



Chairman's Memorandum, January 8, 2020

As we start the new decade, it looks like 2020 should be a year of great progress in combating Alzheimer's disease. Moreover, we are certain this decade will mark the turning point in the successful development of effective treatments for this devastating disease. ProMIS was founded to make a significant contribution to this mission: we remain highly committed and are more convinced than ever that we are on the right track.

It is easy to lose sight of the reasons for this optimism in light of the numerous clinical trial failures over the last two decades despite tremendous investment. But at the last major Alzheimer's meeting of the decade (the Clinical Trials in Alzheimer's Disease [CTAD] meeting in San Diego in early December 2019), many of the reasons for optimism were discussed in depth. Viewed objectively and prospectively, the numerous scientific and clinical advances reviewed in this note paint a clear picture that we have turned the corner in advancing toward effective treatments, and this advance will provide great opportunities for companies like ProMIS.

The most important CTAD presentation of course was the more detailed explanation of Biogen's rectification of their previous decision to discontinue their aducanumab phase 3 pivotal trials. Biogen and many others admitted that it was a mistake to stop the trials, but despite that self-inflicted handicap the data look positive. If you view the Biogen situation through the lens of "will Biogen gain an FDA approval despite their mistake", we and others believe that odds are good, but there is certainly room for debate.

However, if you look through the more important lens of "are we getting closer to an effective treatment in Alzheimer's disease?", it is clear ***for the first time ever, positive data from a pivotal trial line up with an overwhelming body of scientific literature validating a route to an effective treatment for Alzheimer's.*** ProMIS' approach has more validation than ever, and, as many leaders pointed out at CTAD, the foundation has been laid for a decade of dramatic progress in Alzheimer's.

We and others have provided details on the Biogen presentation at CTAD before, but in brief: mid-way through the trial, Biogen amended both phase 3 protocols ("PV4") to increase the highest possible dose for patients genetically at risk for Alzheimer's from 6mg/kg to 10mg/kg. The initial conservatism was based on concerns about the higher risk of the ARIA- E side effect among patients with at least one copy of the APOE4 gene. The rationale for increasing the dose

was strong, since, in the earlier Phase 1b study, there was a dose-response curve (10mg looking much more effective than 6mg).

As part of their updated statistical analysis presented at CTAD, Biogen evaluated the group of patients who had consented to the “PV4” amended protocol and had received the higher dose. That set of patients best represents what will happen on the market if aducanumab is approved, and, in retrospect, 10 mg/kg should have been the administered dose for the entire pivotal trial. In Biogen’s analysis, the patients in both pivotal phase 3 studies had a clinically meaningful benefit in the high dose arm, consistent with the slowing of disease progression.

In addition, both Biogen and Eisai (whose product BAN2401 demonstrated clinical benefit in a Phase 2 study, and is now progressing in Phase 3) showed data that ***clinical benefit is not correlated with amyloid plaque reduction***. These data are consistent with the scientific literature showing that amyloid mis-folded toxic oligomers, not plaque, are the pathogen and need to be the target for therapy.

As many of you will remember, ProMIS was founded in part based on our analysis of the initial Biogen success with aducanumab, announced in December 2014. We analyzed that data through the scientific lens of our founder Neil Cashman, who along with his colleagues including Nobel Prize winner Stanley Prusiner, Larry Walker, Mark Diamond, and others had realized that prion-like toxic oligomers of amyloid, tau, alpha-synuclein, etc. were the disease drivers in neurodegenerative disease. That explained why aducanumab had positive data unlike anything before it: aducanumab was partially selective for the toxic mis-folded form of amyloid and did not bind the amyloid monomer. But aducanumab’s plaque binding led to its dose-limiting side effect of ARIA-E, or brain edema.

The science suggested that a more selective antibody, with no plaque binding, could avoid the ARIA-E side effect, allow for higher dosing, and thus be more effective in the clinic. All scientific and clinical data (in its corrected form) since that time have supported this view. PMN310 was the best of over 300 candidates created by ProMIS with that goal in mind. In early 2018 we announced comparative data and showed scientific superiority to aducanumab. In July 2019, these data were published in Nature journal Scientific Reports.

The positive news from CTAD could not have been more welcome in the Alzheimer’s community after two years of setbacks and disappointments, some based on mistakes and misunderstanding. In 2018 and 2019 for example, there were three major instances of mistakes and miscommunications by the leaders in the amyloid-focused Alzheimer’s field. In February 2018, Biogen disclosed they had amended their pivotal trial to augment it with an additional 500 subjects, but they provided an inadequate amount of explanation, which led to misinterpretation. In July 2018, Eisai mishandled communication about the distribution of APOE4 carriers, at greater risk for the ARIA-E side effect, in their Phase 2 trial of BAN2401. Finally, in March 2019, Biogen mistakenly stopped their pivotal trials of aducanumab based upon a flawed futility analysis that failed to account for the aforementioned mid-trial dose increase. In each case:

- Biogen or Eisai suffered a market cap decline of billions of dollars;
- Wall Street investors and analysts cited the event as more reason to doubt the amyloid hypothesis;
- ProMIS experienced a reversal of positive market and investor momentum.

The mistaken negative sentiment about these programs added to the skepticism and pessimism driven by failures of approaches that are not in line with the latest science (monomer-focused therapies like BACE inhibitors, or non-selective antibodies like Roche's crenezumab). The result was to generally shut down access to capital in Alzheimer's to a large extent, and for amyloid-based approaches completely.

The market sentiment won't turn around completely or immediately: the depth and duration of skepticism is too great. Nearly every biotech success story has a "downturn" or a dark patch somewhere between start-up and success. Immuno-oncology had a period of failure, skepticism, and challenge before turning around and becoming what is now arguably the hottest area in biotech. The last two years were the worst of the downturn – the "dark days" in Alzheimer's – but we believe the turnaround has just begun.

Attending CTAD, the presentations and hallway discussions painted the following picture, a scenario of positive progress in Alzheimer's disease:

- Aducanumab will file for approval in 2020, and will likely become the first ever approved disease-modifying therapy in Alzheimer's in 2021;
- BAN2401 will complete its pivotal trial in 2022, and has a good chance to become the second successful disease-modifying therapy;
- Biomarkers measuring disease progress in blood and CSF will become a mainstay of early AD drug development, and will dramatically improve the speed and cost effectiveness of therapeutic development;
- The Down Syndrome community, which has become very well organized for clinical trials and where Alzheimer's has become the #1 health concern, will enable a rapid route to approval, then extending treatment to elderly, "sporadic" patients. The Down Syndrome community is well positioned to demonstrate prevention;
- Early detection and prevention will increasingly become possible in AD;
- Gene therapy will allow safe and effective antibodies to be "vectorized"; instead of needing monthly infusions, one treatment will last for years and can be administered in a way to eliminate any concerns about crossing the blood brain barrier;
- A portfolio of effective therapies, including those targeting misfolded amyloid and tau, as well as neuroinflammation and neuroprotection, will become available in the long term, giving physicians many options for treatment; and
- All of the above will contribute to a growing availability of institutional investor capital in Alzheimer's, including improved versions of amyloid-targeted therapy.

ProMIS is poised to benefit from all of these trends. Our portfolio already includes differentiated, selective antibodies for toxic amyloid and tau, and our discovery efforts are targeting misfolded proteins involved in neuroinflammation and neuroprotection. As we head

into a decade of breakthroughs in finally treating Alzheimer's disease, ProMIS is well positioned to contribute to and benefit from the positive progress.

Eugene Williams
Executive Chairman