Disease Modifying Therapies for Alzheimer's Disease: Addressing Market Access Challenges to Drive Patient Access across UK, Germany, Brazil, Greece and Saudi Arabia

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Introduction

Alzheimer's disease (AD) is a devastating neurodegenerative condition with no curative treatments currently available. Currently more than 55 million people are living with dementia worldwide, with AD being the most common cause of the condition.[1,2] Many treatments currently available for AD are focused on symptomatic management, but do not alter the underlying pathology of the disease.[3] However, emerging disease modifying therapies (DMTs) aim to slow down or reverse disease progression in early AD and Mild Cognitive Impairment (MCI), [4] potentially leading to an improvement in patient and societal outcomes. Nevertheless, significant challenges are anticipated regarding relevant value demonstration for HTA authorities and the sustainability of the potential budget impact. This may result in significant challenges achieving reimbursed patient access for these DMTs across global healthcare systems.

Objective

This research explores the key challenges and opportunities for the evaluation of DMTs for the treatment of AD across a range of HTA authorities, and requirements to support reimbursed patient access.

Method

Primary research was conducted using the Lightning Insights platform with a sample of 10 HTA representatives across the UK, Germany, Brazil, Saudi Arabia and Greece (n=2 per country). Research insights were thematically analysed to identify perceived value drivers and potential challenges within the evaluation of DMTs for the treatment of AD, as well as strategic recommendations for manufacturers to support HEOR evidence generation to ensure sustainable patient access.

Results

Figure 1. HTA stakeholder perceptions on the key value drivers for AD DMTs across markets

HTA representatives across markets recognise the clinically relevant slowing of disease progression to be the overarching key benefit of a DMT for AD (on the assumption that a curative therapy is not yet clinically feasible). All other potential clinical, humanistic and economic benefits of treatment (shown in figure 1) will be derived from a statistically significant and clinically relevant slowing of disease progression.

HTA stakeholders, particularly in Germany, also note the high importance of favourable safety/tolerability for any DMT for AD, considering the predicted high levels of co-morbidities for indicated patients.

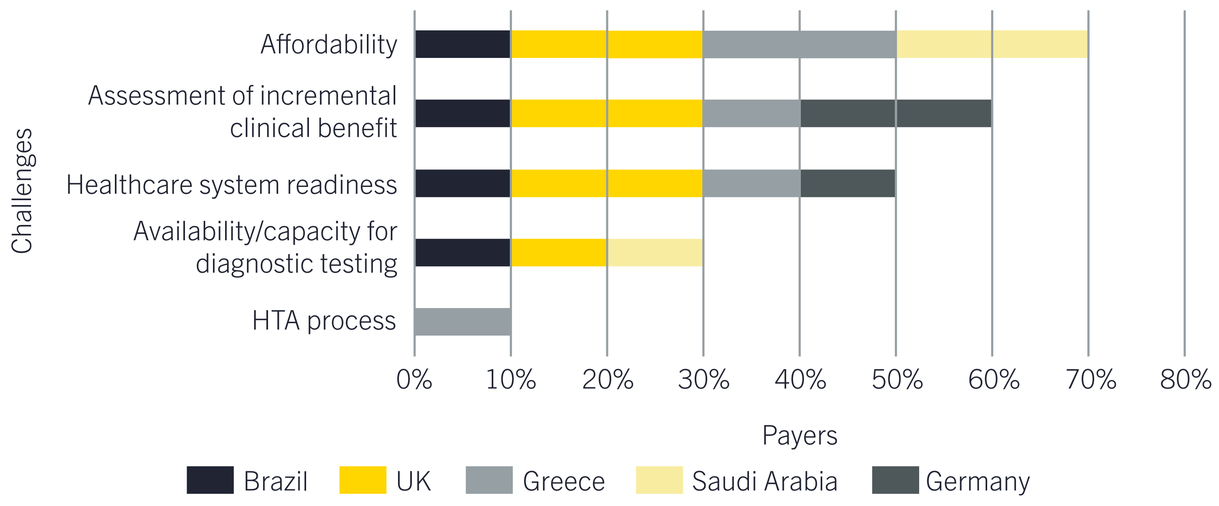
Additionally, the introduction of new therapies for AD will align with national policy objectives to support patients with AD in Brazil and Saudi Arabia, although this will not formally impact the HTA process.

> [Patient access to AD DMTs] aligns with Brazil's ongoing policy efforts to improve QoL for people with AD, expand access to necessary services and reduce stigma and social isolation.
>
> **Brazilian HTA representative**

> As Saudi Arabia is targeting high life expectancy, AD DMTs can provide significant benefits such as delaying disease progression, improving QoL, reducing healthcare costs and addressing the growing elderly population's needs as life expectancy increases.
>
> **Saudi Arabian HTA representative**

There is high consistency across countries regarding the perceived challenges of introducing and evaluating a DMT for AD. This includes the affordability of new therapies, the demonstration/interpretation of clinical efficacy, the availability/capacity for diagnostic testing, and healthcare system readiness to support the adoption of DMTs for AD (see figure 2).

Figure 2. HTA stakeholder perceptions regarding the key challenges with introducing AD DMTs



The majority of HTA representatives across markets (70%) identify the affordability of new DMTs for AD as the key challenge, considering the predicted high volume of patients, the uncertainty regarding diagnostic standards and a potential increase in the rate of early diagnosis if a new DMT is available. This creates concerns on the total annual funding required to support patient access and will likely result in constrained pricing negotiations (with the risk that agreement on a commercially acceptable price may not be possible for manufacturers).

There are also high levels of concern across countries with the interpretation and extrapolation of clinical outcomes for AD DMTs. This includes:

- Uncertainty on the sensitivity of surrogate outcomes to detect changes in early AD patients (e.g. the CDR-SB)
- Uncertainty on the MCID for available clinical/surrogate outcome measures, and the practical clinical/QoL impact of the duration of delay in disease progression
- Challenges regarding the generalisability of clinical trial results due to differences between phase III trial comparator arms and current clinical practice
- Uncertainty on the sensitivity of cognitive and functional outcomes to detect changes in early AD patients (e.g. the CDR[1]SB)

For healthcare systems requiring pharmacoeconomic analysis, the reliance on proxy-estimates for health state utilities can increase the risk of bias, and lack of long-term data results in high levels of uncertainty when attempting to extrapolate the clinical, QoL and economic benefits over the lifetime horizon.

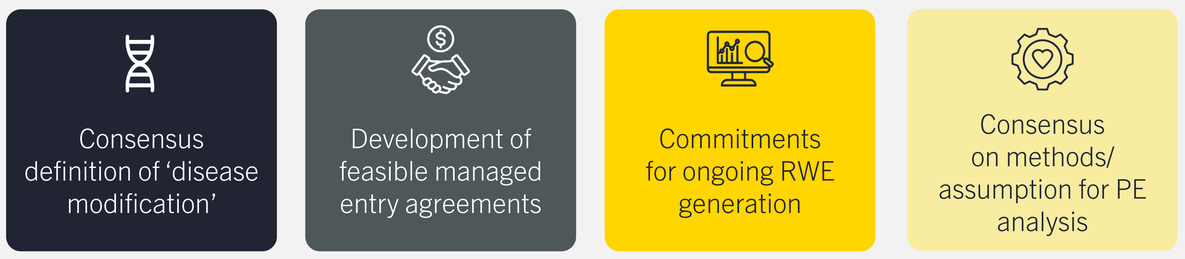
> There is need for robust evidence from RCTs demonstrating patient-relevant improvements in key outcomes such as mortality, morbidity, safety, tolerability, and quality of life.
>
> **German HTA representative**

> The challenge of assessing clinical effectiveness for the local population and appropriate outcome measures remains.
>
> **Saudi Arabian HTA representative**

HTA representatives in Brazil, the UK, Greece and Germany also highlight concerns regarding the lack of infrastructure and service capacity to support a significant expansion in the early diagnosis and treatment of AD patients (and the wider impact on healthcare resource use). A lack of screening/diagnosis capacity is likely to be a key factor, with significant investment and service redesign required for eligible patients to benefit from treatment.

Recommendations

Figure 3. Key considerations to optimise value demonstration and patient access for AD DMTs



A consensus on the MCID for primary and key secondary outcomes is highly important to avoid HTA/payer uncertainty on what constitutes a 'disease modifying effect' (with patient/clinical expert opinion likely to be a key consideration). Any divergence in definitions for 'clinically relevant value' from the manufacturer, clinical literature and clinical experts consulted by HTA authorities will significantly increase uncertainty within the HTA process. Early advice is also recommended to inform pivotal trial design, ensuring the comparator arm reflects current clinical practice for AD patients.

> I'd recommend a proper RCT with a sufficient duration against an appropriate comparator using patient-relevant endpoints.
>
> **German HTA representative**

> Design clinical trials that capture both surrogate endpoints and meaningful clinical outcomes such as cognitive function and QoL.
>
> **Saudi Arabian HTA representative**

A sufficient duration of follow-up is highly important to support value claims regarding a disease modifying effect in AD; a minimum of 18-months follow-up in an RCT is expected (however longer would be preferred to minimise uncertainty at launch). HTA representatives from the UK, Greece and Saudi Arabia emphasise the potential role for post-approval RWE generation (e.g. through registries) to minimise long-term uncertainty regarding clinical/economic value for AD DMTs, however this will still require a matched comparison to inform incremental value vs. current SoC.

> Develop a study that can analyse the long-term effects of DMTs before submitting to any reimbursement evaluation in the country.
>
> **Brazillian HTA representative**

> Invest in robust RWE generation through post-marketing surveillance and patient registries to further validate the impact and value of DMTs [and] strengthen the data collection process by including QoL outcomes and PROs in an AD registry.
>
> **Saudi Arabian HTA representative**

An academic consensus on the optimal approach for pharmacoeconomic analysis of AD DMTs is required. In particular, this will require:

- Health state transition probabilities with 'face validity'
- Credible utility values for AD health states
- An understanding of how stopping rules could be implemented in practice (and the impact on outcomes)
- Country specific data for the cost of administering AD DMTs (including testing/infusion)

In all countries, excluding Germany, managed entry agreements are recommended for AD DMTs. Budget caps/price-volume agreements will be important to minimise concerns regarding total budget impact and outcomes-based risk-share schemes could be considered, provided there is an objective marker for treatment success/failure.

A societal perspective for HTA that incorporates carer costs and outcomes may be justified considering the high levels of potential QoL/productivity benefits associated with a DMT for AD, however this is unlikely to be a key driver of HTA decisions in the short-medium term.

Conclusion

Overall HTA representatives recognise the primary advantage of DMTs for AD is the potential ability to significantly slow disease progression; all other potential clinical, humanistic and economic benefits will derive from this. Stakeholders across all markets express concerns in ensuring the safety and affordability of DMTs for AD, particularly considering anticipated patient volumes and uncertainty regarding diagnostic standards/capacity. Defining clinically relevant outcomes and the need for robust pharmacoeconomic analyses further complicate HTA evaluations. To address these challenges, a consensus on defining clinical value, alignment on optimal methods/assumptions for pharmacoeconomic analysis, and the integration of RWE within decision-making are essential. These strategies will enhance HTA processes and support future value demonstration and reimbursed patient access for DMTs for AD.

References: 1. Nichols E, Steinmetz JD, Vollset SE, Fukutaki K, Chalek J, Abd-Allah F, et al. Estimation of the global prevalence of dementia in 2019 and forecasted prevalence in 2050: an analysis for the Global Burden of Disease Study 2019. Lancet Public Health. 2022 Feb 1;7(2):e105–25. 2. Breijyeh Z, Karaman R. Comprehensive Review on Alzheimer's Disease: Causes and Treatment. Molecules. 2020 Dec 8;25(24):5789. 3. Yiannopoulou KG, Papageorgiou SG. Current and future treatments for Alzheimer's disease. Ther Adv Neurol Disord. 2013 Jan;6(1):19–33. 4. Disease-Modifying Treatments and Their Future in Alzheimer's Disease Management - PMC [Internet]. [cited 2024 Oct 17]. Available from: https://pmc.ncbi.nlm.nih.gov/articles/PMC11014642/#

Abbreviations. AD: Alzheimer's Disease; CDR-SB: Clinical Dementia Rating Scale Sum of Boxes; DMT: Disease Modifying Therapies; HEOR: Health Economics and Outcomes Research; HTA: Health Technology Assessment; MCID: Minimal Clinically Important Difference; MCI: Mild Cognitive Impairment; PRO: Patient Reported Outcomes; PE: Pharmacoeconomic; QoL: Quality of Life; RCT: Randomised Control Trial; RWE: Real World Evidence; SoC: Standard of Care; UK: United Kingdom