MASSACHUSETTS

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Medical Policy

# Aducanumab & Lecanemab for Alzheimer Disease

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## Policy Number: 946

BCBSA Reference Number: 5.01.38
NCD/LCD: N/A

## Related Policies

None

## Prior Authorization Information

| | | |
|---|---|---|
| ☒ **Prior Authorization**<br>☐ **Step Therapy**<br>☐ **Quality Care Dosing** | | **Pharmacy Operations:**<br>Tel: 1-800-366-7778<br>Fax: 1-800-583-6289 |
| | | Policy last updated **7/1/2023** |
| Pharmacy (Rx) or Medical (MED) benefit coverage | ☐ **Rx**<br>☒ **MED** | **To request for coverage:** Physicians may call, fax, or mail the attached form (Formulary Exception/Prior Authorization form) to the address below. |
| **Policy applies to** Commercial Members:<br>• Managed Care (HMO and POS),<br>• PPO and Indemnity<br>• MEDEX with Rx plan<br>• Managed Major Medical with Custom BCBSMA Formulary<br>• Comprehensive Managed Major Medical with Custom BCBSMA Formulary<br>• Managed Blue for Seniors with Custom BCBSMA Formulary | | **Blue Cross Blue Shield of Massachusetts**<br>**Pharmacy Operations Department**<br>25 Technology Place<br>Hingham, MA 02043<br><br>**Individual Consideration:** Policy for requests that do not meet clinical criteria of this policy, see section labeled Individual Consideration |

## Policy

### Commercial Members: Managed Care (HMO and POS), PPO, and Indemnity

The use of aducanumab is considered **INVESTIGATIONAL** for all indications including treatment of Alzheimer disease.

The product label recommends that a baseline brain magnetic resonance imaging (MRI) within 1 year must be done prior to initiating treatment due to the risk of amyloid-related imaging abnormalities (ARIA). Subsequently, MRI should be repeated prior to the 5th, 7th, 9th and 12th infusions. If radiographic severe ARIA-hemorrhage (ARIA-H) is observed, treatment may be continued with caution only after a clinical evaluation and a follow-up MRI demonstrates radiographic stabilization (i.e., no increase in size or number of ARIA-H).

The use of lecanemab is considered **INVESTIGATIONAL** for all indications including treatment of Alzheimer disease.

The product label recommends that a baseline brain magnetic resonance imaging (MRI) within 1 year must be done prior to initiating treatment due to the risk of amyloid-related imaging abnormalities (ARIA). Subsequently, MRI should be repeated prior to the 5th, 7th and 14th infusions. If radiographic severe ARIA-hemorrhage (ARIA-H) is observed, treatment may be continued with caution only after a clinical evaluation and a follow-up MRI demonstrates radiographic stabilization (i.e., no increase in size or number of ARIA-H).

## CPT Codes / HCPCS Codes / ICD Codes

*Inclusion or exclusion of a code does not constitute or imply member coverage or provider reimbursement. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage as it applies to an individual member.*

*Providers should report all services using the most up-to-date industry-standard procedure, revenue, and diagnosis codes, including modifiers where applicable.*

*The following codes are included below for informational purposes only; this is not an all-inclusive list.*

### CPT Codes

There are not any codes for this procedure.

## Description

**Alzheimer Disease**

Alzheimer disease is a fatal neurodegenerative disease that causes progressive loss in memory, language, and thinking, with the eventual loss of ability to perform social and functional activities in daily life. Survival after a diagnosis of dementia due to Alzheimer disease generally ranges between 4 and 8 years; however, life expectancy can be influenced by other factors, such as comorbid medical conditions. It is estimated that 6.2 million Americans aged 65 and older are currently living with Alzheimer disease dementia, and the number is projected to reach over 12 million by 2050.[1]

**Pathophysiology**

The pathologic hallmarks of Alzheimer disease are extracellular deposits of beta-amyloid (A-β), referred to as amyloid plaques, and intracellular aggregates of hyperphosphorylated tau in the form of neurofibrillary tangles. There are different forms of amyloid such as plaques, oligomers, and monomers, and the roles of these different forms and how specifically they are pathophysiologically associated with Alzheimer disease is not well understood. Generally referred to as "amyloid hypothesis", it is believed that aggregation of A-β oligomers in the brain leads to amyloid plaques and thought to be the primary driver of the disease process. Amyloid aggregation is thought to precede accumulation of tau pathology and neurodegeneration. These changes in the brain result in widespread neurodegeneration and cell death, and ultimately cause the clinical signs and symptoms of dementia.[2,3]

Salient known risk factors for Alzheimer disease are older age, genetics, and family history. Of these, increasing age has the largest known impact on risk of developing Alzheimer disease. While several genes have been found to increase the risk of Alzheimer disease, the ε4 allele of the apolipoprotein E (ApoE) gene is the strongest known genetic risk factor.[4,5] Having 1 copy of the gene is associated with a 2- to 3-fold increase in developing Alzheimer disease while 2 copies of the gene may increase risk of

Alzheimer disease by as much as 15 times.[6] Approximately two-thirds of pathology-confirmed Alzheimer disease cases are ε4 positive (homozygous or heterozygous), compared with about 15% to 20% of the general population.[5] Autosomal dominant genetic mutations are estimated to account for less than 1% of Alzheimer disease cases.[7]

The pathophysiological changes and clinical manifestations of Alzheimer disease are progressive and occur along a continuum, and accumulation of A-β may begin 20 years or more before symptoms arise.[8], National Institute on Aging-Alzheimer's Association (NIA-AA) have created a "numeric clinical staging scheme" (Table 1) that avoids traditional syndromal labels and is applicable for only those in the Alzheimer continuum. This staging scheme reflects the sequential evolution of Alzheimer disease from an initial stage characterized by the appearance of abnormal Alzheimer disease biomarkers in asymptomatic individuals. As biomarker abnormalities progress, the earliest subtle symptoms become detectable. Further progression of biomarker abnormalities is accompanied by progressive worsening of cognitive symptoms, culminating in dementia. This numeric cognitive staging scheme is not designed to be used in a clinical setting but to be used for interventional trials such as those of aducanumab.

The phase 3 randomized controlled trials for aducanumab were stratified to include 80% of stage 3 patients and 20% of stage 4 patients. This numeric staging scheme is very similar to the categorical system for staging Alzheimer disease outlined in the Food and Drug Administration (FDA) guidance for industry pertaining to developing drugs for treatment of early Alzheimer disease.[9]

The efficacy of lecanemab was evaluated in a double-blind, placebo-controlled, parallel-group dose-finding trial, Study 201 (NCT01767311) in adult patients with AD (patients with confirmed presence of amyloid pathology and MCI or mild dementia consistent with Stage 3 and Stage 4 AD). The study assessed three doses across two regimens of lecanemab. This numeric staging scheme is very similar to the categorical system for staging Alzheimer disease outlined in the Food and Drug Administration (FDA) guidance for industry pertaining to developing drugs for treatment of early Alzheimer disease.

Many tests are available in the market to detect the underlying core pathology such use of certain biomarkers in the cerebrospinal fluid (CSF) (eg, decreased A-β and increased CSF tau protein levels) and on imaging (e.g., amyloid on positron emission tomography [PET] scans). Approved amyloid PET tracers in the US include [18F]-florbetapir, [18F]-flutemetamol and [18F]-florbetaben. In addition, there are several CSF tests for A-β confirmation that are currently in development in the US. CSF tests and amyloid PET tracers are routinely used in the enrollment of participants in contemporary Alzheimer disease studies.[10]

**Current Treatment**

Current treatment goals for patients with Alzheimer disease are often directed to maintain quality of life, treat cognitive symptoms, and manage behavioral and psychological symptoms of dementia. Treatment remains largely supportive, including creation and implementation of individualized dementia care plans, caregiver education and support, care navigation, care coordination, and referral to community-based organizations for services (eg, adult day care, caregiver training, etc).[11] Non-pharmacologic treatments include physical activity[12,13] as well as behavioral strategies to ameliorate neuropsychiatric symptoms (eg, agitation, delusions, disinhibition), and problem behaviors (eg, resistance to care, hoarding, obsessive-compulsive behaviors).[14] Currently FDA-approved drugs for Alzheimer include cholinesterase inhibitors donepezil, rivastigmine, and galantamine, and the N-methyl-D-aspartate antagonist memantine. Cholinesterase inhibitors are indicated in mild, moderate, and severe AD, while memantine is approved for moderate-to-severe AD. These drugs, either alone or in combination, focus on managing cognitive and functional symptoms of the disease and have not been shown to alter disease trajectory. The evidence for efficacy is limited and associated with significant side effects.[14,15]

Table 1. National Institute on Aging-Alzheimer's Association Numerical Clinical Staging for Individuals in the Alzheimer Continuum[a]

| **Severity Clinical Features** |
|---|
| **Stage 1: Pre-clinical** |
| ▪ Performance within expected range on objective cognitive tests. |

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| ▪ No evidence of recent cognitive decline or new neurobehavioral symptoms. |
| **Stage 2: Pre-clinical** |
| ▪ Normal performance within expected range on objective cognitive tests.<br>▪ Transitional cognitive decline (change from individual baseline within past 1 to 3 years, and persistent for at least 6 months).<br>▪ Mild neurobehavioral changes may coexist or may be the primary complaint rather than cognitive.<br>▪ No functional impact on daily life activities. |
| **Stage 3: Mild Cognitive Impairment (MCI) due to Alzheimer disease** |
| ▪ Performance in the impaired/abnormal range on objective cognitive tests.<br>▪ Evidence of decline from baseline.<br>▪ Performs daily life activities independently, but cognitive difficulty may result in detectable but mild functional impact on the more complex activities of daily life. |
| **Stage 4: Mild Dementia** |
| ▪ Substantial progressive cognitive impairment affecting several domains, and/or neurobehavioral disturbance.<br>▪ Clearly evident functional impact on daily life, affecting mainly instrumental activities.<br>▪ No longer fully independent/requires occasional assistance with daily life activities. |
| **Stage 5: Moderate Dementia** |
| ▪ Progressive cognitive impairment or neurobehavioral changes.<br>▪ Extensive functional impact on daily life with impairment in basic activities.<br>▪ No longer independent and requires frequent assistance with daily life activities. |
| **Stage 6: Severe Dementia** |
| ▪ Progressive cognitive impairment or neurobehavioral changes.<br>▪ Clinical interview may not be possible.<br>▪ Complete dependency due to severe functional impact on daily life with impairment in basic activities, including basic self-care. |

Adapted from Table 6, Jack et al (2018)[16]

[a]Applicable only to individuals in the Alzheimer continuum that fall into 1 of the 4 biomarker groups:

1. A+T+N+
2. A+T-N-
3. A+T+N-
4. A+T-N+ where A: Aggregated Aβ or associated pathologic state (CSF Aβ42, or Aβ42/Aβ40 ratio or Amyloid PET), T: Aggregated tau (neurofibrillary tangles) or associated pathologic state (CSF phosphorylated tau or Tau PET) and N: Neurodegeneration or neuronal injury (anatomic MRI, FDG PET or CSF total tau)

- For stages 1 to 6: Cognitive test performance may be compared to normative data of the investigators choice, with or without adjustment (choice of the investigators) for age, sex, education, etc.
- For stages 2 to 6: Although cognition is the core feature, neurobehavioral changes—for example, changes in mood, anxiety, or motivation—may coexist.
- For stages 3 to 6: Cognitive impairment may be characterized by presentations that are not primarily amnestic.

CSF: cerebrospinal fluid; FDG: fluorodeoxyglucose; MCI: mild cognitive impairment; MRI: magnetic resonance imaging; PET: positron emission tomography.

## Summary

Alzheimer disease is a neurodegenerative disorder leading to progressive, irreversible destruction of neurons and loss of cognitive function and memory. Over time, patients progress to severe dementia, loss of independence, and death. Extracellular deposits of amyloid beta (A-β), referred to as amyloid plaques are considered a hallmark of the disease. Beta-amyloid monomers lead to formation of beta oligomers and fibrils and are deposited as plaques and then interact with tau fibrils, leading to formation of neuro-fibrillatory tangles. These pathophysiological changes and clinical manifestations of Alzheimer

disease are progressive and occur along a continuum, and accumulation of A-β may begin 20 years or more before symptoms arise.

Aducanumab is a human IgG1 anti-A-β antibody targeting amyloid aggregates. The drug is administered by intravenous infusion every 4 weeks. Binding of antibody is intended to lead to clearance of amyloid from the brain. On June 7, 2021, the U.S. Food and Drug Administration approved Aduhelm (aducanumab) for the treatment of Alzheimer disease. It was approved under accelerated approval based on reduction in A-β plaques observed in patients treated with aducanumab. Continued approval for this indication may be contingent upon verification of clinical benefit in confirmatory trial.

Lecanemab is a human IgG1 anti-A-β antibody targeting amyloid aggregates. The drug is administered by intravenous infusion every 2 weeks. Binding of antibody is intended to lead to clearance of amyloid from the brain. On January 6, 2023, the U.S. Food and Drug Administration approved Leqembi (lecanemab) for the treatment of Alzheimer disease. It was approved under accelerated approval based on reduction in A-β plaques observed in patients treated with lecanemab. Continued approval for this indication may be contingent upon verification of clinical benefit in confirmatory trial. Also on January 6, 2023 the company submitted for full approval with results from the Clarity AD (NCT03887455) trial.

**Summary of Evidence:** For individuals with early Alzheimer disease (mild cognitive impairment [MCI] or mild dementia due to Alzheimer disease) who receive aducanumab, the evidence includes 2 randomized controlled trials (RCTs) and 1 dose-finding and proof of concept phase I trial. Relevant outcomes are disease-specific survival, change in disease status, functional outcomes, health status measures, quality of life, and treatment-related mortality and morbidity. ENGAGE (study 301) and EMERGE (study 302) were identical randomized, double-blind, placebo-controlled studies that enrolled patients with early Alzheimer disease. The majority of patients had a diagnosis of MCI due to Alzheimer disease (81.6%) and approximately two-thirds were apolipoprotein E ε4 carriers. The primary clinical outcome was change in mean score on the Clinical Dementia Rating Scale – Sum of Boxes (CDR-SB). Both trials were terminated early following a prespecified interim analysis for futility. In study 301, there was no treatment benefit observed in either the high- or low-dose arms at week 78. In study 302, a statistically significant difference in change from baseline in CDR-SB was observed in the high-dose arm (difference vs. placebo -0.39 [95% confidence interval, -0.69 to -0.09]) but not the low-dose arm at week 78. The observed change of 0.39 was well below the range of 1 to 2 points reported as the minimal clinically important difference in published literature. Approval by the FDA was based on the reduction in A-β plaques, which was observed in both trials and at all doses. However, there are no satisfactory data clearly establishing that individual changes in amyloid correlate with or predict long term cognitive and functional changes. In the absence of clinical data convincingly demonstrating a clinical effect, it cannot be concluded that the observed reduction in amyloid will translate into a clinical benefit to patients. Cognitive decline in early Alzheimer disease generally occurs over years, and thus the follow-up duration may not be sufficient to conclude whether a drug is effective for this disease or whether the safety profile might change with longer follow-up. Pooled safety data showed that about 35% of patients on aducanumab experienced amyloid-related imaging abnormalities (ARIA) as well an increase in the risk of falling. A confirmatory, prospective and adequately powered trial is necessary to assess the net health benefit of aducanumab in patients with early Alzheimer disease. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Study 201 met the criteria for accelerated approval of Leqembi according to the FDA. Change from baseline in brain amyloid plaque, as measured by 18F-florbetapir PET and quantified by a composite standard uptake value ratio (SUVR), was assessed in a subset of patients at Weeks 53 and 79. These data, as shown in Table 3, served as the endpoint supporting accelerated approval. Compared with placebo, the Leqembi 10 mg/kg biweekly arm demonstrated a statistically significant reduction in brain amyloid plaque at Week 79 (mean difference of −0.31 SUVR or −73.5 Centiloids; P <0.001)

| Table 3. Biomarker Results for Leqembi in Study 201 | | |
|---|---|---|
| **Biomarker Endpoints[a]** | **Leqembi 10 mg/kg every 2 weeks** | **Placebo** |
| **Aβ PET Composite SUVR** | N = 44 | N = 98 |
| Mean baseline | 1.373 | 1.402 |
| Adjusted mean change from baseline at Week 79<br>Difference from placebo | −0.306<br>−0.310 (*P* <0.001) | 0.004 |
| **Aβ PET Centiloid** | N = 44 | N = 98 |
| Mean baseline | 78.0 | 84.8 |
| Adjusted mean change from baseline at Week 79<br>Difference from placebo | −72.5<br>−73.5 (*P* <0.001) | 1.0 |
| **Plasma Aβ42/40[b]** | N = 43 | N = 88 |
| Mean baseline | 0.0842 | 0.0855 |
| Adjusted mean change from baseline at Week 79<br>Difference from placebo | 0.0075<br>0.0054 (*P* = 0.0036) | 0.0021 |
| **Plasma p-tau181 (pg/mL)[b]** | N = 84 | N = 179 |
| Mean baseline | 4.6474 | 4.435 |
| Adjusted mean change from baseline at Week 79<br>Difference from placebo | −1.1127<br>−1.1960 (*P* <0.0001) | 0.0832 |

## Individual Consideration

All our medical policies are written for the majority of people with a given condition. Each policy is based on medical science. For many of our medical policies, each individual's unique clinical circumstances may be considered in light of current scientific literature. Physicians may send relevant clinical information for individual patients for consideration to:

Blue Cross Blue Shield of Massachusetts
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## Policy History

| Date | Action |
|---|---|
| 8/2023 | Policy clarified to remove reference to Medicare from the commercial policy. Medicare policy is followed for Medicare Advantage members. |
| 7/2023 | Reformatted Policy. |
| 4/2023 | Updated to add Leqembi (lecanemab) to the policy as investigational. |
| 8/2021 | New medical policy describing investigational indications. The use of aducanumab is considered investigational for all indications including treatment of Alzheimer disease. Effective 8/1/2021. |

## Information Pertaining to All Blue Cross Blue Shield Medical Policies

Click on any of the following terms to access the relevant information:
Medical Policy Terms of Use
Managed Care Guidelines
Indemnity/PPO Guidelines
Clinical Exception Process
Medical Technology Assessment Guidelines

## References

1. 2021 Alzheimer's disease facts and figures. Alzheimers Dement. Mar 2021; 17(3): 327-406. PMID 33756057

2. Alzheimer's Association. 2021 Alzheimers disease facts and figures. Published 2021. Available at https://www.alz.org/media/Documents/alzheimers-facts-and-figures.pdf. Accessed June 28, 2021.
3. Roberts RO, Aakre JA, Kremers WK, et al. Prevalence and Outcomes of Amyloid Positivity Among Persons Without Dementia in a Longitudinal, Population-Based Setting. JAMA Neurol. Aug 01 2018; 75(8): 970-979. PMID 29710225
4. Elias-Sonnenschein LS, Viechtbauer W, Ramakers IH, et al. Predictive value of APOE-4 allele for progression from MCI to AD-type dementia: a meta-analysis. J Neurol Neurosurg Psychiatry. Oct 2011; 82(10): 1149-56. PMID 21493755
5. Mattsson N, Groot C, Jansen WJ, et al. Prevalence of the apolipoprotein E 4 allele in amyloid positive subjects across the spectrum of Alzheimer's disease. Alzheimers Dement. Jul 2018; 14(7): 913-924. PMID 29601787
6. Farrer LA, Cupples LA, Haines JL, et al. Effects of age, sex, and ethnicity on the association between apolipoprotein E genotype and Alzheimer disease. A meta-analysis. APOE and Alzheimer Disease Meta Analysis Consortium. JAMA. Oct 1997; 278(16): 1349-56. PMID 9343467
7. Bekris LM, Yu CE, Bird TD, et al. Genetics of Alzheimer disease. J Geriatr Psychiatry Neurol. Dec 2010; 23(4): 213-27. PMID 21045163
8. Vermunt L, Sikkes SAM, van den Hout A, et al. Duration of preclinical, prodromal, and dementia stages of Alzheimer's disease in relation to age, sex, and APOE genotype. Alzheimers Dement. Jul 2019; 15(7): 888-898. PMID 31164314
9. US Food and Drug Administration. Early Alzheimers disease: developing drugs for treatment guidance for industry. Draft Guidance. Published online Feb 29, 2018. Available at https://www.fda.gov/media/110903/download. Accessed on June 28, 2021
10. Combined FDA and Applicant PCNS Drugs Advisory Committee Briefing Document: Peripheral and Central Nervous System (PCNS) Drugs Advisory Committee Meeting- November 6, 2020. Available at https://www.fda.gov/media/143502/download Accessed June 28 2021
11. Reuben DB, Tan ZS, Romero T, et al. Patient and Caregiver Benefit From a Comprehensive Dementia Care Program: 1-Year Results From the UCLA Alzheimer's and Dementia Care Program. J Am Geriatr Soc. Nov 2019; 67(11): 2267-2273. PMID 31355423
12. Gronek P, Balko S, Gronek J, et al. Physical Activity and Alzheimer's Disease: A Narrative Review. Aging Dis. Dec 2019; 10(6): 1282-1292. PMID 31788339
13. Du Z, Li Y, Li J, et al. Physical activity can improve cognition in patients with Alzheimer's disease: a systematic review and meta-analysis of randomized controlled trials. Clin Interv Aging. 2018; 13: 1593-1603. PMID 30233156
14. Gitlin LN, Kales HC, Lyketsos CG. Nonpharmacologic management of behavioral symptoms in dementia. JAMA. Nov 21 2012; 308(19): 2020-9. PMID 23168825
15. Kaduszkiewicz H, Zimmermann T, Beck-Bornholdt HP, et al. Cholinesterase inhibitors for patients with Alzheimer's disease: systematic review of randomised clinical trials. BMJ. Aug 06 2005; 331(7512): 321-7. PMID 16081444
16. Jack CR, Bennett DA, Blennow K, et al. NIA-AA Research Framework: Toward a biological definition of Alzheimer's disease. Alzheimers Dement. Apr 2018; 14(4): 535-562. PMID 29653606
17. US Food and Drug Administration. Early Alzheimers disease: developing drugs for treatment guidance for industry. Draft Guidance. Published online Feb 29, 2018. Available at https://www.fda.gov/media/110903/download. Accessed on June 28, 2021
18. US Food and Drug Administration. Draft guidance for industry on Alzheimers disease: developing drugs for the treatment of early stage disease. Published online March 28, 2013. Available at https://isctm.org/public_access/FDAGuidance_AD_Developing_Drugs_Early_Stage_Treatment.pdf. Accessed on June 29, 2021
19. Liu KY, Schneider LS, Howard R. The need to show minimum clinically important differences in Alzheimer's disease trials. Lancet Psychiatry. Jun 01 2021. PMID 34087114
20. Cedarbaum JM, Jaros M, Hernandez C, et al. Rationale for use of the Clinical Dementia Rating Sum of Boxes as a primary outcome measure for Alzheimer's disease clinical trials. Alzheimers Dement. Feb 2013; 9(1 Suppl): S45-55. PMID 22658286
21. Andrews JS, Desai U, Kirson NY, et al. Disease severity and minimal clinically important differences in clinical outcome assessments for Alzheimer's disease clinical trials. Alzheimers Dement (N Y). 2019; 5: 354-363. PMID 31417957

22. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res. Nov 1975; 12(3): 189-98. PMID 1202204
23. Chapman KR, Bing-Canar H, Alosco ML, et al. Mini Mental State Examination and Logical Memory scores for entry into Alzheimer's disease trials. Alzheimers Res Ther. Feb 22 2016; 8: 9. PMID 26899835
24. Franco-Marina F, Garcia-Gonzalez JJ, Wagner-Echeagaray F, et al. The Mini-mental State Examination revisited: ceiling and floor effects after score adjustment for educational level in an aging Mexican population. Int Psychogeriatr. Feb 2010; 22(1): 72-81. PMID 19735592
25. Galasko D, Abramson I, Corey-Bloom J, et al. Repeated exposure to the Mini-Mental State Examination and the Information-Memory-Concentration Test results in a practice effect in Alzheimer's disease. Neurology. Aug 1993; 43(8): 1559-63. PMID 8351011
26. Spencer RJ, Wendell CR, Giggey PP, et al. Psychometric limitations of the mini-mental state examination among nondemented older adults: an evaluation of neurocognitive and magnetic resonance imaging correlates. Exp Aging Res. 2013; 39(4): 382-97. PMID 23875837
27. Mohs RC, Knopman D, Petersen RC, et al. Development of cognitive instruments for use in clinical trials of antidementia drugs: additions to the Alzheimer's Disease Assessment Scale that broaden its scope. The Alzheimer's Disease Cooperative Study. Alzheimer Dis Assoc Disord. 1997; 11 Suppl 2: S13-21. PMID 9236948
28. Rosen WG, Mohs RC, Davis KL. A new rating scale for Alzheimer's disease. Am J Psychiatry. Nov 1984; 141(11): 1356-64. PMID 6496779
29. Schrag A, Schott JM. What is the clinically relevant change on the ADAS-Cog?. J Neurol Neurosurg Psychiatry. Feb 2012; 83(2): 171-3. PMID 22019547
30. McDougall F, Edgar C, Mertes M, et al. Psychometric Properties of the Clinical Dementia Rating - Sum of Boxes and Other Cognitive and Functional Outcomes in a Prodromal Alzheimer's Disease Population. J Prev Alzheimers Dis. 2021; 8(2): 151-160. PMID 33569561
31. Vellas B, Bateman R, Blennow K, et al. Endpoints for Pre-Dementia AD Trials: A Report from the EU/US/CTAD Task Force. J Prev Alzheimers Dis. Jun 2015; 2(2): 128-135. PMID 26247004
32. Bullock R, Touchon J, Bergman H, et al. Rivastigmine and donepezil treatment in moderate to moderately-severe Alzheimer's disease over a 2-year period. Curr Med Res Opin. Aug 2005; 21(8): 1317-27. PMID 16083542
33. Tariot PN, Solomon PR, Morris JC, et al. A 5-month, randomized, placebo-controlled trial of galantamine in AD. The Galantamine USA-10 Study Group. Neurology. Jun 27 2000; 54(12): 2269-76. PMID 10881251
34. Doody RS, Thomas RG, Farlow M, et al. Phase 3 trials of solanezumab for mild-to-moderate Alzheimer's disease. N Engl J Med. Jan 23 2014; 370(4): 311-21. PMID 24450890
35. Cummings J. The Neuropsychiatric Inventory: Development and Applications. J Geriatr Psychiatry Neurol. Mar 2020; 33(2): 73-84. PMID 32013737
36. Howard R, Phillips P, Johnson T, et al. Determining the minimum clinically important differences for outcomes in the DOMINO trial. Int J Geriatr Psychiatry. Aug 2011; 26(8): 812-7. PMID 20848576
37. Sevigny J, Chiao P, Bussiere T, et al. The antibody aducanumab reduces A plaques in Alzheimer's disease. Nature. Sep 01 2016; 537(7618): 50-6. PMID 27582220
38. FDA Pre-Recorded Presentation Slides for the November 6, 2020: Meeting of the Peripheral and Central Nervous System Drugs Advisory Committee. Available at https://www.fda.gov/media/143504/download. Accessed on June 28, 2021
39. Prescribing Label: ADUHELM (aducanumab-avwa) injection, for intravenous use Available at https://www.biogencdn.com/us/aduhelm-pi.pdf. Accessed on June 28, 2021
40. Biogen Presentation for the November 6, 2020: Meeting of the Peripheral and Central Nervous System Drugs Advisory Committee. Available at https://www.fda.gov/media/143577/download. Accessed on June 28, 2021
41. Aducanumab for Alzheimers Disease: Effectiveness and Value- Draft Evidence Review. Institute for Clinical and Economic Review (ICER). Available at https://icer.org/wp-content/uploads/2020/10/ICER_ALZ_Draft_Evidence_Report_050521.pdf. Accessed on June 29, 2021
42. NEW DRUG REVIEW Leqembi (lecanemab-irmb). IPD Analytics. January 2023