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Biogen/Eisai Hit 'Send' On High Stakes BLA For Aducanumab In Alzheimer's Disease

by Mandy Jackson

Some analysts see a 50-50 chance of US FDA approval despite the controversial dataset for the anti-amyloid antibody, but at least one expects an eventual CRL requesting a third Phase III trial.

Biogen and partner *Eisai Co. Ltd.* said on 8 July that they completed their highly anticipated biologics license application (BLA) submission for the amyloid-beta-clearing monoclonal antibody aducanumab in Alzheimer's disease, kicking off up to two months of speculation about whether or not the controversial pivotal dataset meets the US Food and Drug Administration's standards for accepting the application.

The FDA has 60 days to decide whether to accept the BLA and if the agency grants Biogen's and Eisai's request for priority review – six months versus the 10-month standard review – aducanumab approval could be granted as early as the first week of March 2021. Many analysts said there is about a 50-50 chance that the FDA will accept the BLA and approve aducanumab, but one analyst said acceptance of the application followed by a complete response letter (CRL) is likely and would give the agency an opportunity to publicly enumerate the reasons aducanumab is not ready for approval.

Aducanumab, which Biogen initially licensed from *Neurimmune Holding AG* and later partnered with Eisai to co-develop and co-commercialize, is a high stakes opportunity for Biogen to significantly boost its stagnant product sales and diversify its revenue as generics and biosimilars threaten the company's growth.

The drug is also a high stakes opportunity for the first disease-modifying treatment to slow or stop the progression of Alzheimer's, which is a rapidly growing multibillion-dollar public health care crisis.

There are 5 million people age 65 and older in the US who have Alzheimer's disease and that

number is expected to triple by 2050, according to the Alzheimer's Association, which said the total cost of treating those patients will be $305bn in 2020 and increase to $1.1tn in 2050 – even without adequate care. The association found in a survey of primary care physicians that few of those front-line doctors have enough training to help patients and caregivers, and they said there are not enough geriatricians and neurologists to help oversee those patients' care.

Biogen and Eisai believe aducanumab will slow Alzheimer's patients' cognitive and functional declines, reducing the burden and cost of care, but results from the Phase III EMERGE and ENGAGE clinical trials have not given a clear picture of whether aducanumab is worthy of FDA approval.

Discussions With FDA Began In June 2019

The companies have been working closely with the agency on the BLA submission and Biogen's comments since October, when the partners announced their plans to seek approval for aducanumab, indicated that discussions about the BLA have been ongoing for more than a year.

Biogen and Eisai said in March 2019 that they would discontinue the EMERGE and ENGAGE trials after an interim futility analysis determined the studies were unlikely to succeed. (Also see "*Why Biogen/Eisai's Aducanumab Failure Is Not The End Of Amyloid Hypothesis*" - Scrip, 21 Mar, 2019.)

However, additional analyses found that EMERGE did meet the study's primary endpoint and improvements observed in patients with early Alzheimer's disease in ENGAGE were positive, though not statistically significant. At that time in October 2019, the companies said they had been in contact with the FDA since June 2019 about the possibility of submitting a BLA based on longer-term data from additional patients that showed aducanumab had time- and dose-dependent effects on the progression of Alzheimer's disease. (Also see "*An About Face As Biogen Says It Will File Aducanumab In Alzheimer's* " - Scrip, 22 Oct, 2019.)

Biogen presented a complex set of results from EMERGE and ENGAGE at the Clinical Trials on Alzheimer's Disease (CTAD) meeting in December that did not provide a clearer picture than the top-line analysis of why the FDA might approve aducanumab based on the available data.

The company's executives indicated at CTAD that patients treated for longer periods with the highest dose across both trials saw statistically significant improvements in various measures of

Biogen's Big Day Arrives, But Aducanumab Results Don't Answer Key Question

By Mandy Jackson

05 Dec 2019

Biogen presented highly anticipated data in Alzheimer's disease at CTAD for its Phase III EMERGE and ENGAGE studies, but one major

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cognition and function. They said the results previously were confounded by dosing starts and stops for individuals with the ApoE4 gene associated with earlier, more rapid decline; dosing interruptions and adjustments were part of the studies' protocols in an effort to reverse amyloid-related imaging abnormalities (ARIA) observed in ApoE4 carriers.

question remains unanswered: will the FDA approve the drug?

Read the full article here

The EMERGE and ENGAGE analyses, which were included in the BLA along with results from the Phase Ib PRIME trial and its long-term extension study, were so complicated that Biogen and Eisai needed more time than originally expected to complete the submission of their application to the FDA. The companies planned to seek approval for aducanumab in early 2020, but in April said the BLA submission would occur in the third quarter of 2020 – a goal they have now met. (Also see "*From Early 2020 To Q3: Biogen Shifts Aducanumab Filing Expectations Again*" - Scrip, 22 Apr, 2020.)

Analysts Expect BLA Acceptance With Priority Review

"We admit that aducanumab's data package is not as clean as we would hope, and that many Alzheimer's specialists don't think the drug should be approved based on the current dataset," SVB Leerink analyst Marc Goodman said in an 8 July note. "However, there are other [key opinion leaders] we have spoken with who still expect approval (from a risk/reward and high unmet need perspective in Alzheimer's) and admit that any new disease-modifying drug is good news and will be tried in many Alzheimer's patients. And given the unusual close working relationship between the FDA and Biogen, we still believe that the FDA wants to approve this drug in early Alzheimer's."

Discussions with regulators about filing for approvals outside the US, including in the EU and Japan, are ongoing.

In the US, it is unclear whether Biogen and Eisai submitted a priority review voucher (PRV) along with their BLA and request for priority review, but Biogen received a PRV in 2016 with the approval of the spinal muscular atrophy (SMA) drug Spinraza (nusinersen). (Also see "*Biogen/Ionis's Spinraza Approved; Second Antisense Drug For Neurodegeneration In 2016*" - Scrip, 28 Dec, 2016.) The company has not publicly disclosed its plans for

Priority Review Vouchers Post Lower Average Approval Times Than Priority NMEs

By Bridget Silverman

15 Oct 2019
US FDA's priority review voucher program

that PRV, but it may still be available to redeem for a speedy approval of aducanumab.

Jefferies analyst Michael Yee said in an 8 July note that "we assume they will get a priority review based on unmet need etc." Yee estimates that aducanumab has a 50-50 or better chance of winning FDA approval given the unmet need in Alzheimer's disease, but noted that "there is now way more focus by FDA on COVID vaccines and resources, and less 'spotlight' on Alzheimer's political pressure, which is interesting to us."

delivers for most sponsors, a Pink Sheet analysis finds; PRVs reliably produce faster approval than priority-reviewed new drugs overall.

Read the full article here

Wedbush Securities analyst Laura Chico made a similar observation regarding the COVID-19 pandemic's potential impact on the aducanumab BLA, noting in an 8 July report that "the filing represents a large and complicated one and while we don't rule out the potential for priority review, in the current COVID-19 environment we do wonder about [FDA] resource availability."

Credit Suisse analyst Evan Seigerman said he expects the FDA to accept the aducanumab BLA for priority review and said the Alzheimer's therapy has about a 50% chance of winning approval after the agency holds an advisory committee meeting. However, "if FDA does not accept the application or does not grant priority review, we see major issues with the aducanumab program," he added.

William Blair analyst Matt Phipps maintained his position that he does not anticipate approval of aducanumab. Phipps said in an 8 July note the FDA is likely to require a third Phase III study of aducanumab to support a future BLA resubmission by Biogen and Eisai.

"We continue to believe the next steps for aducanumab will include acceptance of the application, advisory committee (AdCom) meeting, and complete response letter (CRL)," he said. "The acceptance of the filing and holding of an AdCom meeting is the best way the FDA can publicly disclose the review of the clinical history of aducanumab and the shortcomings of the Phase III studies. We believe this could be an important way for the agency to respond to political and patient advocacy pressures."

"A refuse-to-file or CRL without an AdCom does not allow for disclosures beyond what the company chooses to disclose, and therefore could leave room for pressure on the agency, claiming it is not doing enough to help Alzheimer's patients who have no other options," Phipps added.

Biogen Needs Aducanumab-Fueled Growth

Approval of aducanumab is particularly important for Biogen given various competitive pressures on its commercial portfolio, including new competition for Spinraza from *Novartis AG*'s gene therapy Zolgensma and *Roche*'s risdiplam, which is pending approval. (Also see "*US FDA Extends Roche's Risdiplam Decision Date*" - Scrip, 8 Apr, 2020.)

Also, Biogen's best-seller – the multiple sclerosis blockbuster Tecfidera (dimethyl fumarate) – may face earlier than expected generic competition after *Mylan NV* succeeded recently in overturning a key Tecfidera patent in a US district court. Biogen recently won an injunction to prevent the launch of Mylan's generic, which has not yet been approved, while the case is under appeal. (Also see "*Mylan Blocked By US Tecfidera Injunction*" - Generics Bulletin, 1 Jul, 2020.)

Biogen's Tecfidera Future Uncertain After Patent Challenge Loss To Mylan

By Jessica Merrill

18 Jun 2020
Biogen said it will appeal the district court decision invalidating the '514 patent for Tecfidera but Mylan said it looks forward to launching a generic after final FDA approval is granted. The ANDA has a November action date.

Read the full article here

Biogen already is preparing for the aducanumab launch, but without it – and without other near-term launches – the company expects revenue to hold steady or decline to $14bn-$14.3bn in 2020 from $14.38bn in 2019. (Also see "*Biogen Is Putting Its Money Where Its Mouth Is – Behind The Launch Of Aducanumab* " - Scrip, 30 Jan, 2020.)