes
4. Synaptic plasticity/neuroprotection
5. Tau-related processes

Several trials are evaluating combination therapies designed to leverage drug-drug interactions to enhance effect or drug delivery, such as transport through the blood-barrier.[11] Emerging therapies also include the combination of approved anti-amyloid monoclonal antibodies with experimental agents.

EVOLVING CLINICAL ENDPOINTS FOR AD TRIALS

Clinical trials for AD therapies use a combination of assessments to screen potential trial participants and evaluate efficacy and safety of therapeutic agents. These include tools developed for the Alzheimer's Disease Cooperative Study (ADCS).

- **Cognitive tools** measure memory, attention, language, and other functions. These include the Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog), the Mini-Mental State Examination (MMSE) and the Clinical Dementia Rating Sum of Boxes (CDR-SB). The ADCS Preclinical Alzheimer Cognitive Composite debuted in the first preclinical AD clinical trial, and adaptations as a home-based remote test are employed in longitudinal AD studies.
- **Functional tools** assess a patient's independence and ability to perform daily activities. These include the Alzheimer's disease activities of daily living international scale and the CDR scale.
- **Biomarkers** with molecular activities that correlate with disease progression or modification can be surrogate endpoints. These include quantifying the presence of Aß and tau proteins in the brain with PET images and in cerebrospinal fluid (CSF).
- **Global clinical outcomes** tools are composites integrating cognitive and functional performance into a single measure. These include the ADCS-Clinical Global Impression of Change Scale and the Alzheimer's Disease Composite Score, which is derived from the ADAS-Cog, MMSE and CDR-SB.
- **Patient-reported outcomes** tools record a patient's or caregiver's assessments of health-related quality of life, including functional, emotional and behavioral changes. Preclinical and early stage AD trials increasingly include these as endpoints, such as the ADCS–Activities of Daily Living Inventory–Mild Cognitive Impairment.

BUILDING BETTER AD BIOMARKERS

Detecting preclinical and early stage AD pathologies is significantly evolving due to the increasing availability of precise, non-invasive biomarker tests, which aid screening and monitoring of patients.

The FDA has approved two tests for CSF, Elecsys® ß-Amyloid (1-42) CSF II and Elecsys® Total-Tau CSF. However, PET and CSF testing require considerations for trials. They are expensive and require specialty care, radiology or nuclear medicine settings, adding operational challenges and costs. Also, the invasive nature of both creates burdens that could impact participant compliance. For example, CSF sampling is time-consuming and often demanding for elderly patients. Also, the limited stability of the tracers in PET imaging requires rigid scheduling of patients.

New blood-based biomarkers could bring more AD testing into primary care settings. The protein fragments p-tau181, p-tau217 and p-tau231; glial fibrillary acidic protein (GFAP) and Neurofilament light (NfL) protein; and a ratio of Aβ42/40 proteins all have demonstrated potential as AD plasma biomarkers.

Both plasma p-tau217 and p-tau231 show strong association with PET scan outcomes and in testing captured "the earliest cerebral Aβ changes, before overt Aβ plaque pathology is present."[14] Several blood tests leveraging these biomarkers are nearing the clinic. The FDA granted breakthrough device designations in H2 2024 to Simoa® p-Tau 217 and Elecsys® pTau217 plasma biomarker test.

Another biomarker with promise are toxic Aß oligomers, which may show the diagnostic potential for early AD and may become therapeutic target. These molecules develop before Aß plaques as soluble aggregates of Aβ proteins and they are linked to cognitive decline, even when plaques are not present.

A recent analysis found 44 percent of the AD trials employed fluid-based biomarker endpoints, most frequently Aβ42/40 and p/tTau from CSF sampling.[15] Plasma biomarkers in these studies included pTau, NFL and inflammatory cytokines. Of note, 26 percent of the trials used target engagement biomarkers, primarily for drugs designed to target Aβ and inflammation.

IQVIA Laboratories offers sponsors the ability to analyze endpoint plasma biomarkers using highly sensitive immunoassays, such as the Quanterix Simoa®, which can perform low-level detections. We offer clinical trial sponsors a broad portfolio of assays to detect AD biomarkers, AD genetic markers and inflammation markers. A CRO with such diagnostic expertise can aid sponsors in selecting biomarkers, such as identifying the correct mechanism of action or indication, testing platforms for robust assessments, and aligning biomarkers and companion diagnostics into clinical drug development strategies.

ENHANCING AD CLINICAL TRIAL DESIGNS

To slow or prevent AD progression, an effective, safe therapeutic intervention would need introduction as early as possible, at least a decade before expected cognitive symptoms, a strategy that must employ biomarkers. However, 38 percent of 2024 AD trials did not use any biomarkers at baseline, a factor recognized as a risk for trial failure.[10]

IQVIA Biotech strongly recommends biotech sponsors planning protocols to include biomarkers as endpoints for screening, enrollment, and safety and efficacy outcomes.[11] Regulators like the EMA and FDA also encourage AD plasma biomarkers in their guidance to industry.

A CRO can help a sponsor engage these agencies during protocol development to determine if a particular plasma biomarker is suitable as a primary or secondary endpoint, what confirmatory evidence to collect, the role of companion diagnostics and how to incorporate novel trial design features.

The gold standard for AD studies remains randomized placebo-controlled trials of long duration, mainly because no standard-of-care therapy can be substituted for a placebo. However, sponsors can include strategies that offer flexibility to respond to data, shorten study cycles, and reduce costly resources. Optimized trials help sponsors achieve intermediary milestones that provide critical or pivotal evidence for regulators, partners and investors.

In studies of early AD, a prominent adaptive platform trial example is the phase 2/3 randomized double-blind placebo-controlled Dominantly Inherited Alzheimer Network Trials Unit (DIAN-TU), which evaluates multiple investigational DMTs.[16] DIAN-TU's success spawned Tau Next Generation, the first AD prevention trial to target both tau and Aβ with two drugs given together, E2814 and lecanemab.

The Alzheimer's Disease Neuroimaging Initiative (ADNI) might also aid future trials. ADNI focuses on characterizing AD subpopulations using "clinical, imaging, genetic and biochemical biomarkers for early detection and tracking."[17] ADNI data in a basket protocol could help evaluations of a DMT therapy across multiple AD subtypes, regardless of disease stage. The data might also aid an umbrella trial to test agents with different targets across biomarker-defined subtypes.

ENRICHING EARLY STAGE AD PATIENT RECRUITMENT

Patient recruitment is a challenge shared by Alzheimer's disease investigators and other clinical researchers. For trials of early stage AD, recruitment may be impacted by access to aducanumab and lecanemab, which are indicated for patients with mild cognitive impairment.

This population comprises about a third of the AD therapeutics market.[8] A sponsor might permit these DMTs as background therapies in trials that employ stratification and analytics to show a treatment effect or superiority/non-inferiority across endpoints.

Complicating recruitment efforts in the U.S. is that AD is more likely to develop among black and Hispanic adults, two groups historically underrepresented in clinical trials. Among adults 65 and older, 19 percent of blacks and 14 percent of Hispanics have AD, compared with 10 percent of whites.[4] Lack of inclusion can limit understanding how population differences might impact evaluations of pathology and interventions.

A CRO can help a sponsor incorporate evidence-based DEI practices and leverage established AD trial recruitment programs. In the U.S., the National Institute on Aging funds 35 Alzheimer's Disease Research Centers at medical institutions for activities that include trial enrollment and patient support. The Global Alzheimer's Platform Foundation runs a network of more than 130 clinical research sites spanning North America (GAP-Net NA) and Europe/United Kingdom (GAP-Net EUR) that conduct and support GAP-sponsored and GAP-enabled trials. Also, many nonprofits have established AD initiatives, from clinical research education to registration programs that notify potential participants of recruiting studies.

Conclusion

The urgent public health crisis caused by the lack of DMTs for patients with preclinical and early stage AD is an opportunity for biotech sponsors to leverage state-of-the-science knowledge, data and technologies. Regulatory incentives and AD-specific guidance support these efforts, encouraging engagement to help sponsors optimize trials with novel biomarkers and innovative designs. Partnering with a CRO experienced in AD that offers comprehensive services can help optimize, execute and analyze trials that accelerate clinical development and pathways to approval.

References

1. Pires M, Rego AC. Apoe4 and Alzheimer's Disease Pathogenesis-Mitochondrial Deregulation and Targeted Therapeutic Strategies. Int J Mol Sci. 2023;24(1):778. Published 2023 Jan 1. doi:10.3390/ijms24010778.

2. Fortea J, Pegueroles J, Alcolea D, et al. APOE4 homozygozity represents a distinct genetic form of Alzheimer's disease [published correction appears in Nat Med. 2024 Jul;30(7):2093. doi: 10.1038/s41591-024-03127-y]. Nat Med. 2024;30(5):1284-1291. doi:10.1038/s41591-024-02931-w.

3. Jansen WJ, Ossenkoppele R, Knol DL, et al. Prevalence of cerebral amyloid pathology in persons without dementia: a meta-analysis. JAMA. 2015;313(19):1924-1938. doi:10.1001/jama.2015.4668.

4. 2023 Alzheimer's disease facts and figures. Alzheimers Dement. 2023;19(4):1598-1695. doi:10.1002/alz.13016.

5. Alzheimer's Disease International. Numbers of People with Dementia Worldwide. Alzheimer's Disease International. Published September 2022. https://www.alzint.org/resource/numbers-of-people-with-dementia-worldwide/

6. World Health Organization. Global status report on the public health response to dementia. 2021. https://iris.who.int/bitstream/handle/10665/344701/9789240033245-eng.pdf

7. Horizon Grand View Research. Alzheimer's Therapeutics Market Size & Outlook. ND. https://www.grandviewresearch.com/horizon/outlook/alzheimers-therapeutics-market-size/global Accessed Oct. 12, 2024.

8. Market.us. Alzheimer's Disease Therapeutics Market. January 2024. https://market.us/report/alzheimers-disease-therapeutics-market/ Accessed Oct. 12, 2024.

9. U.S. Food and Drug Administration. FDA Grants Accelerated Approval for Alzheimer's Disease Treatment. January 6, 2023. https://www.fda.gov/news-events/press-announcements/fda-grants-accelerated-approval-alzheimers-disease-treatment

10. Targeted search for studies of Alzheimer's Disease. ClinicalTrials.gov. Accessed Oct. 12, 2024.

11. Kim CK, Lee YR, Ong L, Gold M, Kalali A, Sarkar J. Alzheimer's Disease: Key Insights from Two Decades of Clinical Trial Failures. J Alzheimers Dis. 2022;87(1):83-100. doi:10.3233/JAD-215699.

12. Cummings J, Zhou Y, Lee G, Zhong K, Fonseca J, Cheng F. Alzheimer's disease drug development pipeline: 2024. Alzheimer's Dement. 2024; 10:e12465. https://doi.org/10.1002/trc2.12465

13. Aitken M, Connelly N, Kleinrock M, Pritchett J. Global Trends in R&D 2024: Activity, Productivity, and Enablers. February 2024. IQVIA Institute for Human Data Science https://www.iqviainstitute.org Accessed Oct. 12, 2024.

14. Milà-Alomà M, Ashton NJ, Shekari M, et al. Plasma p-tau231 and p-tau217 as state markers of amyloid-β pathology in preclinical Alzheimer's disease [published correction appears in Nat Med. 2022 Sep;28(9):1965. doi: 10.1038/s41591-022-02037-1]. Nat Med. 2022;28(9):1797-1801. doi:10.1038/s41591-022-01925-w.

15. Oosthoek, M., Vermunt, L., de Wilde, A. et al. Utilization of fluid-based biomarkers as endpoints in disease-modifying clinical trials for Alzheimer's disease: a systematic review. Alz Res Therapy 16, 93 (2024). https://doi.org/10.1186/s13195-024-01456-1

16. Bateman RJ, Benzinger TL, Berry S, et al. The DIAN-TU Next Generation Alzheimer's prevention trial: adaptive design and disease progression model. Alzheimers Dement. 2017;13(1):8-19. doi:10.1016/j.jalz.2016.07.005.

17. Weiner MW, Veitch DP, Aisen PS, et al. The Alzheimer's Disease Neuroimaging Initiative: a review of papers published since its inception. Alzheimers Dement. 2012;8(1 Suppl):S1-S68. doi:10.1016/j.jalz.2011.09.172.

About the authors

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Dr. Marek Bieniek is a board-certified neurologist, with more than 25 years of experience in neurology practice, over 10 years of Medical Affairs experience in pharmaceutical industry, primarily related to multiple sclerosis and Alzheimer's disease, and over 6 years' experience in clinical research industry. His research interests were focused primarily on the use of MRI imaging in understanding MS pathology in different clinical phenotypes. He is currently a part of IQVIA's CNS Center of Excellence, where he applies his practical knowledge related to all stages of medicines' life cycle to support development of innovative therapies for neurological disorders.

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Gijsbert Veerman serves as the Chief Operating Officer at IQVIA Biotech, overseeing global project teams, investigator site services, and therapeutic divisions. With more than 27 years of clinical research experience in the CRO environment and seven years in pre-clinical oncology research, Gijsbert brings a wealth of strategy and operational expertise to his role.

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