ICARE AD-US: Design of a Prospective, Single-Arm, Multicenter, Noninterventional Real-World Study of Aducanumab in the United States

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Introduction

- The accumulation of Aβ plaques in the brain is a defining pathophysiological feature of Alzheimer's disease[1]
- Aducanumab is a human, immunoglobulin gamma 1 monoclonal antibody directed against aggregated soluble and insoluble forms of Aβ[2]
- Aducanumab is approved by the US FDA with the following indication[3]:
  - ADUHELM is an amyloid beta-directed antibody indicated for the treatment of Alzheimer's disease. Treatment with ADUHELM should be initiated in patients with mild cognitive impairment or mild dementia stage of disease, the population in which treatment was initiated in clinical trials. There are no safety or effectiveness data on initiating treatment at earlier or later stages of the disease than were studied. This indication is approved under accelerated approval based on reduction in amyloid beta plaques observed in patients treated with ADUHELM. Continued approval for this indication may be contingent upon verification of clinical benefit in confirmatory trial(s)
- Biogen is establishing ICARE AD as a real-world study to evaluate the safety and effectiveness of aducanumab in ~200 centers representing diverse Alzheimer's disease care settings (e.g., academic centers, memory clinics), with broad geographical representation across the US

ICARE AD-US will collect longitudinal clinical, imaging, and pharmacoeconomic data to evaluate the safety and effectiveness of aducanumab in real-world clinical practice based on the FDA-approved label

AD, Alzheimer's disease; Aβ, amyloid beta; FDA, Food and Drug Administration; ICARE AD, International Collaboration for Real-World Evidence in Alzheimer's Disease.

1. Jack CR Jr, et al. Alzheimers Dement. 2018;14:535-562; 2. Sevigny J, et al. Nature. 2016;537(7618): 50-56; 3. Aduhelm. Prescribing information. Biogen, Inc.; 2021.

Study design and population

- ICARE AD-US is a prospective, single-arm, multicenter study of aducanumab as prescribed in routine clinical practice
  - Clinical measures were selected based on their sensitivity to change in early-stage Alzheimer's disease and their feasibility in routine clinical care
  - Biobanking of longitudinally blood (plasma and serum) collection will enable blood-based biomarker studies

- Patients will be monitored for a period of up to 5 years
- This observational study aims to enroll ~6000 patients with Alzheimer's disease (including ~500 African American and ~500 Hispanic/Latinx patients) from approximately 200 sites in the US over 4 years

- Participating sites have been selected based on ability to implement Core Data Elements

ICARE AD, International Collaboration for Real-World Evidence in Alzheimer's Disease.

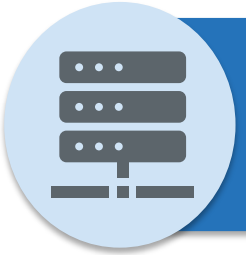
Study objectives and measures

Primary objective	**To characterize and evaluate real-world, long-term changes in cognition, function, and neuropsychiatric status in aducanumab-treated patients**
Primary clinical measures	• Changes in cognition, function, neuropsychiatric status, QOL, and health economics
Secondary objectives	• Evaluate the incidence of AEs, including SAEs, and compare the incidence of SAEs in aducanumab-treated patients with and without ARIA • Assess the incidence and the clinical and potential radiographic outcomes of ARIA-E associated with aducanumab treatment in real-world practice • Estimate the incidence of symptomatic ARIA in real-world clinical practice • Obtain descriptive statistics on the characteristics of the aducanumab user population and on drug utilization

AE, adverse event; ARIA, amyloid-related imaging abnormalities; ARIA-E, amyloid-related imaging abnormalities due to vasogenic edema; QOL, quality of life; SAE, serious adverse event.

Data collection

Data will be captured by trained site personnel as part of a structured tool or interview, or collected prospectively as part of an unstructured interview with the patient and the informant / care partner



Data will be entered directly into the database through web-based eCRFs

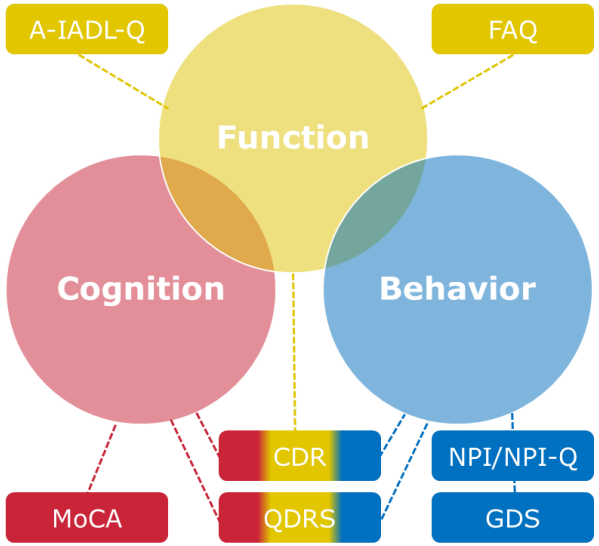
Visits will be conducted within the context of SOC; thus, the schedule for data collection timepoints is approximately every 6 months and not mandated by the study protocol

eCRF, electronic case report form; SOC, standard of care.

Clinical and brain imaging data

Clinical data set[a]

Instruments to measure changes in cognition, function, and neuropsychiatric status



CDR global at baseline: Clinical Dementia Rating

MoCA v8.1: Montreal Cognitive Assessment

QDRS: Quick Dementia Rating System

A-IADL-Q-SV: Amsterdam Instrumental Activities of Daily Living Questionnaire Short Version

FAQ: Functional Activities Questionnaire

NPI-Q: Neuropsychiatric Inventory Questionnaire

GDS-SF: Geriatric Depression Scale Short Form

Instruments to measure changes in QOL and health economics

QOL-AD: Quality of Life–Alzheimer's disease

SF-12 v2: Short Form-12 Health Survey

Zarit Burden Interview

RUD Lite: Resource Utilization in Dementia

PGIC: Patient Global Impression of Change

PGIS: Patient Global Impression of Severity

[a] All instruments will be administered electronically by device/tablet.

MRI data

Baseline and follow up

- MRI methods (e.g., T2*-weighted GRE sequence) from real-world visits
- Patient MRI reports from real-world visits

MRI findings of interest

- ARIA-E status
- Cerebral amyloid angiopathy status
- Number of microhemorrhages (≤1 cm diameter)
- Hemorrhages >1 cm diameter and location
- Superficial siderosis status
- White matter T2 hyperintense lesions
- Lacunar infarct (≤1.5 cm diameter)
- Cortical infarct (>1.5 cm diameter)

A-IADL-Q-SV, Amsterdam Instrumental Activities of Daily Living Questionnaire Short Version; ARIA-E, amyloid-related imaging abnormalities due to vasogenic edema; CDR, Clinical Dementia Rating; FAQ, Functional Activities Questionnaire; GDS-SF, Geriatric Depression Scale Short Form; GRE, gradient echo; MoCA, Montreal Cognitive Assessment; MRI, magnetic resonance imaging; NPI-Q, Neuropsychiatric Inventory Questionnaire; PGIC/S, Patient Global Impression of Change/Severity; QDRS, Quick Dementia Rating System; QOL-AD, Quality of Life–Alzheimer's disease; RUD, Resource Utilization in Dementia; SF-12, Short Form-12 Health Survey.

1. Alzheimercentrum Amsterdam. Amsterdam IADL Questionnaire: Available from: https://www.alzheimercentrum.nl/professionals/Amsterdam-iadl/ (Accessed July 1, 2021).

Schedule of assessments

Assessments	Baseline	Follow-up visits (6m-54m)	End of study visit (60m)
Demographic data (including formal education and family history of AD)	X		
Place of residence	X	X	X
Level of care	X	X	X
AD clinical characteristics (age of onset and age at diagnosis)	X		
Clinical disease stage[1]	X	X	X
Medical history at baseline, and incidence of any new onset or worsening of conditions (selected conditions: diabetes, coagulation disorders, cancer, cardiovascular disease, major depression, cerebrovascular disease, other neurological disease)	X	X	X
AEs (AEs, SAEs, ARIA related clinical AEs per Investigator, and AEs leading to aducanumab discontinuation)		X	X
Biomarker data for Aβ confirmation	X		
Aβ pathology confirmation (method and results)	X		
Other AD biomarkers (p-tau and t-tau)	O	O	O
ApoE ε4 genotyping conducted and ApoE ε4 genotyping result	O	O	O
Blood (plasma and serum) collection for biobank at baseline, M6, 12, 24, 36, 48, 60	X	X	X
CSF collection or sharing of CSF biomarker data[2]	O	O	O
Donation of blood for future genetic/biomarker testing[2]	O	O	O
Concomitant medications at baseline, and new or changed medications during follow-up	X	X	X
Aducanumab dosing (mg/kg)	X	X	X
Brain imaging data	X	X	X
Physical assessments (BMI, vitals, neurological exam)	X	X	X
Lifestyle data (alcohol, smoking, substance abuse)			
Physical exercise	O	O	O
Cognitive measures	X	X	X
Functional and neuropsychiatric measures	X	X	X
Quality of Life and disease burden	X	X	X

AD, Alzheimer's disease; AE, adverse event; ApoE, apolipoprotein E; ARIA, amyloid-related imaging abnormalities; Aβ, amyloid beta; BMI, body mass index; CSF, cerebrospinal fluid; m, month; mg/kg, milligram per kilogram; p-tau, phosphorylated tau; SAE, serious adverse event; t-tau, total tau.

1. (ADI) AsDI. World Alzheimer Report 2015: The Global Impact of Dementia. 2015; 2. Nelson PT, et al. J Neuropathol Exp Neurol. 2009;68(7):774-84.

Summary

- The ICARE AD-US study will:
  - Collect a harmonized, long-term core data set to assess the long-term effectiveness and safety of aducanumab treatment in real-world clinical practice
  - Assess effectiveness and safety of aducanumab treatment in patients from underrepresented racial and ethnic minorities to inform real-world clinical practice

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