Aducanumab's milestone achievement for the Alzheimer's disease community: A ProMIS perspective from CTAD 2019

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- **Biogen provided additional analyses to support their conclusion that high-dose, long-duration aducanumab exposure can modify the Alzheimer's disease process and provide clinical benefit**
- **Distinguished scientific panel experts supported Biogen's analyses, indicating the efficacy results were clinically meaningful and that aducanumab represents the first treatment that targets the core pathology of AD**
- **Data from the aducanumab and BAN2401 programs indicate amyloid plaque reduction is not fundamentally an adequate explanation for clinical benefit and argue that oligomers are the more toxic molecular species to target**
- **Although aducanumab is likely to be approved by regulatory authorities, its limited efficacy and safety justify the need for a next-generation therapeutic that selectively targets toxic oligomers, offering the potential for improved safety and efficacy**

The ramp-up to CTAD 2019: Expectations were high for the December 5th Biogen presentation in San Diego after their announcement six weeks earlier that their initial conclusions from the aducanumab interim analysis for futility conducted in March 2019 were incorrect. Attendees packed the very large CTAD conference room for this session and Dr. Samantha Budd Haeberlein of Biogen detailed the aducanumab datasets during an unusually lengthy 45-minute presentation. After a 15-minute discussion by a panel of four experts and the session wrap-up, the room exploded as everyone immediately began discussing the results with great energy and animation.

Critical insights from the presentation: As indicated in the October 22nd announcement, Biogen amended in March 2017 both the EMERGE and ENGAGE phase 3 trials, that enrolled 3,285 early AD patients, in order to increase the maximum administered dose to 10 mg/kg for subjects with

the apoE4 genotype. The issue with these and other trials stems from the fact that apoE4 carriers have a higher risk of ARIA-E (brain swelling) when administered anti-amyloid antibodies that bind amyloid plaque. This caused Biogen to initially and sub-optimally limit the maximum available dosing to the apoE4-positive AD subjects enrolled in these phase 3 trials (approximately 70% of all enrolled subjects).

At CTAD, Biogen explained in detail how the timing of this protocol amendment differentially impacted the two trials and increased more significantly the number of subjects in the EMERGE trial who received the maximum dose of 10 mg/kg for a prolonged period of time. The EMERGE trial was unequivocally positive when the larger dataset became available and showed a 23% reduction in cognitive decline on the CDR-sb assessment scale amongst those trial subjects administered the high dose (10 mg/kg). The ENGAGE trial did not show an overall treatment benefit like the EMERGE trial for compelling reasons outlined by Biogen, but a post hoc analysis showed that the subset of ENGAGE participants (n=790) who had consented to the high-dose protocol amendment prior to week 16 had a treatment benefit (-27%) on CDR-sb similar to that observed in the equivalent subset (n=887) of the EMERGE study (-30%).

Biogen provided a large amount of additional, persuasive information to justify their conclusion that subjects who demonstrated a reduction in their rate of clinical decline had consistently been administered the highest possible dose of aducanumab over a prolonged duration.

Biogen also showed summary data on their biomarker assessments, and these data support the claim that aducanumab positively affected the underlying Alzheimer's neuropathology. They also summarized the rates of ARIA-E in the EMERGE and ENGAGE trials amongst apoE4 carriers and non-carriers administered 10 mg/kg of aducanumab as 41% to 42% and 18% to 23%, respectively, the highest levels observed in any late-stage anti-amyloid antibody trial to date.

During the question and answer period, Biogen refrained from providing detailed efficacy subset data broken down by apoE4 carrier status at this stage, and this evoked skepticism amongst attendees who expected complete transparency and more extensive data from Biogen at the CTAD meeting.

Key responses from the scientific panel experts: The panelists agreed that despite the complex dataset, high-dose aducanumab exposure benefited trial participants and modified the underlying disease process.

Dr. Stephen Salloway, Professor of Neurology at Brown University, indicated that aducanumab "represents the first treatment that targets the core pathology and opens an era of precision medicine for AD……I think this is a milestone achievement for our field".

Dr Sharon Cohen, Medical Director at Toronto Memory Program and Scientific Advisory Board member at ProMIS, explained "there's absolutely no doubt" that the 40% improvement in the functional outcome score reflects a dramatic difference in the ability of patients "at a mild stage of disease still being able to work, bank, shop, travel and enjoy leisure activities for longer".

Dr. Paul Aisen, Founding Director of the USC Alzheimer's Therapeutic Research Institute, noted that although the March 2019 "futility decision was highly unfortunate", the primary and secondary analyses of EMERGE were "consistent and positive", the biomarker data support the therapeutic mechanism of action, and that data from both EMERGE and ENGAGE should be considered "consistent" and a "major advance for the field". Treatment benefits of a therapy that modifies the disease "continue to accrue with time" according to Dr. Aisen, and he indicated "the data suggests that had the program had not been stopped early, we would have had two successful pivotal trials".

Other key data presented at CTAD: The low and the high doses in both the EMERGE and ENGAGE studies both had a highly statistically significant impact on reduction of amyloid plaque levels in the brain as measured by florbetapir PET imaging. However, the clinical benefit noted above did not correlate with the dramatic PET results suggesting sustained plaque reduction is not the critical factor in providing clinical benefit. Although aducanumab can bind and remove plaque, we know it is only partially selective for toxic amyloid oligomers and therefore likely requires many months at the highest possible dose to demonstrate a limited, but statistically significant effect.

During other CTAD presentations given by Eisai and BioArtic on their joint BAN2401 program, they showed data indicating that BAN2401 has stronger binding to toxic oligomers than aducanumab. BAN2401 binds amyloid plaque and is still therefore associated with ARIA-E, the key side effect of concern with anti-amyloid antibodies that bind plaque. Other data shown by Eisai on the impact of a time "gap" between completion of their phase 2 double-blind study and the initiation of their open-label study also demonstrated the critical discrepancy between sustained amyloid plaque removal on PET and the worsening of clinical benefit once subjects were in the gap period between studies. The Eisai presenter suggested that toxic oligomers were the cause of the cognitive worsening despite stable plaque imaging during the gap period.

Implications for ProMIS and its lead anti-amyloid compound PMN310: Biogen will file their BLA early next year; FDA acceptance of the file and their call for an advisory committee review perhaps as early as 4Q2020 represent risk-reduction catalysts for the field. We know that Biogen has already met twice with FDA who has expressed their willingness to review the filed application despite the absence of a definitively positive second pivotal trial. It's important to note that Biogen stated in October that "the validity of the dataset was the first thing that we analyzed together with the FDA".

Based upon a review of the complete efficacy and safety datasets from EMERGE, ENGAGE and PRIME (the phase 1b trial first reported in 2015), we conclude that aducanumab will most likely be approved by FDA and represents a dramatic turning point in the field.

Dr. Salloway commented that aducanumab's treatment "effects are small, but I think they are meaningful" and he characterized aducanumab, as noted above, as "the first treatment" for Alzheimer's disease. Dr. Dennis Selkoe, Professor of Neurologic Diseases at Harvard Medical School, noted recently that once a drug like aducanumab "got across the finish line with the FDA, it would open the floodgates to make better versions. I'm not talking about me-too drugs, but ones that actually work better than the first ones."

Based upon the tentative timelines provided by Eisai, we know the BAN2401 phase 3 program will be completed in 2022, and it is very likely BAN2401 will represent an incremental step forward with slightly better efficacy and less ARIA-E compared to aducanumab.

However, the AD community awaits development of a therapy that provides both a much more significant treatment benefit and better safety. This is exactly what we plan to do at ProMIS.

Our lead anti-amyloid antibody candidate, PMN310, will not be first in class like aducanumab, but its binding selectivity for only toxic oligomers suggests it has the tremendous potential to be best in class by producing a strong clinical benefit without eliciting ARIA-E. Moreover, by being able to push the dose in the absence of ARIA-E, PMN310 should achieve higher therapeutic levels and focus all its neutralization power on the toxic root cause of Alzheimer's disease.