

Amyloid-Related Imaging Abnormalities Dominate Aducanumab's Complete Post-Marketing Record: A Comparative Pharmacovigilance Analysis

By Leonardo Carvalho

AUTHOR BIO

Leonardo Carvalho is a junior at Groton School, in Groton, Massachusetts. His research focuses on pharmacovigilance and the post-marketing safety of biologic therapies, with a particular interest in spontaneous reporting systems and antibody therapy. He became interested in aducanumab after his grandfather passed from Alzheimer's disease dementia. He has also worked on a robotics research project on assistive exosuits, and he plans to study biomedical engineering with the goal of improving the quality of life of patients through pharmaceuticals and robotics.

ABSTRACT

This is a pharmacovigilance analysis of the complete adverse event record for aducanumab. Aducanumab (brand name Aduhelm), a monoclonal antibody, reduces the aggregation of beta-amyloid plaque, associated with symptoms of Alzheimer's disease, the most common dementia impacting millions annually. However, aducanumab has ambiguous effects due to clinically inconclusive studies. In 2024, Aduhelm was commercially and developmentally discontinued by Biogen for excessive costs for treatment, low adoption, and controversy over its efficacy. Reports are from the Food and Drug Administration Adverse Event Monitoring System Public Dashboard for aducanumab. The procedure was replicated for successors lecanemab and donanemab. Aducanumab received 486 cases between 2016 and 2024, having 266 (54.7%) serious cases, including 29 deaths (6.0%). Five amyloid-related imaging abnormality (ARIA) terms accounted for 253 reaction entries in 181 unique cases (37.2% of all cases). Sex distribution of reports was about even (48.1% female of all cases; 52.8% of cases with known sex; 53.8% female of known sex among ARIA cases), contrasting the female-predominant Alzheimer's population. ARIA cases were reported by healthcare professionals significantly more often than other cases (69.6% versus 48.2%). Relative to lecanemab (25.7%) and donanemab (34.0%), aducanumab had the largest share of ARIA reports (37.2%), and female ARIA cases for both successors (~65%) exceeded that seen for aducanumab. Four hypotheses were proposed: that ARIA terms would dominate the profile,

that women would represent a majority of reports, that ARIA would be disproportionately healthcare-reported, and that reporting volume would track the product life cycle.

Keywords: *pharmacovigilance, aducanumab, amyloid-related imaging abnormalities, Food and Drug Administration Adverse Event Monitoring System, adverse drug reaction reporting, monoclonal antibodies, Alzheimer's disease, lecanemab, donanemab*

INTRODUCTION

The Global Burden of Alzheimer's Disease

Alzheimer's disease (AD) is the most common form of dementia, affecting millions of individuals worldwide and representing a global health crisis. In 2021, 57 million people were estimated to be affected by dementia, and this number increases with 10 million new diagnoses each year (World Health Organization [WHO], 2026). Projections from the Global Burden of Disease 2019 Dementia Forecasting Collaborators (2022) show that this number will increase to 152.8 million by 2050. The impact of dementia is disproportionately concentrated in low income and underdeveloped countries, due to limited access to diagnosis and treatment along with more overall population affected (WHO, 2026). In the United States alone, the Centers for Disease Control and Prevention (CDC, 2024) states that 6.9 million individuals were affected in 2020, a number expected to double to 14 million by 2060. The significance of dementia is seen in its mortality impact: in 2022, it was the seventh leading cause of death among adults overall and the sixth among those aged 65 years and older in the United States.

The societal impact of dementia goes further than health, requiring significant economic costs. Estimates from Lastuka et al. (2024) show that in 2019, healthcare spending attributable to dementia reached \$260.6 billion (95% uncertainty interval: \$131.6–\$420.4 billion), while caregiving costs totaled \$354.1 billion (95% UI: \$190.0–\$544.1 billion), which together amount to a societal cost of approximately \$614.7 billion. These costs are expected to rise, with per capita dementia care expenses expected to more than triple by 2050, pushing total costs well beyond \$1 trillion annually. In low income countries, higher amounts of dementia patients cause increased costs related to caregiving, leading to major economic drag in their development.

Dementia is a term used to describe cognitive impairment through memory loss, critical thinking, and other effects that can impact daily life. AD specifically is separated into several categories, specifically mild, moderate, and severe, in increasing order of the cognitive impairment and functional disability the individuals confront. One of the most common symptoms of AD is episodic short-term memory loss, when patients struggle to retain new information when looking back on long-term memories. Following this, impairments with problem-solving, judgement, executive function, and organization may arise, causing issues with multitasking or creative thinking. Even in the early stages of AD, daily activities such as driving, cooking, financial management, planning, and more can be affected. As the dementia progresses to the moderate stage, other symptoms such as language disorders and impaired visuospatial skills, alongside apathy, social withdrawal, agitation, psychosis, and wandering become common in individuals affected. In the late stages, difficulty with motor tasks (dyspraxia), olfactory dysfunction, sleeping issues, and Parkinsonian symptoms become clear, leading to primitive reflexes and eventually total dependence on caregivers.

The prognosis for individuals with AD is highly variable between cases, but according to the Alzheimer's Association (2025), studies indicate that people 65 and older typically live for another four to eight years after their diagnosis, with some outliers living as long as 20 years. The disease progresses

slowly and is vastly unpredictable; many patients spend most of their remaining lifespan in different stages of impairment. Following the mild, moderate, and severe stages, patients experience corresponding symptoms leading to mental and physical decline and increased vulnerability to other health problems.

A major cause of dementias is the aging process common across all humans. Late-onset AD (LOAD), in which advancing age is the dominant risk factor, accounts for more than 95% of AD diagnoses (Liu, 2022). Prevalence rates (percentage of people affected at any given time) for AD increase from 10% after the age of 65 to 40% after 85, with a doubling in prevalence every 5 years after the age of 65 (Alzheimer's Association, 2025). Although the mechanism that directly corresponds to susceptibility to LOAD is unknown, a significant contributor to the disease is cellular senescence, a phenomenon where a cell is permanently in the state of cell-cycle arrest where damaged cells stop dividing but remain metabolically active. As increase of cellular senescence is directly related to age, there is an increase in prevalence LOAD as well.

Molecular and Cellular Pathology of Alzheimer's Disease

According to Lui and Tsao (2024), AD is characterized by an accumulation of abnormal plaques and neurofibrillary tangles in the brain, caused by accumulation of insoluble, dysfunctional proteins. These problems lead to loss of neurons, specifically in the basal forebrain and neocortex. However, the specific cause of AD is highly debated in the scientific community; there are two main hypotheses based on current pathological findings: the Cholinergic Hypothesis and the Amyloid Hypothesis. The Cholinergic Hypothesis asserts that an early loss of cholinergic neurons (tissue part of the neurotransmitter system that regulates the parasympathetic nervous system, cognitive function, and muscle contraction), leading to reduced levels of acetylcholine, serves a significant role in the progression of AD. Cholinergic function is believed to be negatively affected by beta-amyloid through synaptic loss and acetylcholine release. The Amyloid Hypothesis is a more widely accepted mechanism, suggesting that amyloid beta peptide, which forms the insoluble beta-amyloid plaque, comes from amyloid precursor protein which is typically cleaved by secretase enzymes. However, sequential cleavage by specific enzymes leads to peptides that cause an aggregation of beta-amyloid, creating plaque and causing neuronal toxicity. AD is also characterized by an accumulation of abnormal tau proteins in neuronal tissue. Tau proteins typically stabilize microtubules responsible for holding neuronal structure and transporting nutrients, but in AD, these tau proteins are hyperphosphorylated, causing a detachment from microtubules. This causes an aggregation of proteins that leads to neurofibrillary tangles. The tangles inhibit nutritional transport, impair neuronal communication, and ultimately contribute to neuronal death and eventually tissue death. This suggests that beta-amyloid accumulation, which initiates pathological changes, and tau pathology, which induces cognitive decline, follow the cascade of AD progression proposed by the Amyloid Hypothesis.

Currently available treatments for AD vary between pharmacological therapies and non-pharmacological activities, but both remain insufficient in stopping the progression of the disease. According to the National Institute on Aging (2023), there are several medications approved by the U.S. Food and Drug Administration (FDA) such as cholinesterase inhibitor and NMDA receptor antagonists

that are used to temporarily improve symptoms of cognitive impairment, but are unable to cure or stop AD. In addition to medications, memory care programs, occupational therapy, and physical therapy are also used to support daily functioning or to improve the quality of life of patients. The Centers for Disease Control and Prevention (2024) asserts that these approaches can help people affected by the disease to maintain their independence and reduce behavioral symptoms but cannot prevent the course of the disease. Most of these existing drugs and therapies address the Cholinergic Hypothesis, which may be a fundamental reason for their apparent inefficiency. Furthermore, new treatments, such as monoclonal antibody therapies like aducanumab, provide limited clinical benefit, with inconsistent or negligible improvements accompanied with potential risks. Despite a variety of treatments, AD is still incurable, with current therapies and medications being targeted at managing symptoms rather than prevention of the neurodegeneration itself.

Aducanumab and Other Monoclonal Antibodies

Aducanumab (brand name Aduhelm) represents a shift in the approach to treatments for AD, as it is the first approved therapy designed for pathology of the disease rather than managing symptoms. Previous AD medications, namely donepezil, a cholinesterase inhibitor, and memantine, an NMDA receptor antagonist, are focused on the Cholinergic Hypothesis, unlike aducanumab which directly follows the Amyloid Hypothesis. According to Padma and Parmar (2024), aducanumab is a monoclonal antibody that selectively binds to aggregated beta-amyloid in the brain, especially soluble oligomers and insoluble amyloid plaque. Through this mechanism, aducanumab enables microglial activation which promotes clearance of amyloid plaque, attempting to reduce a defining pathological hallmark of AD.

Despite the new mechanism, aducanumab's efficacy in clinical trials became controversial. According to Knopman et al. (2021), early phase 2 trials were focused on establishing a safe but effective dosage range while providing demonstrations to show that the drug could efficiently reduce amyloid plaque aggregation. The controversy was amplified during the phase 3 EMERGE and ENGAGE trials, designed to determine whether the drug produced meaningful clinical benefits in cognition and daily functioning, when conflicting conclusions were presented: the EMERGE trial showed high dosage of aducanumab could produce a modest slowing of cognitive decline, whereas the ENGAGE trial failed to demonstrate any prominent clinical benefit. Both trials were halted in 2019 after analysis suggested that aducanumab was unlikely to meet its primary goal. The inconsistency of the trials fostered scientific debate regarding the observed benefits and whether they were clinically meaningful or simply a result of statistical uncertainty. Researchers reviewing the data concluded that, though Aduhelm's cognitive benefits are plausible, the data are insufficient to claim efficacy of the drug (Knopman et al., 2021).

The controversy of aducanumab is not limited to the scientific community, as it surrounds its regulatory approval process as well. According to Alexander et al. (2021), the Peripheral and Central Nervous System Drugs Advisory Committee, a panel of external experts assembled to advise the FDA, overwhelmingly advised against approval of the drug in 2020 as available evidence did not demonstrate clinical efficacy in a convincing manner. The committee voted against every efficacy question put to it. On whether the EMERGE trial could serve as primary evidence of effectiveness, no member voted yes,

ten voted no and one was uncertain; on whether EMERGE demonstrated sufficient efficacy, one voted yes, eight no and two uncertain; and on whether the phase 1b PRIME study provided supporting evidence, none voted yes, seven no and four uncertain. Across the three efficacy questions only a single vote in favor was cast. The advisory committee members expressed concern that a positive result from the EMERGE trial was insufficient to outweigh the failure of the ENGAGE trial, bringing up questions regarding whether reduction in amyloid plaque truly translates into meaningful cognitive improvement. Despite the concerns of the committee, the FDA granted accelerated approval to aducanumab under the brand name Aduhelm in June 2021, focusing on its ability to reduce beta-amyloid plaque rather than proven clinical benefits. As advisory boards only give recommendations and not legal decisions, the FDA was free to approve the drug even in the face of opposition from the committee. The move met with immense criticism in both the scientific and medical communities and resulted in the resignation of three prominent members of the Peripheral and Central Nervous System Drugs Advisory Committee, who argued that the drug's approval did not adhere to scientific standards.

Financial concerns made the situation even more controversial. Aducanumab is delivered through monthly intravenous (IV) administration over one hour through a 0.2 or 0.22 micron in-line filter, which necessitates specific clinical monitoring, as well as regular magnetic resonance imaging (MRI) examinations to ensure early detection of any potential side effects caused by this medication. Initially, when Biogen introduced Aduhelm to the market, it set the annual cost of this medicine at around \$56,000. However, in response to harsh criticism voiced by physicians, health economists, policymakers, and patient advocacy groups, Biogen lowered the cost to about \$28,200 per person annually. Despite this reduction in pricing, however, there were still numerous experts who warned that such costs would put enormous pressure on Medicare due to millions of elderly patients with AD being eligible for treatment with aducanumab (Mafi et al., 2022). Studies conducted prior to the approval process showed that the estimated annual cost of Medicare reimbursement for widespread use of this drug would total tens of billions of dollars per year, making it the most expensive health intervention to have ever been proposed on a large scale. This cost was particularly controversial due to the uncertainty surrounding aducanumab's clinical efficacy.

One of the main safety issues included ARIA (amyloid-related imaging abnormalities) that were side effects of anti-amyloid antibodies leading to cerebral edema (brain swelling) and cerebral microhemorrhages. These complications were frequent enough within clinical trials to require MRI screening for patients taking the drug regularly. Along with uncertainty about its efficacy, these risks resulted in poor prescription and patient compliance. Ultimately, the lack of commercial success, limited insurance coverage, and scientific criticisms compelled Biogen to withdraw Aduhelm from the market in 2024. Although aducanumab was withdrawn from the market, its approval has marked a turning point for AD medication by recognizing the potential of using anti-amyloid monoclonal antibodies as a viable therapeutic class. Thus, the introduction of aducanumab created a basis for further research into other monoclonal antibodies, such as lecanemab and donanemab, both of which have shown stronger evidence of clinical benefit in later trials and will continue to undergo research.

Aducanumab has had two successors which are still active: lecanemab (Leqembi), developed by Eisai and co-developed and commercialized by Biogen, and donanemab (Kisunla), developed and commercialized by Eli Lilly. These are monoclonal antibodies that target the same Amyloid Hypothesis treatment as aducanumab in a different way. Lecanemab preferentially binds soluble protofibrils, intermediate, prefibrillar aggregates formed during the self-assembly of beta-amyloid monomers into insoluble amyloid plaques which are commonly considered as most neurotoxic and pathogenic species driving cognitive decline in AD (van Dyck et al., 2023). Like aducanumab, lecanemab first received accelerated approval, in January 2023, but it went on to receive traditional FDA approval on July 6, 2023 (FDA, 2023b) on the strength of the Clarity AD results (van Dyck et al., 2023). A subcutaneous autoinjector formulation (Leqembi Iqlik) was later approved as an initiation dose on July 13, 2026 (Eisai, 2026a) and became available in the United States on August 24, 2026 (Eisai, 2026b). Donanemab targets pyroglutamate-modified amyloid-beta, specifically only targeting preformed amyloid plaque (Sims et al., 2023). Unlike lecanemab and aducanumab, it is given on a limited-duration schedule, as treatment lasts until the amyloid positron emission tomography scan no longer exhibits plaque aggregation. It received traditional approval on July 2, 2024 (FDA, 2024).

The clinical evidence for the two successors is stronger than aducanumab, and their regulatory histories are cleaner as well. In the 18-month phase 3 Clarity AD trial ($n = 1,795$), lecanemab slowed decline on the Clinical Dementia Rating by 27% relative to placebo, with ARIA-E in 12.6% of treated participants compared to 1.7% on the placebo (van Dyck et al., 2023). In TRAILBLAZER-ALZ 2 ($n = 1,736$), donanemab slowed decline on the integrated Alzheimer's Disease Rating Scale by about 35% in the low/medium-tau population, with ARIA-E in 24.0% of treated participants versus 2.1% on placebo (Sims et al., 2023). Both products carry a boxed warning for ARIA as a class effect, with amplified risk in APOE $\epsilon 4$ homozygotes, and both require baseline and scheduled MRI monitoring analogous to the aducanumab protocol (FDA, 2023b, 2024; Eisai, 2026a). With the United States prescribing volumes for both agents now growing under registry-based Medicare coverage, the real-world safety record accumulated by aducanumab is directly relevant to an expanding treated population. This is a central motivation for the reported comparative analysis.

Adverse Event Surveillance for Aducanumab

A major safety concern with aducanumab is that it can lead to ARIA (Table 1), a class of adverse effects common in anti-amyloid monoclonal antibody therapies. ARIA comes in two main forms: ARIA-E, which refers to cerebral edema, and ARIA-H, which refers to cerebral microhemorrhages and superficial siderosis (small areas of bleeding or iron deposition within the brain). While many cases of ARIA demonstrate no symptoms and are only detected through MRI, some patients experience more clinically significant symptoms, including headaches, confusion, dizziness, visual disturbances, nausea, gait abnormalities, and falls. In severe instances, ARIA may cause significant neurological impairment and may require discontinuation of therapy. ARIA is an important clinical marker because it indicates cerebral hemorrhages which stem from drug treatment; these are conditions that can lead to neurologic complications, necessitate discontinuation of treatment, and cause serious injury to patients under extreme circumstances. Furthermore, aducanumab has been reported to cause hypersensitivity reactions, leading to

angioedema and urticaria, which requires a prompt discontinuation of Aduhelm infusion and initiation of appropriate therapy (FDA, 2021).

Table 1
ARIA MRI Classification Criteria

ARIA Type	Radiographic Severity		
	Mild	Moderate	Severe
ARIA-E	FLAIR hyperintensity confined to sulcus and or cortex/subcortical white matter in one location < 5 cm	FLAIR hyperintensity 5 to 10 cm, or more than 1 site of involvement, each measuring < 10 cm	FLAIR hyperintensity measuring > 10 cm, often with significant subcortical white matter and/or sulcal involvement. One or more separate sites of involvement may be noted
ARIA-H, microhemorrhage	≤ 4 new incident microhemorrhages	5 to 9 new incident microhemorrhages	10 or more new incident microhemorrhages
ARIA-H, superficial siderosis	1 focal area of superficial siderosis	2 focal areas of superficial siderosis	> 2 focal areas of superficial siderosis

Note. Radiographic severity bands as defined for MRI monitoring; these describe imaging extent, not clinical severity. Adapted from Aduhelm (aducanumab-avwa) injection, for intravenous use: Prescribing information by FDA, 2021 (https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/761178s000lbl.pdf). FLAIR = fluid-attenuated inversion recovery.

In the ENGAGE and EMERGE phase 3 clinical trials, patients treated with aducanumab had significantly higher rates of ARIA than those receiving a placebo. In the pooled ENGAGE and EMERGE safety analysis, ARIA-E occurred in 35.2% of participants receiving the 10 mg/kg dose compared with 2.7% of those receiving placebo (Salloway et al., 2022). The same pattern held for ARIA-H, as it occurred more frequently in the group receiving aducanumab. These findings point towards the idea that increased risk of treatment-related brain swelling and cerebral microhemorrhages may stem from exposure to aducanumab. Among the patients who developed ARIA-E, 30% had mild radiographic

findings, 58% moderate, and 13% severe (figures do not sum to 100% due to rounding). These categories describe the size and extent of the imaging abnormality rather than its clinical consequence, as the majority of ARIA-E in the trials were asymptomatic and detected only on protocol-mandated MRI. This is why radiographic severity and clinical severity must be reported separately. Furthermore, approximately 10% of patients receiving the approved 10 mg/kg dose of Aduhelm experienced more than one ARIA-E episode (FDA, 2021).

ARIA can be very serious due to its frequency and nature; hence, extensive MRI monitoring is required during therapy. According to the FDA's approved prescription information, a patient should be given an MRI before starting the drug treatment. Moreover, under the 2021 label a patient is advised to receive another MRI before the seventh and twelfth IV infusions of Aduhelm to monitor for treatment-emergent abnormalities. The label was revised in 2023 to add a further MRI before the fifth infusion (FDA, 2023a). Severe adverse radiographic findings that should warrant discontinuation of treatment include having more than ten new microhemorrhages or having more than two lesions of superficial siderosis. The FDA also notes that safety of Aduhelm is still ambiguous in individuals having pre-existing localized superficial siderosis, ten or more brain microhemorrhages, or a brain hemorrhage greater than one centimeter within one year prior to treatment initiation.

While many ARIA cases may be discovered through incidental imaging findings, clinical symptoms are fairly common. According to the FDA (2021), symptoms were reported in about 24% of the patients treated with Aduhelm who developed ARIA-E and/or ARIA-H, in comparison to only 5% of patients on placebo with imaging abnormalities. This comparison emphasizes the potential clinical significance of ARIA and explains why routine imaging is required for monitoring when patients receive the drug. The high frequency of ARIA, along with uncertainty surrounding clinical benefits from treatment with aducanumab, played a significant role in the concerns regarding the risk to benefit profile of the medication.

Once a drug or biological product is approved, there remains an urgent need for continuous safety evaluation, since adverse events seen during real-world clinical practice could be different from those reported in controlled clinical studies. The FDA Adverse Event Monitoring System (AEMS) is one tool that contains records of adverse events reported by various manufacturers, medical practitioners, and users of these drugs in the US. While a clinical trial involves patients who are chosen according to specific criteria and treated under controlled conditions, the AEMS database represents clinical data obtained from ordinary use of a particular drug in diverse patient populations. A significant advantage of the AEMS database is the public involvement in adverse event reporting, as well as public access to collected information. For this reason, the FDA AEMS is a valuable resource to evaluate the real-world safety profile of approved drugs and biologic therapies.

This is a pharmacovigilance analysis. Pharmacovigilance is the science related to detecting, assessing, understanding, and preventing adverse effects of medicines after they enter clinical use, and adverse event reporting systems are its principal data source. AEMS, launched on March 11, 2026, consolidated the FDA's previously separate reporting systems, including the FDA Adverse Event

Reporting System (FAERS) for drugs and therapeutic biologics, into one platform with reports since 1968. Data are available through the Public Dashboard on a daily, approximately real-time refresh (FDA, 2026). Interpreting the data requires extensive care, because the submission of a report does not establish that the drug caused the event; reports may be duplicated, incomplete, or unverified; the circumstances of an event cannot be accounted for because the number of exposed patients and the completeness of reporting are not provided; and reporting intensity varies over a product's life cycle, usually peaking shortly after approval (the Weber effect; Hartnell & Wilson, 2004) and rising temporarily when safety issues attract regulatory or media attention (notoriety bias; Pariente et al., 2007). Within these constraints, spontaneous reports are the primary method to detect drug safety signals in populations larger and more heterogeneous than reports from controlled trials.

Several pharmacovigilance analyses of aducanumab based on FAERS data have been published and identify ARIA-related terms as the drug's dominant safety signals (e.g., Huang et al., 2025). This analysis differs from previous work in two ways: it uses data from the consolidated AEMS record through the drug's complete commercial life cycle, starting from the first reports received through market withdrawal, and it compares the aducanumab profile with directly comparable dashboard extractions for lecanemab and donanemab, the two approved successor antibodies with rapidly growing real-world exposure.

The purpose of this research paper is to use the FDA AEMS database to characterize reported adverse events and trends in adverse event reporting frequency for aducanumab. Based on the female predominance both of the AD population (Aggarwal & Mielke, 2023) and of adverse drug reaction reporting in general (Watson et al., 2019), and on the radiographic nature of ARIA detection, four hypotheses were established. First, ARIA-related terms would dominate the reported adverse event profile of aducanumab. Next, women would account for the majority of overall aducanumab adverse event reports as well as for ARIA reports specifically. Then, ARIA cases would be reported disproportionately by healthcare professionals (HCPs) rather than consumers, because ARIA is primarily detected on MRI rather than as a symptom. Finally, reporting volume would track the drug's regulatory and commercial life cycle rather than remaining constant over time.

METHODS

Data on adverse events were gathered using the FDA AEMS Public Dashboard, retrieved on August 31, 2026. Due to the fact that the dashboard is frequently updated, all counts reported, including lecanemab, donanemab, and database-wide counts, are bound to the retrieval date. The "Launch the FDA AEMS Public Dashboard" button was clicked first, then the disclaimer pop-up was acknowledged. After clicking "Search Drugs and Biologics" in the upper-left, the database was searched using two search terms regarding the same monoclonal antibody: "Aducanumab" and "Aducanumab-Avwa" (brand name Aduhelm). This reflects the generic and nonproprietary drug names that reports may be filed under.

All counts reported in this paper are unique cases as marked by the dashboard. A single case may include more than one reaction term, so reaction-term counts can exceed the number of cases (FDA,

2026). “Received year” refers to the year the case was received by the FDA. Reaction terms are reproduced with the British spellings used by the Medical Dictionary for Regulatory Activities (MedDRA) dictionary and the dashboard (for example, haemorrhage, oedema); United States spellings are used elsewhere in the text.

The process of data gathering involved several steps. First, the summary statistics provided in the upper-right part of the dashboard—total number of reports, number of serious cases, and number of deaths—were noted for both search terms. Second, the data table and time-trend chart were evaluated in order to determine individual report values and time trends. Third, the “Reaction Types” visualization tool was used to find adverse event terms compatible with amyloid-related imaging abnormalities (ARIA). This included ARIA-E, ARIA-H, cerebral haemorrhage, ARIA, and superficial siderosis of the central nervous system. Every term related to ARIA was selected together as a search filter, and the case numbers, demographics, and outcomes obtained were then compared to the rest of the other reaction types in the dashboard.

These results, specifically for sex distribution and reaction types, were replicated using the search terms “Lecanemab” and “Lecanemab-Irmb” (brand name Leqembi) for the lecanemab monoclonal antibody, and “Donanemab” and “Donanemab-Azbt” (brand name Kisunla) for the donanemab monoclonal antibody.

Proportions were compared with two-sided tests at $\alpha = .05$. Departures of the female/male split from parity were assessed with exact binomial tests, excluding cases with unspecified sex. Proportions between independent groups were compared with two-proportion z-tests, and associations between dichotomous variables were compared with chi-squared tests of independence. Comparisons involving the ARIA subset used the non-ARIA cases as the reference group, and effect sizes are reported as odds ratios (OR) with 95% confidence intervals. Chi-square statistics are reported without continuity correction, so that each is the square of its corresponding z statistic. Wilson score methods were used for 95% confidence intervals on single proportions. No adjustment was made for multiple comparisons. As this analysis is meant to be descriptive, p values should be read as descriptive rather than absolute. Analyses were performed in a Python environment using the SciPy library.

The data obtained through these searches were aggregated and used to create summary graphics and trends analyses presented in the Results section.

RESULTS

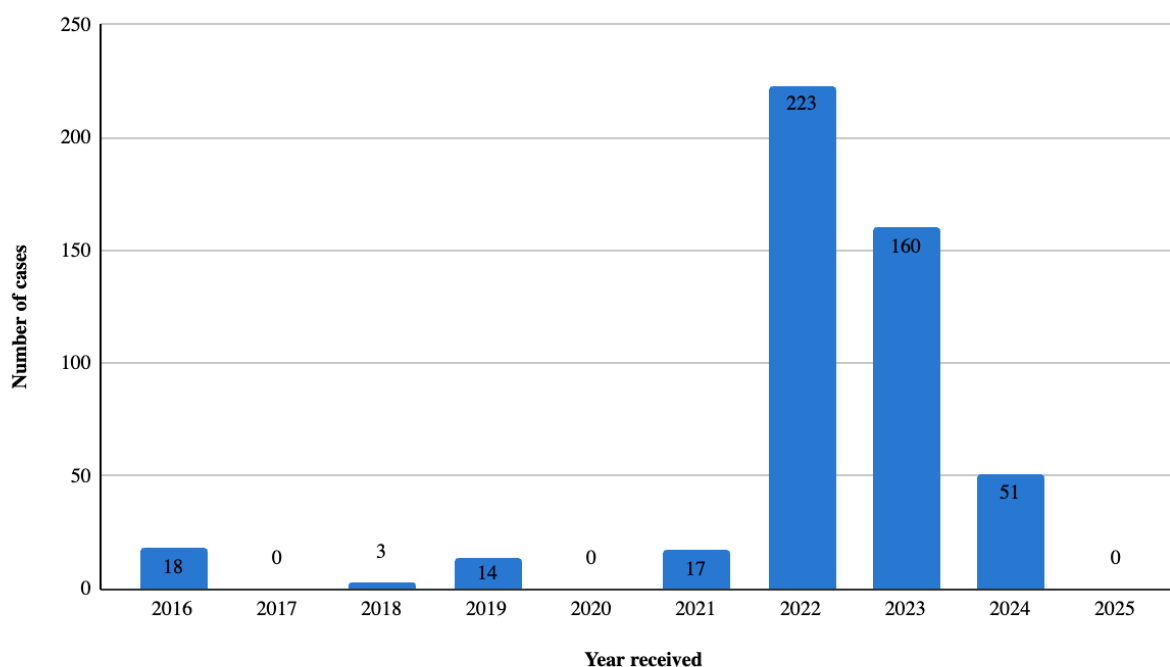
For all the drug and biological products in the FDA AEMS, there were 33,777,205 cases as of August 31, 2026. From these reports, 18,416,722 (54.5%) were categorized as serious excluding death, and 2,964,046 (8.8%) resulted in death. Thus, serious and fatal cases together comprised 63.3% of all cases in the AEMS database.

In the case of aducanumab, 486 unique cases were identified. Of these, 237 (48.8%) were categorized as serious excluding death, while 29 (6.0%) led to death, resulting in a combined percentage of serious and fatal as 54.7%. It can be seen that the figure is much smaller than that of 63.3% in AEMS as a whole. This shows that, on average, cases related to aducanumab are less likely to be categorized as either serious or fatal than the average case for all drugs and biologics in the AEMS database. This should not be read as evidence that aducanumab is safer than other drugs. The comparison reflects the reporting stream rather than its risk profile, as a large proportion of aducanumab cases are radiographic ARIA findings detected on protocol-mandated MRI in patients without symptoms, which are frequently not classified as serious. To analyze the difference between the serious/fatal reporting rate of aducanumab (54.7%) and that of all drugs and biologics in AEMS (63.3%), a two-proportion z-test was performed. The difference was statistically significant ($z = -3.92$, $p < .001$), suggesting that reports about aducanumab contained fewer cases of serious/fatal adverse events compared to those of all drugs in AEMS. Even though the number of samples in the aducanumab report ($n = 486$) is very small compared to that of the full database ($n = 33,777,205$), the large number in the comparison group provides enough statistical power to conclude the difference is unlikely to be a result of chance.

The temporal distribution of aducanumab adverse event reports is shown in Figure 1: 18 in 2016, 3 in 2018, 14 in 2019, 17 in 2021, 223 in 2022, 160 in 2023, 51 in 2024, and no reported cases in 2017, 2020, or 2025. There was a sharp increase in adverse event reports in 2022, which coincides with the first full year of clinical use following the drug's accelerated approval in June 2021, and its consequent clinical usage. The number of cases reported began substantially decreasing following 2022, likely due to the reduced usage of the drug post the initial adoption phase. It should be noted that the ARIA adverse event reports remained almost constant from 2022 to 2023, with 82 and 78 ARIA adverse event reports, respectively, during the same years. Therefore, the year-to-year reduction in the number of total adverse event reports was probably caused by the reduction in the number of non-ARIA adverse event reports. There were no adverse event reports after 2024, which corresponds to the discontinued usage of the drug.

Figure 1

Adverse Event Case Counts for Aducanumab by Year in AEMS Database

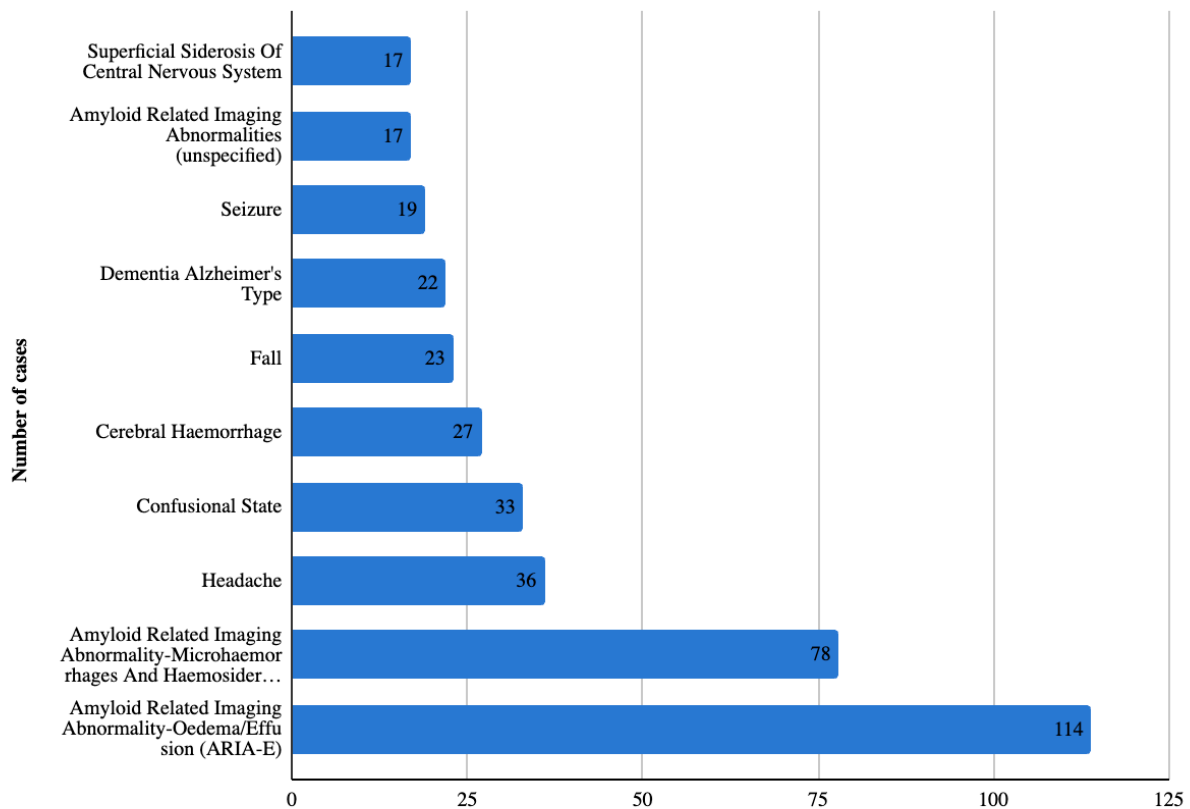


Note. Case counts are unique cases received by year, from the FDA AEMS Public Dashboard, retrieved August 31, 2026. Created by Carvalho, 2026.

The analysis of the 10 most frequently reported reactions to aducanumab represent the following list in the order of their descending frequency, as seen in Figure 2: ARIA-E, ARIA-H, headache, confusional state, cerebral haemorrhage, fall, dementia Alzheimer's type, seizure, unspecified ARIA, and superficial siderosis. As ARIA-E, ARIA-H, cerebral haemorrhage, superficial siderosis, and undifferentiated ARIA are identified criteria for diagnosing ARIA, these five terms have been summated to assess the total incidence of ARIA amongst the reported reactions. Together, these five terms accounted for 253 reaction entries. However, because a single case may be under more than one of these terms, the 253 term entries have 181 unique cases, which represents 37.2% of the 486 aducanumab cases (95% CI [33.1, 41.6]). Of the 181 ARIA cases, 61 were serious and 4 resulted in death.

Figure 2

Ten Most Common Reaction Types for Aducanumab in AEMS Database



Note. Reaction terms may overlap for adverse events, from the FDA AEMS Public Dashboard, retrieved August 31, 2026. Created by Carvalho, 2026.

Classification of reports was based on patient sex: female, male, and unspecified. Table 2 provides a distribution of the classification for ARIA-E and ARIA-H together, and all reports of adverse events for aducanumab.

Table 2

Sex Distribution of ARIA and Overall Adverse Event Reports for Aducanumab

Group	Female, n (%)	Male, n (%)	Unspecified, n (%)	Total (N)
ARIA-E	57 (50.0%)	53 (46.5%)	4 (3.5%)	114
ARIA-H	35 (44.9%)	41 (52.6%)	2 (2.6%)	78

All ARIA	92 (50.8%)	79 (43.6%)	10 (5.5%)	181
All adverse events	234 (48.1%)	209 (43.0%)	43 (8.8%)	486

Note. ARIA = amyloid-related imaging abnormalities; ARIA-E = oedema/effusion; ARIA-H = microhaemorrhages and hemosiderin deposits. “All ARIA” comprises the five ARIA-related terms described in the Methods. AEMS Public Dashboard, retrieved August 31, 2026. Created by Carvalho, 2026.

To determine if the differences in the sex distributions indicated a deviation from parity, two-sided exact binomial tests were conducted on each of the groups to compare females and males as a proportion of the total, excluding reports with no specified sex. None of the four groups was found to deviate significantly from parity: ARIA-E (51.8% female, $n = 110$, $p = .775$), ARIA-H (46.1% female, $n = 76$, $p = .567$), all ARIA cases (53.8% females, $n = 171$, $p = .359$), and all adverse events (52.8% female, $n = 443$, $p = .254$).

Two-proportion z-tests were conducted to determine if there is a significant difference in the proportion of female reports between groups. Because the ARIA cases are a subset of the full series, ARIA cases were compared with the non-ARIA cases rather than with the total. There was no significant difference in the proportion of female reports between ARIA cases (53.8%, 92 of 171 with known sex) and non-ARIA cases (52.2%, 142 of 272; $z = 0.33$, $p = .74$), nor between the ARIA-E group (51.8%) and the ARIA-H group (46.1%, $z = 0.77$, $p = .439$). In combination, these results do not confirm the hypothesis of women reporting adverse effects, including ARIA, on aducanumab more frequently than men. The tests did not produce a significant difference between the sex ratios of any subgroup, though with these case counts the analysis has limited power to detect a difference.

Adverse event reports were also categorized according to whether they were reported by HCPs or consumers. Table 3 shows the breakdown of these categories among ARIA cases and all adverse event reports.

Table 3

Reporter Type for ARIA and Overall Adverse Event Reports for Aducanumab

Group	HCP, n (%)	Consumer, n (%)	Total (N)
All ARIA	126 (69.6%)	55 (30.4%)	181
All adverse events	273 (56.2%)	213 (43.8%)	486

Note. AEMS Public Dashboard, retrieved August 31, 2026. Created by Carvalho, 2026

Two-sided binomial tests revealed that both the ARIA cases and the adverse event reports were significantly skewed towards HCP reporting, relative to an even split: ARIA cases (69.6% HCP, $p < .001$) and all adverse event reports (56.2% HCP, $p = .007$). To assess whether ARIA cases were reported by HCPs more often than other cases, ARIA cases were compared with the 305 non-ARIA cases, of which

147 (48.2%) were HCP-reported. ARIA cases were reported by HCPs at a significantly higher proportion, $\chi^2(1, N = 486) = 21.2, p < .001$, OR 2.46 (95% CI [1.67, 3.63]; equivalently $z = 4.60$). This trend is in line with the character of the ARIA findings, since being detected through radiographic examination (i.e., MRI), ARIA is not a subjectively observed sign by the patient, which is why it is reported by HCPs more often than other adverse events (for example, headache or confusion). ARIA cases were correspondingly less often serious than non-ARIA cases (33.7% versus 67.2%; $\chi^2(1, N = 486) = 51.5$, OR 0.25, 95% CI [0.17, 0.37], $p < .001$), consistent with most ARIA being an asymptomatic finding on scheduled imaging rather than a clinical event.

To compare results with the drug class, the dashboard procedure was repeated for the two successor monoclonal antibodies. Lecanemab represented 3,728 cases (1,579 serious, including 154 deaths) from 2021 onward, and donanemab represented 3,238 cases (1,670 serious, including 74 deaths) from 2024 onward. Of the unique cases, the five ARIA-related terms were involved in 181 of 486 aducanumab cases (37.2%; 95% CI [33.1, 41.6]), 957 of 3,728 lecanemab cases (25.7%), and 1,100 of 3,238 donanemab cases (34.0%) (Table 4; Figure 3). The ARIA proportion of aducanumab reports was significantly higher than that of lecanemab ($z = 5.40, p < .001$) but not significantly different from donanemab ($z = 1.42, p = .16$). For the ARIA-E term alone, aducanumab (23.5% of cases) exceeded both lecanemab (13.5%; $z = 5.82, p < .001$) and donanemab (16.0%; $z = 4.08, p < .001$) in proportion. Headache was the second leading term for lecanemab (490 cases compared to 504 for ARIA-E; retrieved August 31, 2026), whereas ARIA-E was the leading term for aducanumab and donanemab.

Table 4
Aducanumab, Lecanemab, and Donanemab in the AEMS Public Dashboard

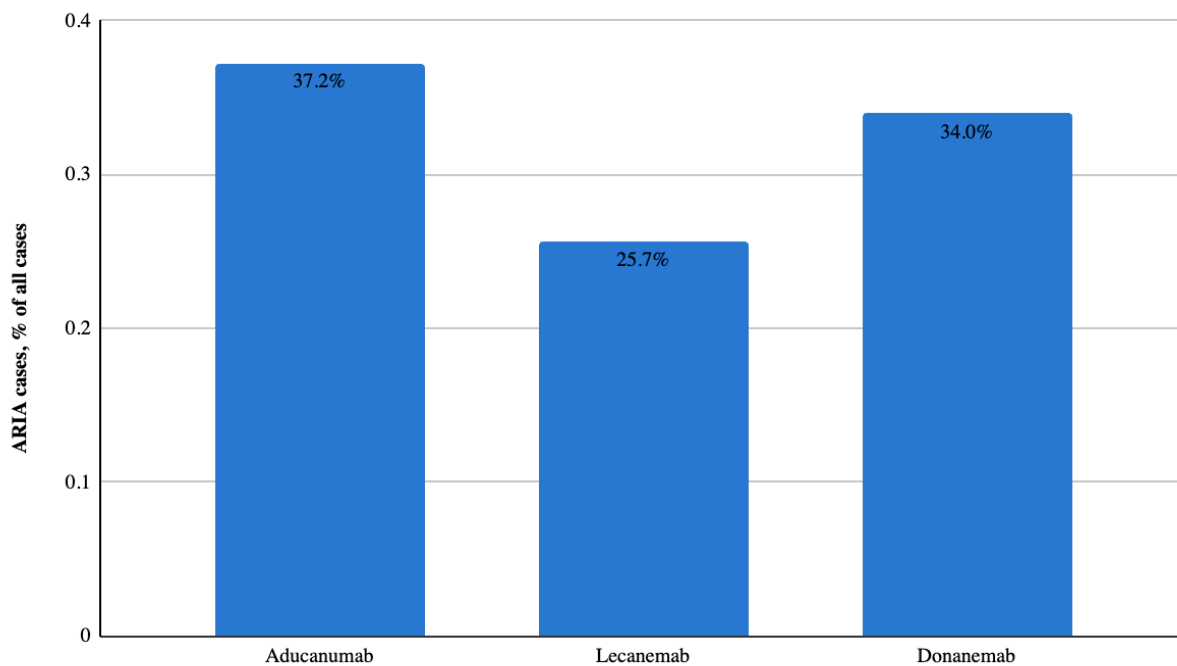
Category	Aducanumab	Lecanemab	Donanemab
Total cases	486	3,728	3,238
Serious cases (including deaths), n (%)	266 (54.7)	1,579 (42.4)	1,670 (51.6)
Death cases, n (%)	29 (6.0)	154 (4.1)	74 (2.3)
ARIA cases, n (%)	181 (37.2)	957 (25.7)	1,100 (34.0)
ARIA-E cases, n (%)	114 (23.5)	504 (13.5)	518 (16.0)
ARIA-H cases, n (%)	78 (16.0)	470 (12.6)	428 (13.2)
Female, % of all cases with known sex	52.8	58.4	61.5
Female, % of ARIA cases with known sex	53.8	64.8	65.6
Healthcare-professional reported, %	56.2	71.2	40.1

First to last received year	2016–2024	2021–2026	2024–2026
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Note. Search terms: “Lecanemab”/“Lecanemab-Irmb” and “Donanemab”/“Donanemab-Azbt.” ARIA cases comprise the five ARIA-related terms described in the Methods. Because AEMS is refreshed daily, comparison counts continue to change, especially because lecanemab and donanemab remain in active use. AEMS Public Dashboard, retrieved August 31, 2026. Created by Carvalho, 2026

Figure 3

ARIA Share of Reported Cases for Aducanumab, Lecanemab, and Donanemab in the AEMS Public Dashboard



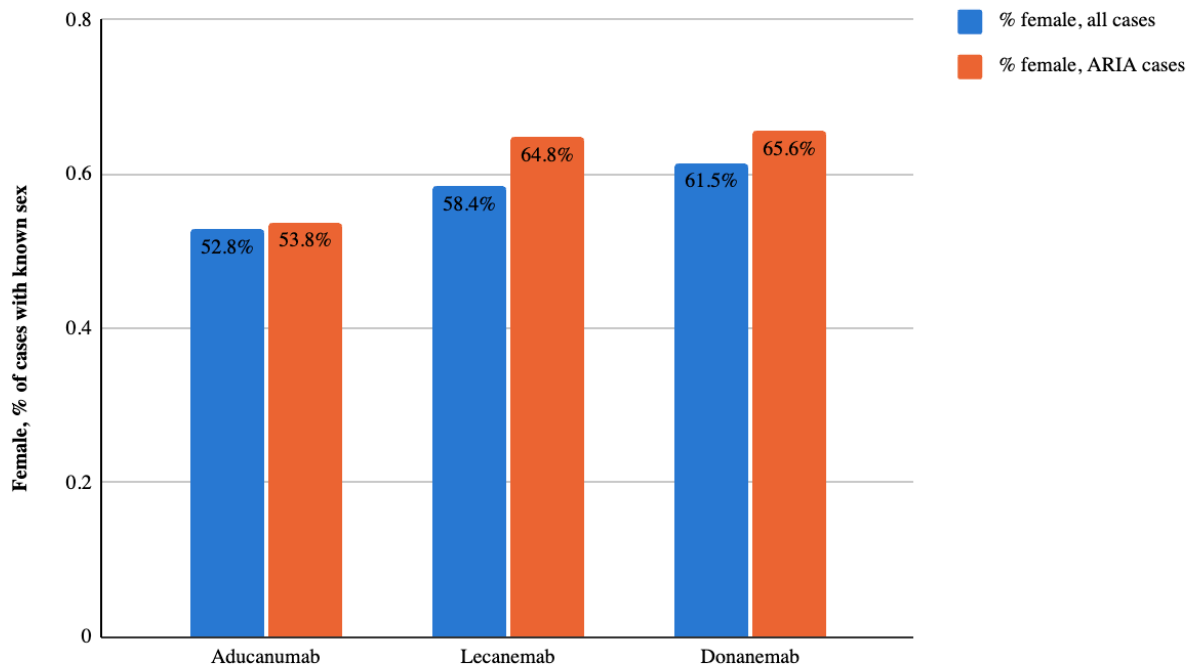
Note. Percentage of ARIA across cases for aducanumab, lecanemab, and donanemab. Retrieved August 31, 2026. Created by Carvalho, 2026.

The sex distributions of the successor antibodies departed from the pattern seen for aducanumab (Figure 4). Among cases with known sex, women accounted for 52.8% of aducanumab reports, 58.4% of lecanemab reports ($z = -2.23$, $p = .026$ vs aducanumab), and 61.5% of donanemab reports ($z = -3.43$, $p < .001$). Donanemab nearly matches the approximately 61% female share of the United States AD dementia population (Alzheimer’s Association, 2025). The contrast was sharper within ARIA cases: 53.8% female for aducanumab compared to 64.8% for lecanemab ($z = -2.71$, $p = .007$) and 65.6% for donanemab ($z =$

-2.95, $p = .003$). Reporter-type distributions also differed by product: HCPs submitted 71.2% of lecanemab reports but only 40.1% of donanemab reports, for which consumers were the dominant channel (59.5%); the remaining 0.4% of donanemab cases had no logged reporter type.

Figure 4

Female Proportion of All Cases Compared to Female Proportion of ARIA Cases for Aducanumab, Lecanemab, and Donanemab



Note. Percentage of female representation in ARIA across cases with known sex for aducanumab, lecanemab, and donanemab. The approximate female share of the United States AD dementia population is approximately 61% (Alzheimer's Association, 2025). Retrieved August 31, 2026. Created by Carvalho, 2026.

DISCUSSION

This analysis of the complete AEMS Public Dashboard record for aducanumab provides five main findings. First, ARIA dominated the reported adverse event profile. A total of 181 of 486 cases (37.2%) involved at least one ARIA-related term, and the two principal ARIA terms were the two most frequently reported reactions overall. Second, in contrast to the specified hypothesis, women did not form the clear majority that the disease demographics would predict. Female patients accounted for 48.1% of all aducanumab cases, and 52.8% of those with known sex. This share matched the composition of the

EMERGE and ENGAGE trials but was clearly below the female share of the AD dementia population and of the ARIA cases reported for the two successor antibodies (64.8% lecanemab and 65.6% donanemab). Third, ARIA cases were reported predominantly by HCPs (69.6% compared to 48.2% of non-ARIA cases), and they were less frequently reported as serious than other cases. Fourth, reporting volume did follow the regulatory and commercial life cycle closely, with a peak roughly one year after approval, and effective stoppage after withdrawal. Finally, in comparison to lecanemab (25.7%) and donanemab (34.0%), ARIA accounted for the largest share of aducanumab reports, significantly against lecanemab but not so much with donanemab. The gap was widest for ARIA-E (aducanumab 23.5% compared to lecanemab 13.5% and donanemab 16.0%).

The predominance of ARIA in AEMS is consistent with the trial data, in which ARIA-E affected 35.2%, ARIA-microhemorrhage 19.1%, and superficial siderosis 14.7% of participants receiving the 10 mg/kg dose (Salloway et al., 2022). With prior FAERS analyses, which consistently identified ARIA-E and ARIA-H as leading safety signals (e.g., Huang et al., 2025), the data are consistent yet again. ARIA-E represented roughly 1.5 to 1.75 times a larger percentage of aducanumab cases than lecanemab or donanemab cases (23.5% aducanumab compared to 13.5% lecanemab and 16.0% donanemab). This follows the observation that ARIA was the leading event for aducanumab whereas there appeared to be a lower trial incidence of ARIA-E with lecanemab (12.6%; van Dyck et al., 2023) and donanemab (24.0%; Sims et al., 2023) compared to aducanumab. However, though the AEMS proportions are close for lecanemab and donanemab in regards to ARIA-E (13.5% compared to 16.0% respectively), donanemab's trial incidence for ARIA-E was nearly double lecanemab's share (24.0% compared to 12.6%).

The observation that ARIA cases were less often coded as serious than other aducanumab cases may seem paradoxical for the class's principal safety concern, but it is consistent with the clinical picture: in the trials three quarters of ARIA-E was asymptomatic, was detected on scheduled MRI and resolved radiographically in 98% of cases (Salloway et al., 2022), and in AEMS the serious ARIA cases were a minority (33.7% compared with 67.2% of non-ARIA cases), following the symptomatic ARIA being the exception rather than the rule. The non-ARIA reports, by contrast, included a majority of the deaths in the series and the reporting of the underlying disease itself: dementia Alzheimer's type was the seventh most frequently reported term, a pattern typical of consumer reporting that inflates the seriousness of a drug used in a more frail elderly population. The finding that aducanumab reports were, on average, less often serious or fatal than the database as a whole should not be interpreted as evidence of relative safety; it reflects the large share of non-serious, MRI-detected ARIA reports and the composition of the reporting population.

The absence of the expected female predominance is the most unexpected result from this analysis. The lifetime risk of developing AD after 65 years is approximately 21.2% in females against 11.6% in males (Alzheimer's Association, 2025). Further, females are considerably more likely than males to develop AD dementia at every age stratum above 65 due to female longevity, APOE ε4 associated risk for females (especially between 65–75 years), and risk factors specific to females such as early menopause and history of preeclampsia. Women make up about 61% of Americans with AD dementia and roughly two thirds in some cohorts (Aggarwal & Mielke, 2023; Alzheimer's Association,

2025). Aggarwal and Mielke (2023) attribute these differences to biological and demographic factors rather than to diagnostic bias alone. Women also submit about 60% of adverse drug reaction reports worldwide, a pattern that holds across regions, reporter types and age groups beyond puberty (Watson et al., 2019). The ARIA cases reported for lecanemab and donanemab in the same database were 64.8% and 65.6% female. Against these three data points, aducanumab stands out as abnormally balanced. The sex distribution of reports depends on the sex distribution of the treated population, on sex-specific susceptibility to the event, and on sex-specific propensity to report. The data here point to the first of these. The 52.8% female share among cases with known sex closely matches the 52% female enrollment of EMERGE and ENGAGE (Salloway et al., 2022), and aducanumab saw little use outside research settings after the Centers for Medicare & Medicaid Services (CMS) coverage determination confined Medicare reimbursement to randomized trials (CMS, 2022). EMERGE and ENGAGE enrolled participants aged 50 to 85 years with confirmed amyloid pathology and mild disease (Salloway et al., 2022), and their composition, at 52% female, sat well below the female share of the disease population. The close to even sex ratio of aducanumab reports therefore most probably reflects the sex composition of the small, trial-like population that actually received the drug.

Two alternative explanations warrant consideration, but only one can be addressed with the data. If men were more susceptible to ARIA than women, the female share of ARIA cases would be lower than that of non-ARIA cases; it was not, as the female share was in fact slightly higher among ARIA cases (53.8% versus 52.2%; $p = .74$), and the trials identified APOE $\epsilon 4$ genotype and dose, not sex, as the determinants of ARIA risk (Salloway et al., 2022). A second possibility, that women were simply less likely than men to report adverse events while taking aducanumab, cannot be separated from the composition of the treated population in these data, because the dashboard does not distinguish spontaneous from study-derived reports. Previous FAERS analyses concluded that aducanumab's signal profile was similar in women and men (Huang et al., 2025), which is compatible with the present findings but addresses a different question. The point of practical importance is that the sex ratio of a spontaneous-report series is not a measure of sex-specific risk. The female predominance among lecanemab and donanemab ARIA cases is what would be expected from a real-world treated population with the demographics of AD dementia and the general female excess in reporting, and it should not be taken, without denominator data, as evidence that women are at higher risk of ARIA. This same caution applies to any sex-stratified comparisons reported for lecanemab and donanemab. Sex-stratified analyses of registry and claims data with known treated populations are required to answer that question.

ARIA cases had roughly 2.5 times the odds of other cases being submitted by an HCP (odds ratio 2.46, 95% CI [1.67, 3.63]). This is the expected consequence of ARIA being a diagnosis made on scheduled MRI, usually in the absence of symptoms, by the prescribing neurologist or radiologist, whereas headache, confusion, falls or infections are experienced and reported by patients and caregivers. The finding is consistent with lecanemab in the same dashboard, whose reports were 71.2% HCP submitted. However, 59.5% of donanemab reports are classified as consumer-submitted, most likely because the manufacturer's patient-support program collects and forwards events from patients and caregivers. Reporter type in AEMS thus reflects both the incidence of the event and the reporting

infrastructure built around each product, and comparisons across drugs should account for that infrastructure.

The time course of aducanumab reporting shows the pattern predicted by the Weber effect, with reports peaking in the first two years after approval and then declining (Hartnell & Wilson, 2004). The peak at 223 cases in 2022 matched the period of maximal clinical uptake before and immediately after the CMS determination, the decline to 160 in 2023 with the contraction of use to trial settings, and the fall to 51 in 2024 with the discontinuation and withdrawal. The share of cases involving ARIA nevertheless rose over the same period, from 36.8% in 2022 to 48.8% in 2023, which coincided with the traditional approval of lecanemab in July 2023 (FDA, 2023b) and the intense attention it brought to ARIA. This may have inspired retrospective reporting, a form of notoriety bias (Pariante et al., 2007). The pattern demonstrates that trends in report counts describe exposure and attention rather than changes in risk, which is why the proportion of ARIA among cases in the two years of substantial use (36.8% in 2022 and 48.8% in 2023) is a more informative statistic than the absolute counts.

Although aducanumab has been withdrawn, its post-marketing record is directly relevant to lecanemab and donanemab, which share its mechanism and its principal toxicity. First, ARIA-specific MedDRA terms are class-specific, which makes disproportionality analyses of any one anti-amyloid antibody highly sensitive to the reference group. As such, analyses should set any one antibody against the others rather than against the database as a whole, as the direct three-drug comparison reported here does. Second, because most ARIA is asymptomatic and physician-detected, the completeness of its capture in spontaneous reporting depends on clinicians' willingness to report incidental MRI findings. The proportion of ARIA cases in AEMS (37.2% of aducanumab cases, 25.7% of lecanemab, and 34.0% of donanemab cases) is far below trial incidence and should not be used to estimate real-world rates. Third, the demographic composition of a report series must be checked against the treated population before sex or age patterns are interpreted. For the successor antibodies, whose real-world use is expanding under registry-based coverage (CMS, 2022), this comparison will become feasible as registry data accumulate. For clinicians, the reports reinforce the labeled safeguards for the class: baseline and scheduled MRI, APOE ϵ 4 genotyping to inform risk discussions, vigilance for headache, confusion and seizures as possible symptomatic ARIA, and caution with antithrombotic and thrombolytic therapy (FDA, 2021).

LIMITATIONS

The limitations of this analysis are mainly those of spontaneous reporting itself, and the FDA attaches them to every dashboard query (FDA, 2026): the existence of a report does not establish that the monoclonal antibody caused the event, and reports may be duplicated, incomplete, or unverified, and the same patient may appear under more than one report. Because the size of the exposed population is unknown, neither incidence rates nor between-drug risk comparisons can be computed from report counts. Under-reporting is substantial and uneven, as asymptomatic, MRI-detected ARIA is captured only when a clinician chooses to file it, so the ARIA proportions reported are far below trial incidence and should not be read as real-world rates. Several features of this dataset warrant caution as well. Sex was

unspecified in 8.8% of aducanumab cases, and more often for the other drugs within the class (10.1% for lecanemab, 19.8% for donanemab), which widens the uncertainty of the sex comparisons. The profiles for the successor antibodies also remain moving targets, as both drugs are in active, expanding use on a dashboard refreshed daily, so their counts and any statistics derived from them are tied to the August 31, 2026 retrieval date, whereas the aducanumab record is effectively closed. Finally, the subgroup analyses rest on case counts and multiple unadjusted comparisons, and should be treated as descriptive.

CONCLUSION

Across its complete post-marketing record, aducanumab's adverse event profile was dominated by ARIA, the same imaging abnormalities that affected the EMERGE and ENGAGE trial participants, while the volume of reporting simply followed the drug's brief and contested commercial life from accelerated approval to withdrawal. The near-even sex distribution of its reports, sitting well below the female share of both the AD population and the successor antibodies' ARIA cases, is most likely a signature of the small, trial-like population that actually received the drug rather than a sex-specific susceptibility. For pharmacovigilance practice, it illustrates both the value and the limits of spontaneous reporting for a drug whose principal toxicity is detected by scheduled imaging, and it supplies a closed baseline against which the accumulating lecanemab and donanemab records can be judged. Future work should extend this surveillance approach to the growing family of monoclonal antibody therapies beyond neurology, including oncology and autoimmune disease, where the same reporting dynamics apply.

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