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# ProMIS Neurosciences offers comments on recent FDA Advisory Committee meeting on aducanumab for the treatment of Alzheimer's disease

## FDA Office of Neuroscience argues for approval; non-binding recommendation from the Peripheral and Central Nervous System Drugs Advisory Committee is negative

TORONTO and CAMBRIDGE, Mass., Nov. 09, 2020 (GLOBE NEWSWIRE) -- ProMIS Neurosciences, Inc. (TSX: PMN) (OTCQB: ARFXF), a biotechnology company focused on the discovery and development of antibody therapeutics targeting toxic oligomers implicated in the development of neurodegenerative diseases, today commented on the November 6th FDA Peripheral and Central Nervous System Drugs Advisory Committee meeting and its review of Biogen's Biologics License Application (BLA) for aducanumab for the treatment of Alzheimer's disease.

The key BLA components reviewed at the advisory committee meeting consisted of three clinical trials: two pivotal phase 3 trials of similar design (Study 301, 302) and one phase 1b trial (Study 103). Both Biogen and FDA acknowledged Study 301 (ENGAGE) was negative and could not contribute to the evidence for aducanumab's effectiveness. Demonstration of effectiveness for licensing generally requires two adequate and well-controlled clinical trials that are positive. However, under certain circumstances and consistent with the 1997 FDA Modernization Act, FDA can conclude that one adequate and well-controlled clinical investigation plus confirmatory evidence is sufficient to establish effectiveness. Whether Study 302 (EMERGE) provided adequate evidence as a single study – a position strongly expressed by the FDA Office of Neuroscience – represented the key issue debated by the Advisory Committee.

Dr. Billy Dunn, Director of the Office of Neuroscience, who convened the Advisory Committee and ultimately has the authority to approve the BLA, gave the FDA presentation; he summarized the Study 302 results, stating they were "compelling", "exceptionally persuasive", and represented a "homerun". However, the written review by Dr. Tristan Massie, Office of Biostatistics, embedded in the FDA briefing documents for the Advisory Committee, addressed some Study 302 inconsistencies and argued against a conclusion of substantial evidence because of the conflicting results of the two phase 3 studies. FDA and Biogen conducted a number of subgroup analyses to explore why Study 301 and Study 302 were divergent in their results, but none of them provided a definitive answer and the committee members decided it was not possible to conclude aducanumab was effective for the treatment of Alzheimer's disease.

Thus, on the first and most critical question to the committee, "*Does Study 302, viewed independently and without regard for Study 301, provide strong evidence that supports effectiveness of aducanumab for the treatment of Alzheimer's disease*?", the committee vote was negative, with 1 Yes, 8 No and 2 Uncertain. To a large degree, the other three questions assumed a Yes vote to the first question, including the last question as to whether Study 302 could be considered as primary evidence of effectiveness.

It is important to note that, prior to and during the advisory committee meeting, the FDA Office of Neuroscience made several key arguments supporting approval of aducanumab, as outlined below:

- Analysis of the data supporting the March 2019 decision to discontinue the trials because of futility did not provide "*an accurate reflection of individual studies*". The futility decision was based on pooled data from both Study 301 and Study 302. However, if the two studies had been independently reviewed for futility, Study 302 would not have met the futility criteria and the magnitude of effect in the high-dose arm (10mg/kg) in fact improved over time as additional data were collected. FDA commented that it would have been more appropriate if futility had not been declared and noted that assumptions supporting the futility analysis had been violated.
- In response to Biogen's argument that anti-amyloid beta (Aβ) antibodies differ considerably with respect to their molecular characteristics, FDA agreed that "*anti-Aβ therapies do not represent a single class of drugs*" and previous late-stage failures of such therapies "*do not constitute a demonstrated 'class failure"*. During committee discussion, this point was briefly noted as members acknowledged that a more nuanced discussion of oligomers as the most toxic molecular Aβ species was beyond the scope of the committee's responsibility.

"Although FDA will most likely accept the non-binding recommendations of the advisory committee, it is disappointing for patients, their caregivers and the research community that the committee viewed the inconsistencies in data as too significant to reach a conclusion that aducanumab is clinically effective", said Dr. James Kupiec, Chief Medical Officer for ProMIS Neurosciences. "We are however encouraged by FDA's position on anti-Aβ antibodies. The amyloid hypothesis is far from dead now that the research community is focused on the most toxic molecular species, and we anticipate that PMN310, which selectively targets toxic Aβ oligomers, could demonstrate best-in-class effectiveness and safety in clinical studies".

After the Advisory Committee meeting, Mr. Michael Vounatsos, Chief Executive Officer at Biogen, expressed his gratitude for the patients and advocates who spoke at the meeting and reflected on the significant unmet need for a treatment for Alzheimer's disease. Biogen noted they will continue to work with FDA as it completes its review of the BLA.

**About ProMIS Neurosciences**

ProMIS Neurosciences, Inc. is a development stage biotechnology company whose unique core technology is the ability to rationally predict the site and shape (conformation) of novel targets known as Disease Specific Epitopes (DSEs) on the molecular surface of proteins. In neurodegenerative diseases, such as Alzheimer's, ALS and Parkinson's disease, the DSEs are misfolded regions on toxic forms of otherwise normal proteins. In the infectious disease setting, these DSEs represent peptide antigens that can be used as an essential component

to create accurate and sensitive serological assays to detect the presence of antibodies that arise in response to a specific infection, such as COVID-19. ProMIS proprietary peptide antigens can also be used to create potential therapeutic antibodies, as well as serve as the basis for development of vaccines. ProMIS is headquartered in Toronto, Ontario, with offices in Cambridge, Massachusetts. ProMIS is listed on the Toronto Stock Exchange under the symbol PMN, and on the OTCQB Venture Market under the symbol ARFXF.

Visit us at www.promisneurosciences.com, follow us on Twitter and LinkedIn. To learn more about protein misfolding diseases, listen to Episodes 11, 24, of Saving Minds, a podcast available at iTunes or Spotify.

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