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## **Biogen raises a new spark of hope for people with Alzheimer's disease**

Two days ago, Biogen (which we don't own in any of our portfolios) made an astonishing U-turn, reviving hope for Alzheimer's patients. We remind our investors that more than 400 clinical trials have failed since the last Alzheimer's drug was approved in 2003, and the discontinuation from Biogen of the two Phase III studies (EMERGE and ENGAGE) on its Alzheimer's drug, Aducanumab, in March 2019, left patients and investors with no hope, sliding Alzheimer's treatments into a trough of disillusionment.

The company at that time decided to stop the Aducanumab program following disappointing results of an earlier and smaller patient dataset, indicating a low probability to meet the primary endpoint (reduction in the cognitive decline of patients treated with high dose Aducanumab vs. placebo).

Despite the study shutdown, the company kept collecting and analyzing data together with the FDA. Following the discussions it had with the drug agency, Biogen plans to submit Aducanumab for approval in January 2020.

The new dataset includes a higher number of patients, taking the highest dose of Aducanumab for a more extended period (EMERGE study included an additional three months of data, through March 20, 2019). The company introduced significant changes in the EMERGE and ENGAGE protocols (respectively 10 and 18 months after the beginning of the studies) to include more patients to the highest dose of the drug (10 mg/kg every month).

Results were controversial as one of the studies (EMERGE) met the primary endpoint while the other missed it. The FDA usually requires both studies to be positive to approve a new therapy. However, according to the company, the EMERGE study provides compelling evidence about Aducanumab efficacy.

Given the devastating nature of this disease (for patients and families) and the lack of effective treatments, time is a priority. We believe that despite incomplete results, the FDA might end-up approving the drug without requiring additional data.

We continue to closely monitor the neurodegenerative sector, as we believe that Biogen's move (and potential approval of Aducanumab) is going to restore investor enthusiasm over Alzheimer's treatments and spur R&D in this field. Moreover, we think that companies like **Cortezyme (CRTX)**, **Neurocrine Biosciences (NBIX)**, or **Sarepta Therapeutics (SRPT)**, which are all part of our Biotech/Healthcare M&A certificates, could now be on Biogen's radar, as they could contribute to leverage Biogen's neuroscience expertise.

### **Do we believe in the amyloid theory?**

Alzheimer's is a very complex disease, affecting more than 47M people worldwide. Its root causes are still unknown, but in most of the patients it develops a series of neuropathological processes (starting 10 to 15 years before the first symptoms appear) that ultimately lead to the loss of the synapses (the connection between neurons) and the loss of cognitive functions.

#### **1. Development of neuropathology**

- Change in the beta-amyloid metabolism → The brain is no longer able to clean beta-amyloid clusters which start aggregate and turn into toxic plaques

- Hyperphosphorylation and accumulation of the tau protein → Tau proteins become abnormal and start destabilizing the neuronal cytoskeleton
2. Loss of synapses and neurodegeneration

Aducanumab is a human monoclonal antibody that binds to the beta-amyloid aggregates and triggers their removal. We consider that cleaning the brain from the accumulation of beta-amyloid plaques could help to slow down the progression of the disease, as long as the drug is administered at an earlier stage of the disease when the quantity of beta-amyloid plaques has not caused irreversible damage.

A pre-clinical study led by MIT neuroscientists has recently published some striking results supporting the amyloid theory. The new approach by the MIT uses light and sound to remove the amyloid plaques. The trials on mice have demonstrated a substantial increase in their cognitive functions, and the scientists are now ready to move forward into clinical trials.

In parallel, companies are working on treatments that could stop the dephosphorylation and accumulation of the tau protein. We think those amyloid plaques are just a piece of a puzzle and that treatments combining several neuropathological processes (such as beta-amyloid plaques, tau's hyperphosphorylation, and some others perhaps) could lead to better and more effective ways to treat Alzheimer's.

Novel hypotheses are pursuing bacterial infections as the root of the disease. **Cortezyme** is one of them as they want to prove that Alzheimer's has its origins in a gingival bacterial infection. These hypotheses are still to be confirmed, but what is clear is that timing is an essential factor for the success of these treatments. As long as we are not able to diagnose Alzheimer's before patients start exhibiting symptoms, no effective therapies are in sight. Noninvasive and cheaper technologies are currently in development, with some promising initial results. The FDA has recently been incentivizing the development of these technologies, granting a faster path to approval of two blood-based tests developed by **C2N Diagnostics** and **Fujirebio Diagnostics**.

We continue to monitor the Alzheimer's landscape closely, and if any significant adjustments to the portfolios take place, we will communicate it to our investors.

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