Evidence development for early Alzheimer value substantiation

New FDA guidance and impact on payer and EU HTA asessments

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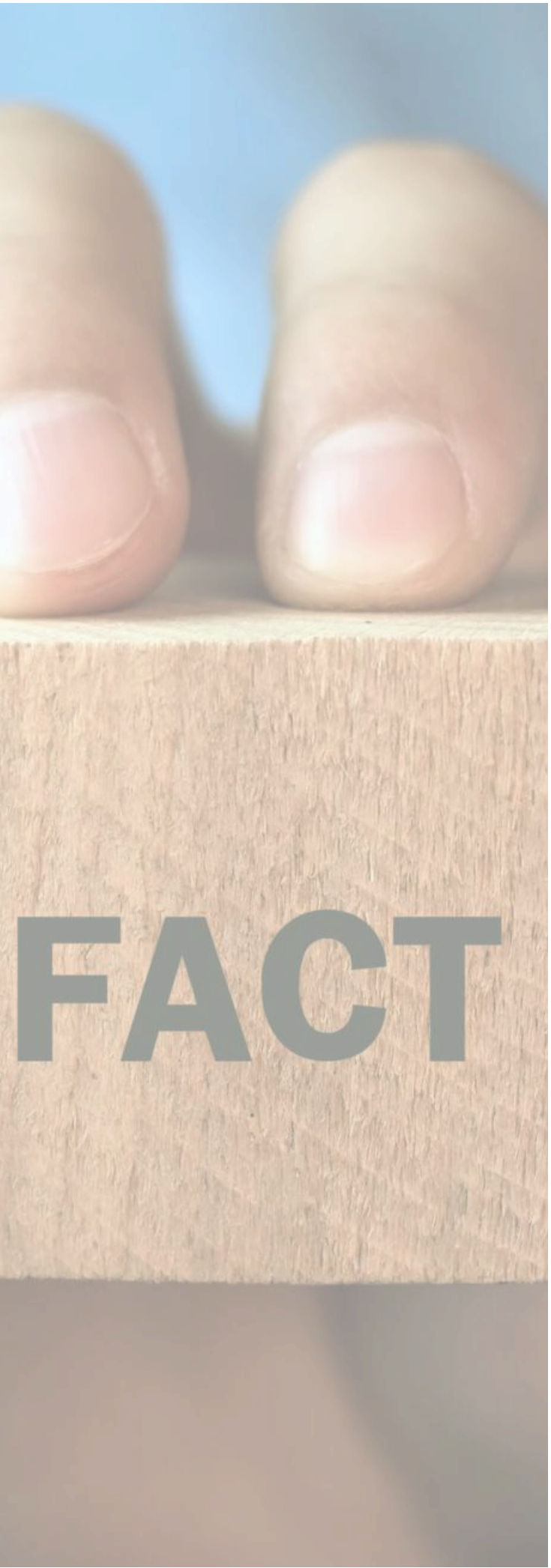


CONTENT

Ensuring that clincial value is evidenced to what matters most to regulators, payers and EU HTA

THE CHALLENGE

Harmonization between the FDA and the EMA guidance, and greater precision by both, could improve trial design as well as clinical and economic value assessment in early AD.

In March 2024, the US Food and Drug Administration (FDA) published revision 2 of its draft guidance for industry on drug development in early Alzheimer's disease (AD). The European Medicines Agency (EMA) last published guidance for industry on this topic in 2018. This research compares these two sets of guidance and identifies implications for EU health technology assessment (HTA) and US payer evaluation.

Objectives: In March 2024, the FDA published draft guidance for industry on drug development in early Alzheimer's disease. The research aims to (a) compare this draft guidance with the latest guidance from EMA on the topic (from 2018), and (b) identify implications for HTA.

Methods: Two reviewers examined and analyzed the latest draft guidance from the FDA and EMA on the topic, compared the agencies' guidance, and identified key implications for EU HTA and US payer evaluation of drugs developed according to the guidance.

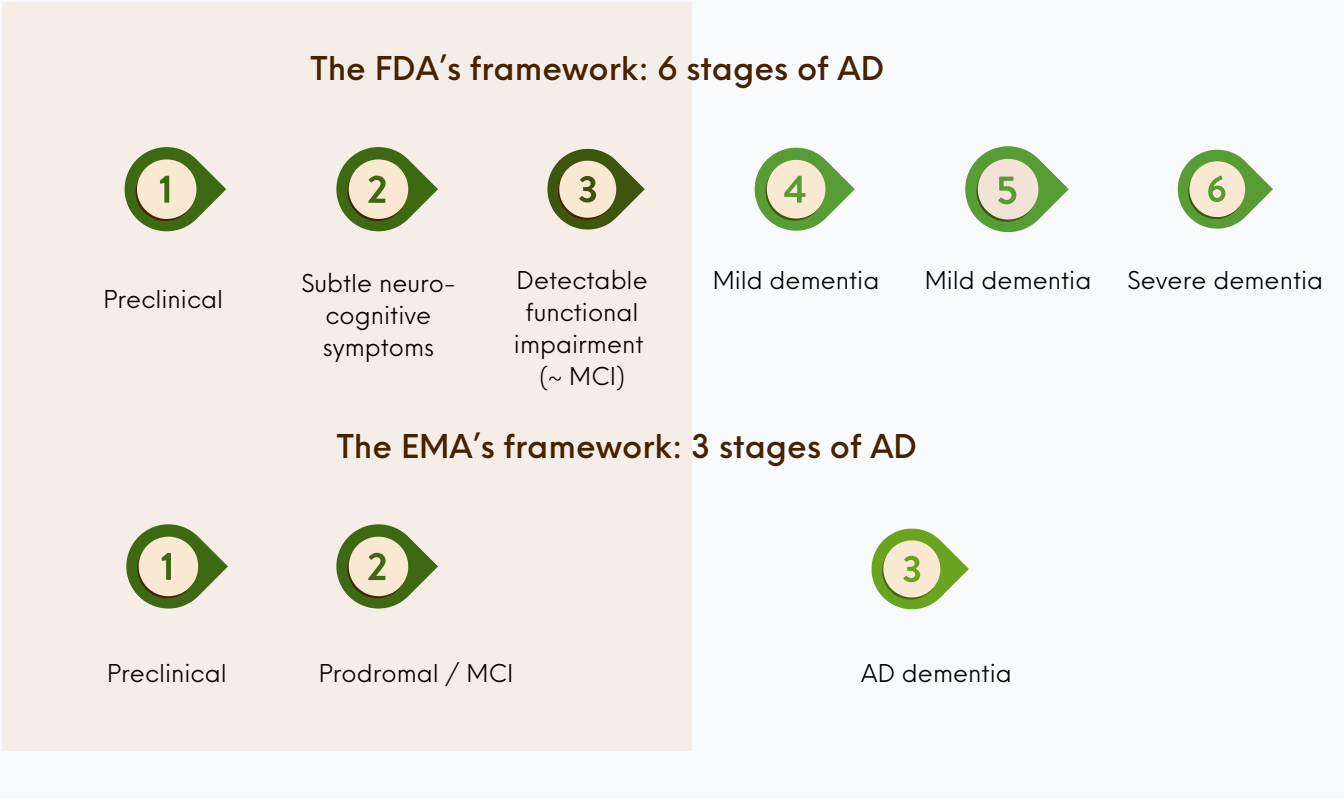
Results: Imprecise definitions of AD stages, and differences between FDA and EMA guidance, will complicate the clinical assessment of EU HTA, the value and health economic evaluation of HTA agencies and payers, and the trial design work of sponsors.

Conclusions: Increasing the precision of AD stage definition and harmonizing guidance between the two regulatory agencies will simplify evidence generation for sponsors and value assessment for HTA agencies and payers.

1. Patient selection for trials in early Alzheimer's Disease (AD)

The FDA and EMA define AD stages differently (see Figure 1). The FDA uses a six-stage framework in which early AD corresponds to Stages 1 through 3. The EMA uses a three-stage framework in which early AD corresponds to Stages 1 and 2.

Figure 1: FDA and EMA Framework ' Definition of Alzheimer's Disease stages



Stage 1 in both frameworks is preclinical AD, when patients have pathophysiological evidence of AD but no symptomatic evidence.
Prodromal disease / mild cognitive impairment (MCI) corresponds to Stages 2 and 3 for the FDA, Stage 2 for the EMA. Both agencies' definitions of these stages are imprecise. The FDA's stage 2 describes patients with "subtle detectable abnormalities on sensitive neuropsychological measures of AD," with no further clarification of what "subtle" means, or which measures qualify as "sensitive." The FDA's stage 2 may also involve "subjective complaints of mild cognitive symptoms" without a definition of "mild."

The FDA's stage 3 describes patients with "generally more apparent detectable abnormalities" without defining the threshold for "generally more apparent" relative to Stage 2. The FDA notes that its Stage 3 "roughly corresponds with the syndrome of mild cognitive impairment" but also recognizes that MCI may include late Stage 2 or early Stage 4.

The EMA leaves open the precise definition of its Stage 2 – because the definitions of prodromal AD/MCI due to AD from the International Working Group (IWG) and the National Institute on Aging – Alzheimer's Association (NIA-AA) differ.

Both agencies recognize heterogeneity of patient progression at the prodromal stage (e.g., some patients compensate better than others for early symptoms; some patients' presentations fit more than one stage).

The differences between FDA and EMA disease progression frameworks and the uncertainty in both agencies' characterization of prodromal AD will complicate sponsors' preparation for EU HTA and US payer evaluation of drugs in early AD. Implications are in Tables 1 and 2.

Table 1: Implications for EU HTA and US payer evaluation - different definitions of early/prodromal stage Alzheimer's disease

Perspective	What's the issue with the regulatory guidance?	Challenges for evidence development	Selected implications for preparing payer/EU HTA submissions
EU HTA	Lack of precise definition of prodromal/ MCI stage	Uncertain parameters for data collection to support disease presentation, health impact, impact on care delivery, and positioning in treatment pathway	Implications to support the background section of the EU HTA dossier (draft stage as of April 2024): Problems describing and evidencing sections on prognostic factors affecting the disease, description of symptoms and burden of medical condition, description of target population and sub-populations and description of clinical pathways.
US payer evaluation	Lack of precise definitions for AD Stages 2 and 3		Same problems described above, plus difficulty reliably modelling budget impact

Table 2: Implications for EU HTA and US payer evaluation – patient selection for trial enrollment in early AD/prodromal stage clinical trials

Perspective	What's the issue with the regulatory guidance?	Challenge for evidence development	Selected implications for preparing submissions
EU HTA	EMA guidance: lack of precise definition of prodromal/MCI stage	Trial enrolment criteria: in-and exclusion criteria uncertainty due to demarcations between disease stage not clearly defined or defined differently along FDA and EMA guidance Enrichment strategies May be accepted/not accepted by different member states and impact expected outcomes and populations when defining PICO	Implications to support the Assessment Scope section EU HTA dossier draft stage as of April 2024: PICO assessment may yield a variety of populations and comparators across EU member states. Implications to support the Description of methods section EU HTA dossier draft stage as of April 2024: inclusion and exclusion criteria may be accepted / not accepted along PICO.
US payer evaluation	Lack of precise definitions for AD Stages 2 and 3	Varying populations across trials within same indication	Will complicate indirect treatment comparison and budget impact estimation

2. Trial designs and outcome measures in early Alzheimer's Disease (AD)

Trial duration

While the FDA prioritizes shorter trials of two years or less in early AD, the EMA distinguishes between stages. In preclinical AD, the EMA advises a duration of at least three years to ensure adequate time to capture cognitive changes which occur over long time periods. The EMA would be open to shorter trials in preclinical AD, once reliable surrogate endpoints are identified. In prodromal AD / MCI due to AD, the EMA advises trials of at least 18 months.

Outcome measures

In prioritizing shorter trials, the FDA is willing to consider as the basis for approval both cognition-only endpoints (without function) and surrogate endpoints in early AD. Cognition-only endpoints should be supported with large effect sizes and statistical robustness.

The EMA advises close consideration of mechanism of action, stage of disease, expected treatment effect, and development goal, in endpoint selection. As a result, the EMA offers one set of recommendations for endpoints at the preclinical stage, another at the prodromal / MCI stage.

At the preclinical stage, pending development of reliable surrogate endpoints the EMA perceives no "gold standard" endpoints. The EMA notes that primary & secondary prevention trials have leveraged as endpoints dementia diagnosis, significant cognitive decline, and change in cognitive function. Due to the likely long duration of trials in preclinical AD, with expected high rate of discontinuation, the EMA advises consider of the subset of patients who are on drug long enough to show the expected treatment effect. This strategy needs to include a method to account for potentially confounding vascular, cardiac, or metabolic events.

At the prodromal stage, current endpoints are limited by ceiling effects, and patients are highly heterogeneous. Patients with prodromal disease vary widely in their ability to compensate for mild functional impairment. Patients in this stage also have widely varying rates of disease progression. Potential solutions include focus on sub-domains shown to be impaired homogeneously at this stage, or use of a composite scale with cognition and its impact on daily function as a single primary endpoint.

The EMA advises a holistic approach in prodromal disease trials: they should include measures across a wide variety of morbidity and quality of life domains: cognition, function, instrumental activities, executive function, and health-related quality of life (HRQL).

Prodromal patients are unlikely to be on a standard background therapy at trial initiation. As a result, the EMA sees the experimental therapy's effect if the non-experimental therapy had not been initiated as a potentially acceptable outcome measure. Alternatively, the outcome could integrate initiation of non-experimental treatment by defining a non-responder as a progressor or a user of additional symptomatic therapy.

Time to event (TTE) analysis

While the FDA describes TTE analysis as an acceptable primary outcome measure in early AD trials, the EMA characterizes its use in preclinical AD as a "complementary" measure which supports the selected endpoint – provided that the event in question is clinically important.

Controlling for confounds

According to the EMA, potential confounds that require particular attention in early AD are treatment discontinuation, use of non-experimental AD drug treatment (e.g., currently approved symptomatic therapy for AD), use of behavioral therapy, use of therapies not primarily related to AD, and death.

Monotherapy vs. combination therapy

Finally, the EMA suggests that sponsors designing trials in early AD carefully consider intended use as monotherapy, combination with a currently approved symptomatic therapy, or in an entirely novel combination.

Differences in trial design and endpoint guidance between the FDA and the EMA is likely to complicate sponsors' evidence planning and payers' evaluation of product value. Specific implications are in Table 3.

Table 3: Implications for EU HTA and US payer evaluation – trial design and outcome measure considerations in early AD

Perspective	What's the issue with the regulatory guidance?	Challenge for evidence development	Selected implications for preparing submissions
EU HTA	Trial duration FDA suggests two years or less; EMA suggest 'long trials' with referral to 3 years or 18 months Outcomes FDA guidance: Time to event analysis EMA guidance: Outcomes can be along 'experimental therapy's effect if the non-experimental therapy had not been initiated' or 'initiation of non-experimental treatment'. Outcome measures at prodromal stage may include composite endpoints along cognition and functioning. Relevance of HrQoL at prodromal stage.	Trial length and outcomes Definitions of expected trial length and outcome definitions deviate between FDA and EMA guidance. EMA requires measuring cognition and function even at prodromal stage AD using a composite endpoint measure.	Implications to support the Results section EU HTA dossier draft stage as of April 2024): Sponsors must pay particular attention to assessing the certainty of results and reflecting all component results when using a composite endpoint. Using 'time to event' measure as complementary may include an assessment along different time points measuring effect over time; this may need to include repeated-measures analysis of variance for continuous outcomes or require Cox regression for time-to-event data in the single studies. Similarly defining the 'time to event' or 'initiation of non-experimental treatment' may require a hypothesis alignment across European member states as different hypotheses may be used. Sensitivity analysis needs: The primary estimand has to be defined very closely along: (1) population, (2) treatment, (3) variable (endpoint), (4) intercurrent events (ICEs) and (5) the summary measure
US payer evaluation	Variations in design guidance between the FDA and the EMA	Varying trial lengths and outcome measures across trials within same indication	Will complicate indirect treatment comparison

3. Surrogate endpoints in early Alzheimer's disease trials

The FDA encourages use of endpoints that facilitate shorter trials in early AD. This includes surrogate endpoints, provided they pass the FDA's standard surrogate endpoints test: "reasonably likely to predict clinical benefit." For the FDA, the acceptability of a surrogate endpoint depends on disease stage and trial population, mechanism of action, and availability of current treatments – implying that a surrogate endpoint's appropriateness is highly trial-dependent. This draft guidance allows for the possibility of appropriate surrogate endpoints in not only preclinical disease, but also prodromal disease.

In contrast, the EMA's view of surrogate endpoints varies by stage. The EMA is open to use of a surrogate primary endpoint in Stage 1 (i.e., preclinical AD), once a surrogate endpoint has proven itself reliable in this context. The EMA will not accept a surrogate primary endpoint in Stage 2 (i.e., prodromal AD / MCI due to AD).

It will be interesting to see how the two regulatory agencies' guidance evolves as surrogate endpoints in AD evolve. Sponsors of trials in preclinical AD who take advantage of the less demanding "reasonably likely to predict clinical benefit" test employed by the FDA are likely to face challenging HTA in Europe, especially among HTA agencies that take a dim view of surrogate endpoints (e.g., in Germany). Specific implications are in Table 4.

Table 4: Implications for EU HTA and US payer evaluation: surrogate endpoints

Perspective	What's the issue with the regulatory guidance?	Challenge for evidence development	Selected implications for preparing submissions
EU HTA	EMA acceptance of reliable/validated surrogate endpoints for stage 1 but no acceptance for disease stage 2.	Requirement of validation of a surrogate endpoint along criteria for EU HTA and for EMA – though only fordisease stage 1.	Validation may require scientific demonstration that the surrogate endpoint is a reliable indicator of health outcomes in cognition and, potentially, functioning. This may add significantly to the drug development timeline. In addition, individual HTA agencies may take differing views of clinical value demonstration based upon a surrogate endpoint for value ratings (such as in Germany, France or Italy).
US payer evaluation	FDA's acceptance of a certain surrogate endpoint in one trial does not imply acceptance in any other trial	Inherent uncertainty every time a surrogate endpoint is used – even if it has been accepted previously	Comparing therapies' relative value becomes more difficult when there is no "standard" endpoint used in most/all trials

4. Conclusions

Sponsors developing drugs for treatment of patients with early AD will face trial design challenges due to (a) imprecise FDA and EMA guidance and (b) differences between FDA and EMA guidance.

Imprecise definitions of prodromal AD / MCI due to AD by both the FDA and the EMA will make it challenging for sponsors to align on evidence generation to support early AD disease presentation, health impact, impact on care delivery, and positioning of new treatments in the treatment pathway.

In addition, imprecise definitions of prodromal disease will make for varying trial inclusion and exclusion criteria. PICO assessment for EU HTA may yield a variety of populations and comparators across member states. These problems will in turn make it difficult to accurately and consistently describe disease burden and target populations, to reliably predict budget impact, and to compare therapies to each other.

Differences between FDA and EMA guidance on trial duration, outcome measures, and surrogate endpoints will lead to high heterogeneity across trials in early AD. This will lead to methodological challenges complying with EU HTA requirements, difficulties in all jurisdictions for comparison of drugs to each other, and jurisdiction-specific challenges related to rejection of surrogate endpoints in HTA (e.g., in Germany).

These challenges could be mitigated through greater precision in definitions as well as harmonization across the two regulatory agencies.

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