Economic Impact of PET-^{18}Flutemetamol Guided Treatment Allocation in the Diagnosis and Management of Alzheimer Disease. A Budget Impact Model for European Payers.

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INTRODUCTION

- Alzheimer's disease (AD) affects more than 10 million patients in Europe.[1] From a healthcare payer perspective, the correct diagnosis and management of these patients are paramount.
- Amyloid-targeting therapies (ATTs), such as lecanemab and donanemab, represent a paradigm shift in the treatment of AD.
- Initiation of ATTs requires confirmed β-amyloid pathology, as these agents specifically target and remove amyloid plaques.
- The European Medicines Agency (EMA) considers ATTs contraindicated in apolipoprotein E ε4 (ApoE ε4) homozygous patients, given their elevated risk of amyloid-related imaging abnormalities (ARIA).[2,3]
- β-amyloid pathology assessment relies on a combination of biomarker-based techniques, including β-amyloid positron emission tomography (PET) and cerebrospinal fluid (CSF) biomarker analysis.
- Quantitative β-amyloid PET is increasingly used in specialized care settings, as an adjunct to visual assessment.

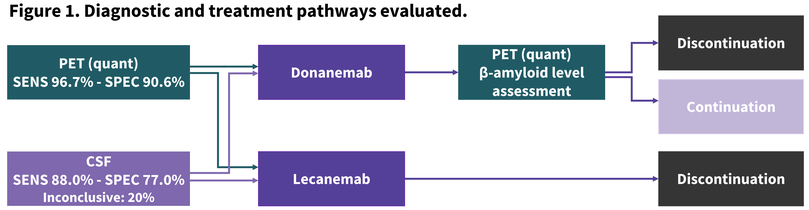
OBJECTIVE

- The study aims to: (i) estimate the budget impact of adopting ^{18}F-flutemetamol PET with quantification for patients with mild cognitive impairment (MCI) or dementia undergoing AD diagnosis and treatment planning in Italy, Spain, France, Germany, and the Netherlands, and (ii) evaluate the economic consequences of potential misallocation of patients to inappropriate treatment in the context of emerging ATTs.

METHODS

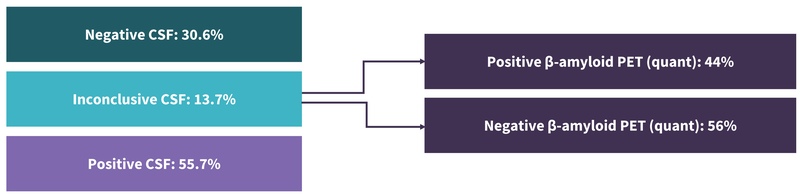
- A budget impact model (BIM) was developed to simulate diagnostic and treatment outcomes over a five-year horizon from the European payer perspective for Italy, Spain, France, Germany, and the Netherlands.
- Key model assumptions include:
  - i. Population and epidemiology: The modeled population consists of patients with MCI or dementia who are eligible for ATTs (heterozygous ApoE ε4 carriers or noncarriers). Country-specific inputs were used to estimate the national population size.
  - ii. Diagnostic modalities: The BIM considers ^{18}F-flutemetamol PET with quantification and CSF.
    - Blood-based biomarkers were incorporated within the conceptual model structure to reflect their emerging role in AD diagnostic pathways and anticipated future adoption; however, they were not parameterized in the present analysis due to the limited and evolving evidence base. Future analyses will incorporate these inputs as robust data become available to support quantitative implementation.
  - iii. Diagnostic modality shares: Current and projected diagnostic modality shares were informed by country-specific market research and modeling assumptions. The base case scenario considers the same modality shares for all considered countries.
  - iv. Diagnostic accuracy inputs: Sensitivity and specificity were used to classify diagnostic outcomes and guide downstream treatment allocation within the model (**Figure 1**).
  - v. Treatment strategies following diagnosis: Two ATTs were evaluated: donanemab and lecanemab.

Figure 1. Diagnostic and treatment pathways evaluated.



  - vi. Treatment discontinuation and β-amyloid level assessment were modeled as follows:
    Treatment duration assumptions were based on EMA product information where available and simplified for modeling purposes.
    - Donanemab: treatment duration was capped at 18 months, consistent with EMA guidance. Two PET scans were considered (during the 1st and 2nd year of treatment) to evaluate β-amyloid pathology levels; >75% of patients discontinued at 18 months.[3,4]
    - Lecanemab: treatment discontinuation due to progression to moderate AD was not explicitly modeled in the base case; instead, it was assumed that patients remain on treatment for 18 months.
  - vii. Screening accuracy estimation methods:
    - As the sensitivity and specificity of β-amyloid PET were estimated in a real-world setting by comparing brain imaging with autopsy outcomes, these diagnostic accuracy estimates were applied directly in the analysis.[5]
    - CSF diagnostic accuracy was estimated using the two-cutoff approach described by Brendel et al. (2024). Eligible patients were allocated to positive, negative, or inconclusive CSF results based on the reported proportions. Patients with inconclusive CSF results were assumed to undergo confirmatory β-amyloid PET imaging and were subsequently reclassified as positive or negative according to the reported distributions (**Figure 2**).[6]

Figure 2. CSF diagnostic accuracy assumptions.



- Imaging-based assessment of β-amyloid plaque burden, including quantitative β-amyloid PET with quantification and magnetic resonance imaging (MRI) for safety surveillance (e.g., ARIA), was explicitly modeled for donanemab and lecanemab in line with EMA recommendations.[2,3]
- Costs of ATTs: Considering the recent approval of ATTs by EMA, treatment costs were estimated using international price benchmarks. AD monitoring requirements followed EMA guidance and were costed using country-specific tariffs.
- Model outcomes include:
  - Number of correctly and incorrectly diagnosed patients, patients incorrectly receiving treatment (false positives), patients missing treatment (false negatives), and patients requiring confirmatory testing before receiving ATTs.
  - Total diagnosis- and treatment-related costs, additional costs related to unnecessary therapy and confirmatory tests and budget impact.

RESULTS

- Across all countries, results suggest that increased usage of ^{18}F-flutemetamol PET with quantification as the first line vs CSF could reduce the proportion of patients incorrectly receiving ATTs by approximately 8% and decrease those missing appropriate therapy by about 10%.
- The proportion of patients requiring confirmatory testing for AD diagnosis was reduced by 15.5% (**Table 1**) with greater uptake of ^{18}F-flutemetamol PET with quantification.
- The use of ^{18}F-flutemetamol PET with quantification was estimated to increase cumulative budget impact, ranging from around 0.18% in the Netherlands to 0.47% in Spain over a five-year horizon. Simultaneously, increased usage of PET resulted in decreased cumulative cost of unnecessary therapy by around 8.45% for all countries over a five-year horizon.

Table 1. Incremental diagnostic outcomes and cost results of ^{18}F-flutemetamol PET with donanemab (current vs projected scenarios).

Outcome	Italy	Spain	Germany	France	the Netherlands
Number of individuals incorrectly receiving treatment	-15,864	-5,919	-15,543	-2,765	-2,234
Number of individuals missing treatment	-11,971	-4,140	-11,536	-1,534	-1,717
Number of individuals requiring confirmatory tests	-40,516	-14,692	-39,433	-6,241	-5,757
Total costs	€184,154,015	€129,098,461	€329,947,330	€49,122,724	€20,186,632
Diagnosis costs	€184,154,015	€129,098,461	€329,947,330	€49,122,724	€20,186,632
Cost savings related to unnecessary therapy	-€822,697,170	-€293,167,552	-€821,603,982	-€115,061,210	-€121,229,831

Results were generated assuming modality shares of 23.9% vs 76.1% for PET with quantification and CSF, respectively in the current scenario and 35.7% vs 64.3%, respectively in the projected scenario. Negative outcomes indicate fewer people in the scenario with increased usage of ^{18}F-flutemetamol PET. Calculations are based on the total number of adults with early-stage AD (MCI/dementia) in each country.

- Scenario analyses incorporating alternative modality shares, including a scenario (2) that assumes 100% ^{18}F-flutemetamol PET with quantification as sole diagnostic modality confirmed the direction of the results, demonstrating consistent cost savings driven by reductions in unnecessary therapy use across countries (**Table 2**).

Table 2. Incremental diagnostic outcomes and cost results of ^{18}F-flutemetamol PET with donanemab (scenario analysis).

Outcome	Italy	Spain	Germany	France	the Netherlands
Scenario 1: Modality shares based on the country-specific data from market research*					
Total costs	€238,775,968	€123,628,187	€321,558,838	€37,050,190	€20,186,632
Cost savings related to unnecessary therapy	-€1,066,717,517	-€280,745,198	-€800,715,745	-€86,783,455	-€121,229,831
Scenario 2: Current scenario uses base-case modality shares; future scenario assumes 100% ^{18}F-flutemetamol PET with quantification					
Total costs	€1,187,637,334	€832,575,665	€2,127,880,661	€316,779,937	€130,186,671
Cost savings related to unnecessary therapy	-€5,305,699,545	-€1,890,682,263	-€5,298,649,406	-€742,047,298	-€781,829,675

** Modality shares assumed for PET with quantification in current scenario: Italy – 23.7%; Spain – 22.3%; Germany – 22.8%; France – 29.2%; the Netherlands – 23.9% (EU4 average); in projected scenario: Italy – 39%; Spain – 33.6%; Germany – 34.3%; France – 38.1%; the Netherlands – 35.7% (EU4 average). Modality shares for CSF were calculated as 1-PET.*

- Although only donanemab results are presented, the diagnostic pathway prior to initiation of ATTs is identical across scenarios. Consequently, the estimated outcomes for patients receiving lecanemab remain unchanged, with differences limited to treatment-related costs.

CONCLUSION

- Regardless of the ATT considered, the budget impact of adopting ^{18}F-flutemetamol PET with quantification as the first line diagnostic modality was projected to be modest. However, given the substantial costs associated with ATTs, accurate identification of eligible patients and effective treatment management – including β-amyloid plaque burden assessment and appropriate treatment discontinuation – are critical from a payer perspective.
- With Europe's rapidly ageing population, treatment allocation must be optimal; ^{18}F-flutemetamol PET with quantification remains a stand-alone diagnostic modality capable of independently informing treatment allocation, by reducing unnecessary therapy (42,325 patients across the five EU countries considered), avoiding drug costs, MRI monitoring, and adverse events without clinical benefit.
- Missed diagnoses are minimized, while simultaneously enabling appropriate treatment and maximizing potential clinical gains. This dual effect – avoiding over-treatment and minimizing under-treatment – optimizes resources while enhancing patient safety and outcomes.

Abbreviations: AD, Alzheimer's disease; ARIA, amyloid-related imaging abnormalities; ATTs, amyloid-targeting therapies; ApoE ε4, apolipoprotein E ε4; BIM, budget impact model; CSF, cerebrospinal fluid; EMA, European Medicines Agency; MCI, mild cognitive impairment; MRI, magnetic resonance imaging; PET, positron emission tomography.

References: 1. Alzheimer Europe. Dementia in Europe Yearbook 2019: Estimating the prevalence of dementia in Europe. Luxembourg: Alzheimer Europe. ISBN 978-99959-995-9-9. 2019; 2. LEQEMBI SMPC, available here: https://www.ema.europa.eu/en/documents/product-information/leqembi-epar-product-information_en.pdf; 3. Kisunla SMPC, available here: https://www.ema.europa.eu/en/documents/product-information/kisunla-epar-product-information_en.pdf; 4. Mintun M., Donanemab in Early Symptomatic Alzheimer's Disease: Efficacy and Safety from the TRAILBLAZER-ALZ 2 Long-Term Extension. Eli Lilly and Company, Indianapolis, IN. AAIC 2025; 5. Frisoni B. et al., New landscape of the diagnosis of Alzheimer's disease, Lancet, 2025, 406, p. 1389-1407; 6. Brendel M. et al., Aβ status assessment in a hypothetical scenario prior to treatment with disease-modifying therapies: Evidence from 10-year real-world experience at university memory clinics, Alzheimers Dement (Amst), 2024, 16(4).

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