A New Hope In Alzheimer's Treatment; Lecanemab

Abstract:

Lecanemab's apparent effectiveness follows years of disillusionment with earlier, comparable medications that were meant to delay or stop the course of Alzheimer's disease. It contains monoclonal antibodies that were created in laboratories with the goal of purging the brain of a material called as beta-amyloid, exactly like a lot of those other medicines. People with Alzheimer's disease tend to have an accumulation of beta-amyloid in their brains, which leads to the development of the sticky plaques that have come to be associated with the condition. As a result of this, the objective of his research paper is to investigate background information about the drug lecanemab. In addition to this, the study offers information regarding the approval procedure for lecanemab, the drug's mode of action, and, lastly, the most recent discoveries.

Key words: Lecanemab, Monoclonal antibodies, Alzheimer's, drug target.

Introduction:

Lecanemab and other monoclonal antibodies accomplish their therapeutic goal by stimulating the body's immune system to launch an assault on a specific intracellular target. [3]. Amyloid beta, a substance that builds up in the brains of Alzheimer's sufferers, is the focus of this treatment. Even though this protein has been implicated in Alzheimer's disease, the disease's causative role can only be inferred rather than proven at this point. Or that there are significant benefits associated with reducing it for those who have Alzheimer's disease [5]. In the meanwhile, some researchers are of the opinion that Alzheimer's disease is caused by an accumulation of a different protein called tau. Others hypothesize that not just beta but also tau might have a role.

Since a recent clinical research indicated that lecanemab delayed the progression of Alzheimer's disease in a similar manner as drugs that reduce amyloid beta levels, it has garnered a lot of support from those interested in the treatment. In addition, lecanemab has been shown in recent trials to have the potential to lower tau levels. Those who have the

ailment seem to get some more time as a result [4]. The precise number is not known with any degree of certainty at this time.

However, some antibodies that target beta-amyloid were not successful in preventing Alzheimer's disease from causing memory and cognitive decline [5]. Because of the failure of so many treatments, some researchers began to question the amyloid hypothesis, which states that amyloid is a key contributor in the death of brain cells, which in turn leads to deficits in memory and thinking.

Alzheimer's disease is a degenerative ailment that places a significant burden not only on the person who has the disease but also on their loved ones [6].Because the treatments that are currently available for Alzheimer's disease are insufficient, the discovery of innovative therapeutics is strongly encouraged. Eisai employees have spent time with those coping with Alzheimer's disease in order to gain a comprehensive understanding of the difficulties they face on a day-to-day basis. "Eisai employees have been working tirelessly for a number of years in order to develop new treatments," stated Eisai CEO Haruo Naito.

Patients suffering from Alzheimer's disease who have been waiting for novel treatment options that address the illness's underlying pathology will benefit significantly from the approval of lecanemab's biologic license application (BLA) for priority review[14]. There has been a concerted effort made to cooperate completely with the study being conducted by the FDA in the belief that patients and their families will benefit from having access to this innovative Alzheimer's disease treatment option as soon as it is practically possible.

Literature Review:

The humanized IgG1 monoclonal antibody known as lecanemab is able to prevent the production of amyloid beta (A) plaques in the body. It is predicated on a monoclonal antibody known as mAb158, which was first created in mice[1, 2]. Because of lecanemab's ability to reduce the amount of amyloid plaque and the drug's high selectivity for A protofibrils, it is now being investigated for use as a disease-modifying biologic therapy for Alzheimer's disease (1000-fold greater selectivity compared to monomers) [1, 3]

The primary objective of a clinical study that lasted for 12 months and compared lecanemab to a placebo in terms of its ability to delay the course of Alzheimer's disease was not achieved. Even though certain clinical and biomarker endpoints indicated a slowing of deterioration after treatment started, tests done 18 months later revealed a reduction in brain

amyloid [9]. This was discovered despite the fact that some endpoints showed a slowing of deterioration after treatment began. Clinical trial design for phase 3 is ongoing for moderate cognitive impairment.

During the preclinical development of mAb158, the Swedish biotech company BioArctic Neuroscience found that there was a reduction in the number of Aprotofibrils in the brain and CSF of Tg-ArcSwe mice [12]. Subsequent research conducted in mouse neuron-glial co-cultures revealed that mAb158 may protect neurons, i.e., reduce the toxicity caused by A protofibrils, by preventing the aberrant development of these protofibrils in astrocytes [10]. This was accomplished by inhibiting the production of A protofibrils. The anti-amyloid antibodies aducanumab and gantenerumab exhibited a predilection for more highly aggregated forms of A, but the researchers discovered that lecanemab attached to A protofibrils in a way that was far more secure than that of aducanumab and gantenerumab. (News on the November 2021 meeting).

Eisai was awarded the rights to develop BAN2401 as a therapeutic antibody, and in March 2014, the business entered into a collaboration with Biogen to accomplish so. Biogen is helping Eisai with this endeavor. The results of current clinical trials for Alzheimer's disease have been supported by data from preclinical research that used postmortem brain slices from patients with Down syndrome [13]. These investigations showed that lecanemab binds to A deposits in this condition. A hexavalent antibody based on mAb158 is now being developed by researchers as part of an effort to increase the binding strength selectively to A protofibrils.

LecanemabApproval process

After receiving positive topline data from Eisai's global Phase 3 confirmatory Clarity AD clinical study with lecanemab, Biogen made them available to the public. Lecanemab, an investigational anti-amyloid beta (A) protofibril antibody, may help people with mild Alzheimer's disease (AD) and mild AD with amyloid pathology [10]. The study's primary goal was met since, after 18 months, there was a 27% reduction in patients who were worsening on the CDR-SB (a global scale of functional and cognitive decline) as compared to the placebo group [14]. There were a total of 1,795 people with early-onset Alzheimer's disease who participated in the Clarity AD investigation, a placebo-controlled, double-blind, parallel-group randomized controlled trial that was conducted around the world (AD).

Members of the therapy group received lecanemab injections every two weeks at a dose of 10 mg/kg.

12.5% of patients experienced anti-amyloid antibody-related adverse events such as amyloid-related imaging abnormalities-edema/effusion (ARIA-E), whereas only 1.7% of persons who were given a placebo experienced these side effects. Both groups had a same number of individuals who had isolated cases of ARIA-H, which included cerebral macrohemorrhages, superficial siderosis, and arrymalmicrohemorrhages. Eisai is making a tremendous effort to respect the standards of the Alzheimer's disease community, and positive results from the lecanemab Clarity AD research are significant for both Eisai and our efforts. The findings of this study are in line with the amyloid hypothesis, which postulates that the progression of Alzheimer's disease can be slowed or stopped entirely by using protofibril-binding treatment to prevent the aberrant accumulation of amyloid in the brain. The company's chief executive officer, HaruoNaitano, is of the belief that relaxing these requirements will be to everyone's benefit [3].

Patients with early-stage Alzheimer's disease were included in the Clarity AD study that was conducted by Eisai and Biogen. The researchers found that eliminating amyloid beta from the brain was associated with a delay in the progression of the disease. Priority Review status was granted to Eisai's lecanemab BLA by the FDA in July 2022, so enabling the company to proceed with the development of the pharmaceutical in accordance with the accelerated approval procedure. The Prescription Drugs User Fee Act (PDUFAFAFA) is scheduled to become law on January 6, 2023. This date has been set in stone.

In March 2022, Eisai began the process of submitting application data to the Pharmaceuticals and Medical Devices Agency (PMDA) of Japan under the prior assessment consultation system with the intention of obtaining early approval for lecanemab. This would allow people with early Alzheimer's disease to have access to the therapy as soon as it became available. The findings from the Clarity AD research were not incorporated into this.

The research and development of lecanemab, as well as the filings necessary by regulatory agencies, are both the responsibility of Eisai. Eisai and Biogen will collaborate to market and sell the medicine, but Eisai will be in charge of all significant business decisions. Biogen will be a partner in the project. The Biologics License Application (BLA) that Eisai submitted for lecanemab in July 2022 received Priority Review from the FDA. This enabled the company

to continue the speedy development of the medicine. The Prescription Drug User Fee Act (PDUFA) will become law on January 6, 2023, and will then go into force.

Mode of action

Lecanemab, a humanized IgG1 monoclonal antibody, is now being investigated as a potential therapy for Alzheimer's disease. Alzheimer's disease is an illness that is distinguished by the deposition of amyloid beta (A) peptide plaques and neurofibrillary tangles. 2 In contrast, A peptides may exist in a vast array of conformations, ranging from soluble monomers to soluble aggregates of varied sizes to insoluble fibrils and plaque. Soluble monomers are the most common form [3]. It is not the monomers themselves but rather the soluble A aggregates, such as A protofibrils, that are the most toxic; insoluble A fibrils are not toxic at all. Therefore, it has been suggested that lecanemab might be used as a treatment for Alzheimer's disease by concentrating on and reducing the amount of A protofibrils in the body.

Findings

All of the doses of BAN2401 that were put through their paces, which went up to 10 mg/kg every two weeks over a period of four months, were found to be well tolerated. The antibody was able to infiltrate the CSF and showed dose-dependent exposure, despite the fact that its serum elimination half-life was just seven days. The brand-new ADCOMS cognitive test battery was used in order to evaluate a patient's progression over the course of a year [2]. The antibody was able to reduce the amount of amyloid in the brain by as much as 93% in the group that received the highest dose [3]. At the next-lowest dose of 10 mg/kg monthly, there was a non-significant trend toward slower cognitive impairment compared to the highest dosage.

Less than ten percent of study participants had MRI scans that revealed the presence of ARIA, whereas those with ApoE4 had a 15 percent incidence. In March of 2019, Eisai kicked up a Phase 3 trial that will be known as Clarity AD [4, 5]. This study will be carried out at 250 sites across 50 nations. Participants in the study were going to be given either the real medicine at a dose of 10 mg/kg or a placebo every two weeks for a total of 18 months, with an open-label extension of two more years possible if enrolment targets were reached. The experiment is expected to continue until 2024, and preliminary results are anticipated to be made available in the fall of 2022. Eisai and Biogen have initiated the process of filing for

marketing permission after the Food and Drug Administration (FDA) categorized lecanemab as a breakthrough medication. This classification would speed up the regulatory examination.

The first participant was dosed in September of 2020, and by January of 2022, there were already 99 centers throughout the world actively recruiting new people to take part in the study. One thousand individuals who have an amyloid PET scan that is positive will be recruited in the A45 study. Measurements of blood A42/40 will be used to weed out individuals who have a low likelihood of having high levels of amyloids in the brain before going on to PET imaging [5]. The month of September 2021 saw the beginning of Eisai's Phase 1 research of subcutaneous lecanemab. A total of sixty healthy people took part in a study that compared the pharmacokinetics, bioavailability, and safety of a single subcutaneous abdomen injection of 700 mg to an intravenous dose of 10 mg/kg.

It was announced in November 2021 that the DIAN-TU drug will be used in the very first anti-amyloid/anti-tau concurrent trial[5]. The medication was chosen for this investigation. (News on the November 2021 meeting). In September of 2022, eisai revealed that the Phase 2 study had shown encouraging top-line results.

According to Reiman, it had an influence on a variety of cognitive and functional parameters that are significant to families and those who care for family members in the family. It would surprise me if the FDA did not give them complete clearance to the product[15]. It is anticipated that the agency would consider granting a conditional permission early on in the year 2023, followed by a complete approval later on in the year. It is anticipated that approval of lecanemab would restrict its use to patients in the early stages of Alzheimer's disease [13]. They account for around 2 million of the total 6 million patients diagnosed with the condition [16].

However, lecanemab and the majority of other medications that remove amyloid from the brain still have certain safety issues that need to be resolved. A disorder known as ARIA, which stands for amyloid-related imaging abnormalities, is the source of the majority of patients' worries [10]. On brain scans, two different types of ARIA are often seen in patients who are taking amyloid medications. In one type, there is bleeding, while in the other, there is swelling. More than one in five participants in the lecanemab research had edema, and more than one in seven participants experienced bleeding as a side effect of the medicine [17].

Conclusion

In conclusion, it is important to point out that Lecanemab, a humanized monoclonal antibody developed by Biogen and Eisai and administered intravenously once every two weeks, targets beta amyloid, a harmful protein that accumulates in the brain to form plaques and is believed to be one of the primary causes of Alzheimer's disease. 5 It is predicted that the agency would consider a conditional permission early in the year 2023, followed by a complete approval later the same year. In the event that it is given the go light, lecanemab will most likely only be supplied to patients who have mild to severe Alzheimer's disease. They are responsible for around 2 million of the 6 million people who are affected by the illness. Following the release of the phase 2b data, the Japanese pharmaceutical firm suggested a possible annual value-based pricing range for lecanemab of $9,249 to $35,605.

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