Aduhelm: A Catalyst for a Shift in Sentiment

At the 2022 Biotech Showcase on January 11, 2021 several leaders in the field of neurodegenerative therapies came together to discuss recent trends in the space. A notable shift has emerged since the approval of Aduhelm eight months ago that has led to a resurgence of interest and investment in Alzheimer's Disease (AD). Substantial new capital flows toward private and public companies have occurred including material cash infusions and initial public offerings (IPOs) in companies advancing AD research. To explore some these trends and where they might be headed, six industry experts gathered at the 2022 Biotech Showcase investor conference to contribute to a panel entitled Aduhelm: Stimulating the Next Generation of AD Treatment. The roster included:

1) Phyllis Barkman Ferrell, Global Head, External Engagement Alzheimer's disease and Neurodegeneration at Eli Lilly;

Phyllis Barkman Ferrell

Global Head, External Engagement, Alzheimer's disease and Neurodegeneration

Eli Lilly & Company

2) Travis Bond, CEO of Altoida, Inc;

Travis Bond

CEO

Altoida, Inc.

3) Michael McFadden, CEO of Alpha Cognition, Inc;

Michael McFadden

CEO

Alpha Cognition, Inc.

4) Lisa Ricciardi, CEO of Cognition Therapeutics, Inc;

Lisa Ricciardi

CEO

Cognition Therapeutics, Inc.

5) Brent Vaughan, CEO of Cognito Therapeutics;

Brent Vaughan

CEO

Cognito Therapeutics

6) Eugene Williams, CEO of ProMIS Neurosciences.

Eugene Williams

Chairman and CEO

ProMIS Neurosciences

The panel was moderated by John Vandermosten, CFA, Senior Biotech Analyst at Zacks Small Cap Research.

John Vandermosten

Senior Biotechnology Analyst

Zacks Investment Research

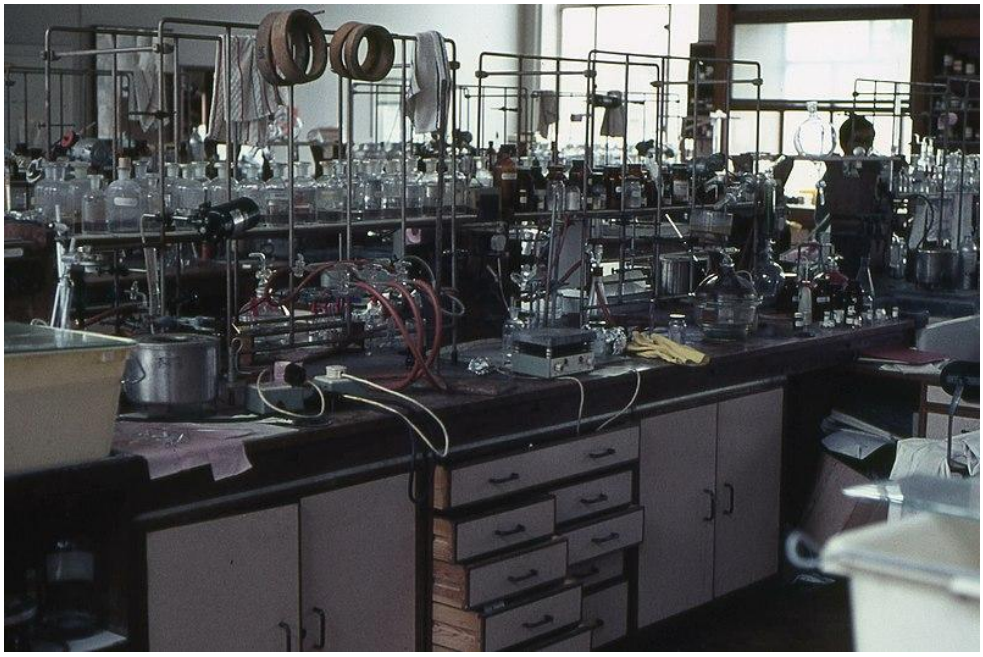
Some Background

During the mid to late 2010s, there was a slow but accelerating exodus from investment in neurodegenerative programs, especially in Alzheimer's Disease. Perhaps it is the natural response on the difficult road to success, since the space was often perceived as a graveyard of failed programs and there had been no new drugs approved since memantine received the FDA nod in 2003. A lengthy list of —mabs, —stats and —ines were jettisoned after missing endpoints or producing unacceptable safety issues in late stage trials resulting in most of the big pharma players reducing their exposure to the area. AstraZeneca dropped lanabecestat, Johnson & Johnson cut atabecestat, Amgen and Novartis discontinued their program for ubibecestat and Roche's crenezumab failed trials to name a few. But the capitulation arrived when Pfizer pulled out of neuroscience drug discovery with 300 position cuts and a sale of the division in 2018 after bapineuzumab's poor results. Even though programs by Biogen and Eisai continued, the luster had faded.

Investor interest in neurodegenerative disease and especially AD had reached a nadir by 2019, and expectations were low. When Biogen announced that it would halt its aducanumab trials, many were not surprised. What little interest had remained in pursuing AD had faded even further and many smaller companies developing AD programs de-emphasized or delayed them. However, over the next two years, aducanumab, later branded Aduhelm, would go on to experience a wild roller coaster of ups and downs which eventually resulted in approval for the drug and a new hope for AD drug development.

Where the Science Takes Place[1]

[1] Credit: Michael D. Turnbull. https://commons.wikimedia.org/wiki/File:Laboratory_122_Cambridge_Chemistry.jpg



New Financings

Following the Aduhelm approval news in early June 2021, several transactions took place in the Alzheimer's space. Initial public offerings for Acumen Pharma (ABOS), Alzamend Neuro (ALZN), Cognition Therapeutics (CGTX) and just recently Vigil Neurosciences (VIGL). Additional equity investments were also made following the landmark approval, including companies represented on our panel: ProMIS Neurosciences and Alpha Cognition. Panelists observed that not only did AD garner interest from investors, but ALS and other neurodegenerative disease also saw renewed attention from stakeholders.

New Learning

But it wasn't just FDA approval for the first disease modifying therapy in the space; other factors were also driving the resurgence of interest in AD. Compelling data from Eli Lilly's (LLY) donanemab and Eisai's (ESALY) lecanemab (BAN2401). Investors recognized that a regulatory pathway is now available supported by biomarkers and a large market opportunity exists with few other therapies available for treatment. The FDA seemed to be loosening the regulatory constraints, recognizing that the industry needed encouragement if we are to solve this unmet need. Furthermore, understanding of the disease has improved dramatically over the last decade and better imaging is able to show protein buildup in the brain without autopsy. Sentiment also shifted in the wake of the approval and portfolio managers who previously may have felt their AD investments were open to criticism were now more confident in their investment thesis. What may have appeared to be a string of failures to the uninitiated is now perceived an intense learning process that has continued to build off of improvements in technology.

Panel Themes

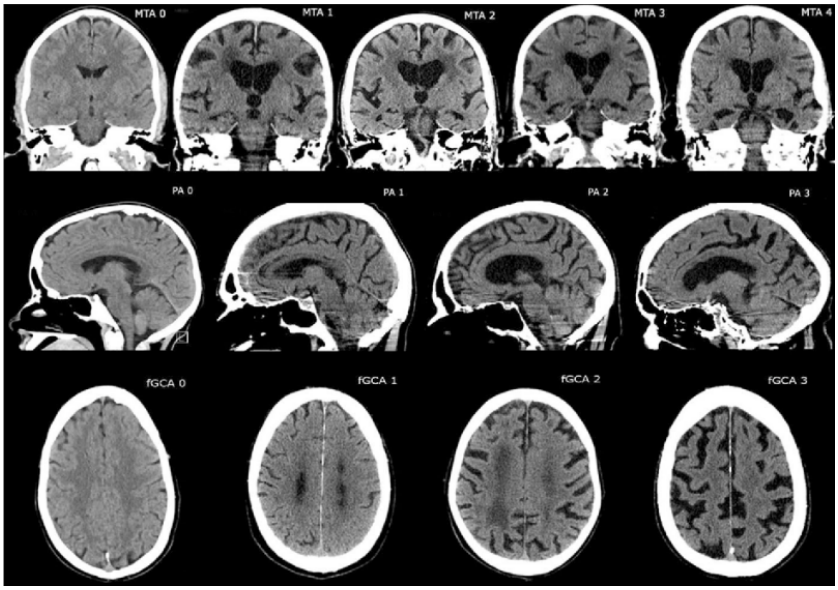
Several themes arose during our panel discussion including the importance of biomarkers, recognizing AD as a multifactorial disease, the benefit of being in the vanguard and the role of devices and diagnostics for advancing treatment.

Biomarkers

Biomarkers may be one of the most important tools to quickly and inexpensively identify therapies that work, saving time, money and patient lives. The FDA's position on biomarkers has evolved over time as recently described in a 2018 guidance update. The most notable element provided in the document was the acceptability of biomarkers for determining efficacy. Now that biomarkers are encouraged, clinical trials for Lilly's donanemab are using Positron Emission Tomography (PET) scans to measure amyloid plaque clearance. Future trials for other candidates may use cerebrospinal fluid (CSF) constituents neurofilament light chain (NfL), Aβ1-42, T-tau, and P-tau 181, 217 and 231 to measure changes in cognitive health and AD.

Biomarkers help clinicians narrow down clinical trial populations to only those that present the characteristics that are desired. Phyllis provided an example of this phenomenon from her experience at Lilly where samples were tested from patients from previous trials using current diagnostic techniques for CSF analysis. The analysis found that a material proportion of the patients who were included in past amyloid β trials did not in fact have amyloid β in their brains. New imaging techniques are able to effectively identify the target population, allowing for more focused research and smaller and more efficient trials.

Brain Imaging[2]



Biomarkers are especially important in earlier stage trials as they can provide a signal as to whether or not the drug is working. If the drug is driving outcomes towards the desired endpoints, the trial will go on; however, if the early read shows no benefit, the trial can be cut short and funds allocated to more successful endeavors elsewhere.

Multifactorial Disease

[2] Velickaite, V. *et al.* Head CTs of cerebral atrophy by different grades. "Cognitive function in very old men does not correlate to biomarkers of Alzheimer's disease". BMC Geriatrics. 2017.

AD is a multifactorial disease with many target proteins and other risk factors contributing to its etiology. Some of the best recognized components include amyloid beta, tau, ubiquitin, protein misfolding, inflammation, oxidative stress among others. The variety of influences supports the use of multifunctional compounds for different disease subgroups. Stratification of patients by disease subgroups and by stage of disease may be necessary to develop disease modifying drugs that can address each of the differentiated types. There are at least five subgroups of AD that may be driven by different mechanisms and it stands to reason that the different subgroups may respond differently to any given therapeutic drug. This suggests that successful strategies for preventive and therapeutic agents for AD must approach it from multiple angles.

Are The Blockbusters Always In The Vanguard?

Sovaldi, Lipitor and Humira were the top drugs of their class, however, they were not the first in class. In 1998, lamivudine was the first anti-viral drug to be approved for hepatitis B, however, it was not until Sovaldi was approved in 2013 that the most dominant anti-viral drug was available. By 2014, Sovaldi generated $10.3 billion in sales. The same phenomena occurred in statins. Zocor was approved and generated first sales in 1988, but the greatest success in the class turned out to be Lipitor, which was the fourth drug available. First sales for Lipitor did not occur until 1997, but eventually it achieved sales of almost $13 billion by 2006. We also saw a follow-on product take the lead in the anti-TNF space where Remicade was launched in 1998 to modest success until 2011 when Humira exploded on the scene in the US with almost $8 billion in sales at over twice the levels of Remicade.

These examples show that the best in class may not be the first in class and in the Alzheimer's space, perhaps we shouldn't worry that Aduhelm is not the panacea that we had hoped for. As Lisa Ricciardi noted, the leaders in the space may end up with arrows in their back, but they have helped clear a path for others to follow that may later benefit us all. Other contenders that have the advantage of additional years of scientific understanding and learning from those that have come before might become the blockbuster cure we are waiting to see. Several candidates in development, including Lilly's donanemab, Alpha Cognition's Alpha-1062, Cognition Therapeutics' CT1812, Cognito's GammaSense or ProMIS' PMN-310 might just be that fast follower blockbuster that we have been waiting for.

Devices and Diagnostics

Most focus in neurodegenerative treatment is on the pharmaceuticals and biologics being developed, but there is a portfolio of devices and diagnostics which can both treat and guide the use of other therapies for AD. Our panelist Brent Vaughan leads Cognito Therapeutics which is developing an approach to treating AD using gamma band frequencies to reduce amyloid β levels. Studies conducted in mice have shown reduced levels of amyloid β and boosted activity of microglia in clearing harmful debris using Cognito's GammaSense stimulation device.

Other AD devices and diagnostics that we have run across include NeuroEM's Transcranial Electromagnetic Treatment (MemorEM), C2N Diagnostics' PrecivityAD test which is available in much of the United States, and Functional Neuromodulation which is developing deep brain stimulation therapies. In our work with neurodegenerative-focused companies we have also come across mass

spectrometry, surface plasmon resonance, brain imaging[3] as effective methods to identify AD-related biomarkers.

ProMIS' Gene Williams identified Down syndrome patients as an important group to apply digital and biologic biomarkers and measure the effect of therapeutics for prevention. We know with a high degree of certainty that this patient population will have amyloid β buildup making this an appropriate population to attempt early stage treatment.

Another element of diagnostics uses AI to sort through data to diagnose dementia. Some examples include data generated by online behavior and from smartphone sensors to identify symptoms of the disease. Michael identified a tool used by an online retailer that is able to identify dementia through buying patterns and Travis highlighted a recently conducted study that identifies digital patterns in the brain which can diagnose COVID with a high degree of accuracy. Travis leads Altoida, which received a breakthrough designation for its augmented reality application just weeks after Aduhelm was approved. The application is a digital biomarker that can predict if older individuals with mild cognitive impairment will convert to AD within 12 months, further demonstrating the FDA's willingness to support new products where there is an unmet need.

Devices and diagnostics may be complementary approaches along with pharmaceuticals and biologics to address AD. In conjunction with traditional routes, electrical stimulation devices may allow providers to address AD from multiple directions, responding to the disease's multifactorial origins. Combined with effective diagnostics, providers will further be able to measure progress with biomarkers. Digital diagnostics may also reduce cost, improve data quality and save time in clinical trials through automation. The ability to monitor a subject from home can improve compliance with data submission and provide troves of information which then may be analyzed by AI to refine the therapeutic effect of the intervention.

Summary

Following years of neglect, investors have shifted their attention back towards AD and the neurodegenerative space following the Aduhelm approval. While the approval is the dominant driver for the sentiment shift, other factors include supportive data from ongoing trials and the emergence of regulatory feasibility for AD candidates. Allowing Aduhelm to be marketed shows the FDA's willingness to step up for disease areas where there is an extreme unmet need. Our panel provided input on a number of key themes including the expanded use of biomarkers, recognition that AD is a multifactorial disease that requires a multimodal approach, that the first in class is not necessarily the best in class and that devices and diagnostics play an important role in the future of AD therapy. We are eager to see what the next years bring!

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[3] Such as Magnetic resonance imaging (MRI), computerized tomography (CT) and positron emission tomography (PET).
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