The position of the European Alzheimer Disease Consortium (EADC) on the Approval of Acuanumab for the treatment of Alzheimer's disease by the FDA

On June 7th, in a highly anticipated global decision, the U.S. Food and Drug Administration (FDA) approved aducanumab (Aduhelm®, an anti-amyloid antibody) for the treatment of Alzheimer's disease at 10mg/kg body weight, while requiring the drug's manufacturer, Biogen, to conduct an additional post-approval clinical trial (Phase IV) to verify the drug's clinical benefit. If that study fails to demonstrate clinical benefit, the FDA may revoke the drug's approval. In November 2020, the FDA's independent advisory committee had voted against approval, stating that the data presented in the available clinical trials were not convincing enough. However, the FDA has now backed away from the requirement of proof of clinical efficacy and followed a different regulatory pathway, that of a surrogate end point (i.e. approval on the basis of the evidence of reduction of amyloid deposits).

An initial small Phase 1 study to investigate the safety of aducanumab had shown significant brain amyloid load reduction, as demonstrated through positron emission tomography (PET) imaging, and the preliminary clinical data suggested that this could slow cognitive decline. As a result, the FDA allowed Biogen to skip the otherwise standard Phase 2 trials and conduct two Phase 3 studies (ENGAGE and EMERGE) right away, each with about 1,640 patients. Those trials were halted early in March 2019 when the independent data monitoring committee decided, based on an interim analysis, that there was too high a likelihood that aducanumab would not be effective. Consequently, 37 percent of participants were unable to complete the 78-week study period. However, in October 2019, Biogen announced that after a re-evaluation, evidence for efficacy did exist. This conclusion was based on data from an additional 318 participants collected before the trials were stopped but after the cut-off date for the interim evaluation. In one of the two studies (EMERGE), the highest dose significantly slowed the severity of disability by 22 percent compared to placebo arm. A lower dose in this study and both doses in the second study (ENGAGE) showed no statistically significant superiority over placebo. Only a post-hoc analysis of the completers in the high dose subgroup in the overall negative second study (ENGAGE) showed evidence of efficacy.

The accelerated approval pathway now granted by the FDA for aducanumab is intended for drugs for serious diseases that are expected to have a meaningful benefit over available therapy even if there is residual uncertainty about the drug's ultimate clinical benefit. To be approved through this pathway, there must be substantial evidence of the drug's efficacy on a "surrogate endpoint" - usually a biomarker in this case amyloid or its deposition that reflects the underlying disease pathology. In the expedited process, it must be known that the effect on this surrogate endpoint results in the clinical benefit.

The manufacturer's prescribing information (SmPC) for aducanumab plainly states "…indicated for the treatment of Alzheimer's disease", without further specifications. It includes a warning for amyloid-related imaging abnormalities (ARIA), which can be visualized on magnetic resonance imaging and most commonly presents as transient swelling or focal microhemorrhage in small areas of the brain, usually without symptoms. To monitor for ARIA, a recent (within one year) brain magnetic resonance imaging (MRI) prior to initiating treatment is required. The most common side effects of aducanumab were ARIA and associated headache, confusion/delirium/altered mental status/disorientation, as well as falls and diarrhea. Rare side effects of aducanumab include hypersensitivity reactions, including angioedema and urticaria.

The European Alzheimer Disease Consortium (EADC) would like to highlight that this treatment is at this point approved only for the US. It is also important to note that aducanumab trials only enrolled a group of patients with a narrow disease–specific stage, namely mild cognitive impairment (MCI) due to Alzheimer's disease or early-stage Alzheimer's dementia, and that Aducanumab should be given to this group of patients only.

Further research is needed to better understand which patients and at what disease stage respond best, what is the optimal duration of treatment (current data do not span more than a year and a half) and what side effects may occur after long-term use. For this, in addition to the phase IV study required by the FDA, so-called registry studies will also be of great importance. Many other unkonwns and uncertainties still remain including the very long time frame for the phase IV study (9 years). Finally, the approval of Aducanumab may open the door for many other applications for approval based on proven amyloid reduction but without solid evidence for clinical efficacy. Due to the absence of convincing clinical benefits, the topic is and will remain controversial until more evidence is collected.

This approval is currently not valid for EU and UK. It is uncertain what decision the European regulatory authority will make here, including type of approval pathways, indications relating to disease stage, patients' ages, types of requirements for amyloid positivity, treatment duration and monitoring etc. It is also unclear how each individual European country and corresponding health care and insurance systems and institutions will act in relation both to setting up systems for such hospital-based treatments and to cost coverage issues. Emergency approvals without clear clinical proof of efficacy should generally be applied with caution. As much as all physicians and patients have been hoping for a new and better drug for Alzheimer's disease for years - caution is advisable in view of the expected costs, the expectations of patients and the uncertainty around the lack of clear clinical proof of efficacy as well as the necessary safety studies.

Thus, although this drug does not provide a cure and is still subject to uncertainties, this first treatment against the pathophysiology of Alzheimer's disease is of great importance. If eventually proven, slowing the progression of cognitive decline in people in the mild cognitive impairment (MCI) stage of Alzheimer's disease or early Alzheimer's dementia would be a major advance and the known side effects of aducanumab appear tolerable. In addition to aducanumab, other antibodies directed against amyloid are currently in registered trials (gantenerumab, lecanemab, donanemab). Hopefully, the use of aducanumab, which has now become possible at least in the USA, will represent a breakthrough for additional therapies against Alzheimer's disease and encourage more pharmaceutical companies to resume research activities for the development of therapies against neurodegenerative diseases, including targets other than amyloid.

https://www.fda.gov/drugs/postmarket-drug-safety-information-patients-and-providers/aducanumab-marketed-aduhelm-information

https://www.fda.gov/drugs/news-events-human-drugs/fdas-decision-approve-new-treatment-alzheimers-disease

https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/761178s000lbl.pdf

For the EADC: Lutz Frölich, Frank Jessen, Mercè Boada, Sebastiaan Engelborghs, Patrick Kehoe, Milica Kramberger, Alexandre Mendonca, Flavio Mariano Nobili, Nikolaos Scarmeas, Pieter Jelle Visser, Gunhild Waldemar (Executive Board)