

Sample Question—Answer Pairs From the MACg Hallucination, Accuracy, and Contextual Understanding Study

1. What were the key inclusion criteria, including disease stage, age range, and amyloid confirmation method, for enrollment in the Clarity AD trial?

- **Disease stage**
 - Early Alzheimer's disease, defined as:
 - Mild cognitive impairment (MCI) due to Alzheimer's disease or
 - Mild Alzheimer's disease–related dementia, both per NIA–AA criteria.
 - Required global *CDR score ≥ 0.5 , with 0.5 as the threshold for Alzheimer's disease and typical baseline CDR-SB around 3.2, consistent with early AD.
- *(MACg used CDR information from the baseline table footnote)
- **Age range**
 - Participants were **50 to 90 years of age** at enrollment.
 - **Amyloid confirmation method**
 - Mandatory evidence of brain amyloid pathology, established before randomization by:
 - Amyloid-positive PET (using standard amyloid tracers) or
 - Cerebrospinal fluid (CSF) evidence of amyloid pathology via A β 1–42 measurement, indicating amyloid positivity.
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2. Describe the timing and pattern of ARIA-E and ARIA-H events (e.g., early vs throughout the trial; isolated ARIA-H vs ARIA-H with ARIA-E).

ARIA-E (edema/effusions)

- Timing over the trial

- Majority occurred early:
 - $\approx 71\%$ of ARIA-E events with lecanemab occurred during the first 3 months of treatment.
 - ARIA-E was monitored over the full 18-month period, but the peak incidence was early after initiation.
- Resolution:
 - $\approx 81\%$ of ARIA-E events resolved within 4 months after detection on MRI.
 - Events were described as generally self-limited with appropriate monitoring and dose management.
- Severity:
 - $\approx 91\%$ were mild or moderate on central read using protocol-defined severity criteria.
 - ARIA-E rarely led to treatment discontinuation when mild.
- Symptomatology
 - Most ARIA-E was asymptomatic: $\approx 78\%$ of events had no associated symptoms.
 - When symptomatic (2.8% of lecanemab-treated participants):
 - Common symptoms: headache, visual disturbance, and confusion.
 - Symptomatic ARIA-E events were included under ARIA-E (not double-counted as symptomatic ARIA-H).

ARIA-H (microhemorrhage, superficial siderosis, macrohemorrhage)

- Pattern: isolated ARIA-H vs ARIA-H with ARIA-E
 - Isolated ARIA-H (no concurrent ARIA-E):
 - Lecanemab: 80/898 (8.9%).
 - Placebo: 70/897 (7.8%).
 - These events represent background microhemorrhage/siderosis signal plus any treatment effect and were relatively similar between arms.
 - Concurrent ARIA-H with ARIA-E:
 - Lecanemab: 74/898 (8.2%).
 - Placebo: 9/897 (1.0%).
 - These combined events account for much of the excess ARIA-H in the lecanemab group.
- Timing over the trial
 - ARIA-H occurring with ARIA-E:
 - “Tended to occur early (within 6 months)” of treatment, paralleling the early window for ARIA-E.
 - Isolated ARIA-H (without ARIA-E):
 - “Occurred throughout the trial”, i.e., events were seen across the 18-month period and not confined to early dosing.

- Symptomatic ARIA-H
 - Symptomatic ARIA-H overall:
 - Lecanemab: 6/898 (0.7%).
 - Placebo: 2/897 (0.2%).
 - Isolated symptomatic ARIA-H (no ARIA-E):
 - Lecanemab: 0.7%.
 - Placebo: 0.2%.
 - Most common symptom in isolated symptomatic ARIA-H: dizziness.

Overall clinical course and management implications

- ARIA-E:
 - Typically early-onset, mild–moderate, and often asymptomatic, with radiologic resolution in most cases within ~4 months.
 - Mild events generally did not require permanent discontinuation; management relied on MRI surveillance and temporary treatment interruption/dose adjustments per protocol.
- ARIA-H:
 - Early ARIA-H was usually linked to ARIA-E, while isolated ARIA-H accumulated across the 18-month period.
 - Symptomatic ARIA-H was rare, and when present, symptoms were often non-focal (e.g., dizziness) rather than catastrophic hemorrhagic presentations.

*(MACg compiled data from tables, footnotes, and several areas of the publication to provide a detailed and accurate response.)

3. Describe the **safety population** and how serious adverse events were defined and collected, including the tools (e.g., Columbia-Suicide Severity Rating Scale) used for safety monitoring.

Safety Population Definition

- The safety set included all patients who received at least one dose of double-blind study drug (zuranolone or placebo).
- Due to two randomization errors (placebo-assigned patients receiving a single dose of zuranolone), the safety population comprised:
 - Zuranolone: 78 patients (including 2 who were randomized to placebo but received ≥ 1 zuranolone dose)
 - Placebo: 73 patients

- Safety analyses, including adverse events (AEs), were conducted on this safety set.

Collection and Definition of Adverse Events

- Treatment-emergent adverse events (TEAEs) were defined as:
 - Any AE with onset after the start of study drug
 - Or worsening of a pre-existing medical condition after starting study drug.
- Severe AEs were defined as AEs that were incapacitating with inability to perform normal activities.
- Serious AEs (SAEs) followed standard regulatory criteria and were defined as any untoward medical occurrence that:
 - Resulted in death
 - Was life-threatening at the time of the event
 - Required inpatient hospitalization
 - Resulted in persistent or significant disability/incapacity
 - Or was a congenital anomaly.
- TEAEs, severe AEs, and SAEs were systematically collected at study visits throughout treatment (days 1–15) and follow-up through day 45.

Safety Monitoring and Assessment Methods

- Safety and tolerability were evaluated using multiple modalities:
 - Adverse events (AEs): collected via patient reports and investigator assessment at scheduled visits.
 - Vital signs: blood pressure, heart rate, etc.
 - Clinical laboratory tests: standard hematology, chemistry, and other routine safety labs.
 - Electrocardiogram (ECG) parameters: to monitor for cardiac effects.
 - Columbia-Suicide Severity Rating Scale (C-SSRS):
 - Used as a standardized tool to assess suicidal ideation and suicidal behavior.
 - Applied serially during the study to detect any emergent or worsening suicidality.
- The trial reports no evidence for increased suicidal ideation or behavior compared with baseline, based on C-SSRS evaluations.

Summary

- Safety population: all dosed participants (78 zuranolone, 73 placebo), analyzed according to actual exposure.
 - SAEs: defined using standard death/life-threatening/hospitalization/disability/congenital anomaly criteria.
 - Safety data collection: structured, multi-modal (AEs, vitals, labs, ECGs) with C-SSRS specifically for suicidality monitoring.
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4. Describe how **symptomatic skeletal event–free survival** and **time to first symptomatic skeletal event** were defined and measured in the study.

Symptomatic Skeletal Event–Free Survival (SSE-FS)

- **Endpoint type and time origin**
 - Time-to-event variable, measured from randomization to the earliest of:
 - First symptomatic skeletal event (SSE), or
 - Death from any cause.
 - Patients without an SSE and alive at data cutoff were censored at the date of the last assessment for this endpoint, using regular 12-weekly visits.
- ***What counted as a “symptomatic skeletal event” (per trial convention for mHSPC/ mCRPC trials)**
 - Although the main NEJM article refers readers to the Supplementary Appendix for exact definitions, SSEs in ARASENS followed the standard definition used in contemporary prostate-cancer trials, including:
 - Pathologic fracture (symptomatic).
 - Spinal cord compression.
 - Radiation therapy to bone for cancer-related symptoms.
 - Surgery to bone (orthopedic procedures) for tumor-related complications.
 - Only symptomatic events qualified; purely radiographic skeletal progression without symptoms did not count as an SSE.

*(MACg correctly mentioned that the detailed definitions of key endpoints were located in a Supplementary Appendix that was not available in the provided PDF. It then used prior domain knowledge from its training (standard endpoint definitions in prostate cancer trials) to infer what those definitions were likely to be and generated them. When we checked the Supplement, the inferred definitions matched the trial's actual endpoint definitions, showing that MACg's extra-document inference was accurate even though it was not directly supported by the main-text article at the time of generation.)

- Assessment schedule and methodology
 - Patients were evaluated every 12 weeks for:
 - Symptomatic skeletal events,
 - Initiation of subsequent systemic antineoplastic therapy,
 - Opioid use ≥ 7 consecutive days,
 - Other secondary endpoints.
 - Imaging (CT/MRI and bone scan) was performed:
 - At baseline,
 - Within 30 days after the last docetaxel cycle,
 - Yearly thereafter during trial treatment.
 - SSE-FS was summarized using Kaplan–Meier estimates, with stratified log-rank testing and stratified Cox models for hazard ratios and 95% CIs, stratified by metastasis stage (M1a/M1b/M1c) and ALP.

Time to First Symptomatic

Event

- Endpoint type and time origin
 - Time-to-event variable, measured from randomization to the first occurrence of an SSE.
 - Unlike SSE-FS, death without a prior SSE did not count as an event; such patients were censored at the date of death or last assessment (standard approach implied by separate reporting of this endpoint and by the table labeling it “time to first SSE”).
- Event definition
 - The same set of qualifying SSEs used for SSE-FS was used here:
 - Symptomatic pathologic fracture.
 - Spinal cord compression.
 - Radiation therapy to the bone for tumor-related symptoms.
 - Surgery to bone for tumor-related complications.
 - Only the first qualifying event per patient was counted for this endpoint.
- Assessment and analysis
 - Assessed on the same 12-weekly visit schedule, using clinical review plus imaging as needed to confirm events.
 - Analyzed with:
 - Kaplan–Meier curves for time to first SSE,
 - Stratified log-rank test (same stratification factors),

- Stratified Cox model to estimate the hazard ratio 0.71 (95% CI 0.54–0.94; P = 0.02) for darolutamide vs placebo.

Summary

- SSE-FS is a composite endpoint (first SSE or death), whereas time to first SSE isolates skeletal morbidity alone by ignoring deaths without prior SSE as events.
- Both endpoints were rigorously captured at 12-weekly visits and analyzed with stratified time-to-event methods, forming part of the hierarchically tested key secondary endpoints in ARASENS.

5. How were **clinical deteriorations/exacerbations** defined, and what were the rates of exacerbations and hospitalizations during the extension compared with the pre-REGAIN period?

Definition of Clinical Deterioration / Exacerbation

- Operational definition in the open-label extension
 - A clinical deterioration/exacerbation was defined as any one of the following:
 - Myasthenic crisis.
 - Substantial symptomatic worsening on MG-ADL, defined as:
 - Increase to a score of 3, or
 - ≥2-point worsening in any single non-ocular MG-ADL item.
 - Investigator judgement that the patient's “health was in jeopardy if rescue therapy was not given.”
 - These events triggered eligibility for rescue therapy (IV steroids, IVIg, or plasma exchange) at investigator discretion.

Exacerbation Rates: Pre-REGAIN vs Open-label Eculizumab

- Overall number of exacerbations in the extension
 - 59 MG exacerbations occurred in 29/117 patients before the interim data cutoff.
- Event rates per 100 patient-years (model-based)

• Period / Treatment phase	• Exacerbation rate (per 100 PY)	• Relative change vs pre-REGAIN	• p-value
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• Pre-REGAIN year (prior to entering REGAIN)	• 102.4	• –	• –
• REGAIN placebo group	• 73.5	• 28% reduction vs pre-REGAIN	• 0.0061
• Open-label eculizumab (extension)	• 25.4	• 75.2% reduction vs pre-REGAIN	• <0.0001

Thus, long-term eculizumab reduced the MG exacerbation rate from 102.4 to 25.4 events per 100 patient-years, a ~75% decrease relative to the year before REGAIN.

MG-related Hospitalization Rates: Pre-REGAIN vs Extension

- Event rates per 100 patient-years (model-based, MG-related hospitalizations)

• Period / Treatment phase	• MG-related hospitalization rate (per 100 PY)	• Relative change vs pre-REGAIN	• p-value
• Pre-REGAIN year	• 81.3	• –	• –
• REGAIN placebo group	• 48.4	• 40% reduction vs pre-REGAIN	• 0.0228
• Open-label eculizumab (extension)	• 13.7	• 83.1% reduction vs pre-REGAIN	• <0.0001

- Compared with the year before REGAIN, long-term eculizumab therapy reduced MG-related hospitalizations from 81.3 to 13.7 events per 100 patient-years, an >80% reduction.