NEWS RELEASE

BioVie Issues Letter to Shareholders

2023-07-18

- Treatment with NE3107 led to >50% reductions in DNA methylation of 400 CpGs [1] and some in a manner that was significantly correlated to observed clinical improvements in cognition and various biomarkers.
- Over 3,000 significant correlations were found linking reductions in DNA methylation of various CpGs and cognitive, biomarker and neuroimaging endpoints.

CARSON CITY, Nev., July 18, 2023 (GLOBE NEWSWIRE) -- BioVie Inc., (NASDAQ: BIVI) (“BioVie” or the “Company”) a clinical-stage company developing innovative drug therapies for the treatment of advanced liver disease and neurological and neurodegenerative disorders, today issued the following letter to shareholders:

Dear Shareholders,

The company has made tremendous progress since I last wrote you in December, and the totality of the data we have shared lead me to be increasingly excited and optimistic about what we hope to see when our Phase 3 trial for NE3107 in Alzheimer’s Disease (AD) reads out later this year. I have prepared this letter to shareholders to provide an update that synthesizes all the information that we have released and presented at recent medical conferences.

What we know from completed clinical trials

Let me start by reviewing the Phase 2 exploratory biomarker study we completed in 2022. The trial was a small, open-label study intending to observe the impact of treatment with NE3107 for 3 months on 23 patients with moderate cognitive impairment (MCI) and mild AD, as described below.

- MCI and mild AD patients treated with NE3107 experienced enhanced cognition as measured by multiple assessment tools, including a 2.1 points improvement on the ADAS-Cog11 scale (p=0.0173). Furthermore, this improvement in cognition was significantly correlated with reductions in inflammation (TNFα).
- NE3107 reduced CSF phospho-tau levels by -1.66 pg/mL (p=0.0343) and the ratio of p-tau to amyloid beta 42

($A\beta_{42}$) by -0.0024 (p=0.0401). P-tau and Aβ are traditional biomarkers of AD progression and have been the focus for AD researchers for decades.

- 18 of 22 patients with abnormal baseline scans showed improvement in one or more brain regions as seen from advanced MRI techniques
- Patients saw significant reductions in the methylation of their DNA, which was equivalent to -3.3 years on the Horvath DNA methylation Skin Blood Clock
- No drug-related adverse events were observed

As we analyzed the vast amounts of data generated from this study, we believe we have now uncovered the possible reason for why NE3107 was associated with the impressive results described above, and our team presented the data this past weekend at the Alzheimer's Association's International Conference held in Amsterdam.

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[1] Sites on DNA strands where cytosine is next to guanine, which is the location where DNA can be "methylated." See the end of this letter for a basic primer on genetics and epigenetics, including the role of CpGs.

To explain the data, let me start with the basic fact that everything in our body is encoded by our DNA and genes, and that epigenetic factors (diet, exercise, aging, etc.) affect the way our genes are decoded. DNA methylation (DNAm) is perhaps the most studied arena in epigenetics, and a modern analyzer from Illumina can measure the degree of DNAm of over 850,000 "CpG probes" associated with the over 25,000 genes in our genome (see the end of this letter for a basic primer on genetics and epigenetics, including the role of CpGs).

In Amsterdam, our team presented **this poster** showing how treatment with NE3107 led to >50% reductions in DNAm of over 400 CpGs and some in a manner that is significantly correlated to observed clinical improvements in cognition, biomarkers and imaging endpoints. Using Illumina analyzers, we found that treatment with NE3107 over three months resulted in the reduction in the DNAm of:

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1) 14 CpGs related to anti-inflammatory genes that are significantly correlated with reduction in plasma TNFα levels, which is considered to be the master regulator of inflammation. We believe this provides part of the epigenetic understanding for:
   a) Why our study saw a correlation between improvements in cognition and reduction in TNFα.
   b) Why experimental therapies targeting TNFα in humans have been associated with improved cognitive function. [1]
   c) Why a real-world evidence study found that patients taking anti-TNF drugs for various conditions saw a 50% lower risk of developing AD. [2]
   d) Why many other researchers have associated inflammation with DNAm, [3] which in turn has been shown to impact a wide range of diseases, including various forms of cancers, [4] age-related cognitive impairment and dementia, [5] Parkinson's disease, [6] cardiovascular disease, [6, 7] COPD and respiratory disease, [8] chronic kidney disease, [9] inflammatory bowel disease, [10] sepsis, [11] and many others.
2) 43 CpGs related to antioxidant genes which are significantly correlated with increases in precuneus glutathione levels in the brain. Decreased glutathione levels have been shown to be associated with cognitive decline. [12]
3) Numerous CpGs associated with genes related to insulin signaling and antioxidant responses that are significantly correlated with volumetric changes in the brain, which have been associated with alterations in cognitive function in patients with MCI and dementia. [13]
4) Numerous CpGs associated with insulin signaling, antioxidants, anti-inflammatory, anti-apoptotic, anti-amyloid, and neurostimulation that are significantly correlated to improvement in cognition and traditional AD biomarkers.

In total, our analysis identified over 3,000 statistically significant correlations between reductions in DNAm of various CpGs and cognitive, biomarker and neuroimaging endpoint assessments in our trial.

Taken it its totality, we believe the data suggest that NE3107 may have the potential to reduce epigenetic changes driven by inflammation and that NE3107 may have the potential to reduce inflammation and oxidative stress, restore homeostatic regulation and enable the recovery of gene expression that may then improve neuronal health and thus potentially improve the clinical measures of MCI and AD. We believe that NE3107 treatment-associated changes may be indicative of potential broad and multisystemic regulatory activities within mechanisms associated with the diagnosis and progression of cognitive disorders, MCI, and dementia. [14, 15]

Implications for Phase 3 AD trial

Our NM101 trial has been fully enrolled since February 2023 and is nearing its completion by the end of September. Topline data readout is expected in the October-November timeframe.

As we approach data readout, I am increasingly optimistic about what we hope to see based on the totality of the data that we have disclosed. The data described above is suggestive that NE3107 may have an active epigenetic effect associated with improvements in inflammation, insulin signaling, and other critical biological processes in a manner that is significantly correlated to improvements in cognition, AD biomarkers, and imaging endpoints. This small exploratory trial involving just 23 patients provided statistically significant data on so many measures and correlations. Assuming that epigenic changes seen in the Phase 2 trial is coming from NE3107 activity and not some placebo or random effect, one would expect the 200 patients treated with NE3107 in the NM101 trial should have dramatically different results from the 200 patients in the placebo arm on these same measures.

Additionally, the data we recently presented at the 83rd Scientific Sessions of the American Diabetes Association that took place June 23-26 give[s] further support for what we can expect. **This poster presentation** did not provide any results or readouts. Instead, it provided the first data on the 400 patients in the NM101 trial as they started the trial (i.e., at baseline), including:

- The large majority of patients had elevated inflammatory markers and were overweight. Large portions have some degree of metabolic dysregulation, including hypertension (61%), impaired glucose metabolism (52%), insulin resistance (47%), hypertriglyceridemia (40%) and hypercholesterolemia (30%).
- Patients who are amyloid beta positive (Aβ+) had comparable CDR-SB scores at baseline as those who are Aβ negative (Aβ-). This supports our thesis all along that Aβ cannot be the only factor driving AD or cognitive decline.

- Aβ+ patients had worse ADAS-Cog12 and MMSE scores (indicating lower cognitive functioning) than the Aβ- patients, while the Aβ- patients had significantly higher inflammation, insulin resistance, IFG, and hypertension, compared to their Aβ+ counterparts. We interpret this data to mean that metabolic factors are critical drivers of cognitive decline for everyone, and that the presence of Aβ is a contributory – but not a causal – factor for the cognitive decline.

Patients treated with NE3107 in prior trials have seen improvements in inflammation, glucose metabolism, insulin resistance, hypercholesterolemia, hypertriglyceridemia, etc. We believe the fact that patients started the trial with elevated levels of these factors provides additional cautious optimism for the NM101 trial as NE3107 has demonstrated a potential impact on these areas in previous studies.

Conclusions

In the end, we believe cognitive decline or improvement starts with neuronal health. Neurons do not spontaneously accumulate Aβ plaques that leads patients to decline cognitively. Neurons are perhaps the cells that require the highest degree of homeostasis to maintain health. We believe the cumulative dysregulation of many disparate systems in the body contribute to deteriorating neuronal health – insulin resistance and impaired glucose signaling contributes to lower glucose availability (the key energy source for cells); reduced antioxidants contributes to mitochondrial stress and other factors leading to cell death, and hypertension can lead to lower oxygen availability.

Based on our understanding of how NE3107 potentially works and the data that have been revealed, we believe that NE3107 may have a broad and multisystem regulatory effect. Data shows that NE3107 may have reduced inflammation by potentially modulating the production of TNFα, which in and of itself may lead to breaking the pro-inflammatory cycle, reduce insulin resistance, and reduce the phosphorylation of tau into p-tau. Additionally, the data from the exploratory Phase 2 trial suggests that NE3107 may potentially have an epigenetic effect affecting over 400 CpGs and with links to over 3,000 statistically significant correlations between reductions in DNAm of various CpGs and cognitive, behavioral, and neuroimaging endpoints. We believe all this collectively contributes to better neuronal health, which should have an impact on cognitive improvement.

Based on all of this, we believe we have a sound scientific and epigenetic explanation of why NE3107 may work, and we now await the NM101 trial readout to confirm all this.

Basic primer on genetics and epigenetics

Everything in our body is encoded by our DNA and genes, and various agents then decode the genes to enable the body to make all the proteins, enzymes, cells, etc. that it needs. Modern human genetics started in the 1990s when The Human Genome Project took 13 years and $2.7 billion to sequence the first human genome, thereby providing

the first complete map of every gene in one body. We now know that there are more than 25,000 genes (many of which are still not fully understood) in our genome that is coded for by over 6 billion DNA base pairs. This understanding started to allow researchers to examine how changes in specific genes can affect disease. Technology has advanced significantly since the 1990s, and researchers now can use analyzers from companies such as Illumina to sequence a whole genome for a few thousand dollars within days.

We also know that our own behavior (things such as diet and exercise) and environmental factors can affect how our body functions. Epigenetics is the study of how behavior and environment affect the way our genes work in addition to the genetic code itself. The best way to visualize epigenetics is with an analogy. A DVD has all the encoded information needed for the laser in a player to decode and create beautiful pictures and sound. With repeated use, that DVD may become scratched and smeared with fingerprints that prevent the laser from clearly decoding the information, thereby leading to playback problems. Epigenetic factors are similar to the smearing and scratching of the DVD in that they get attached to our DNA and prevent their normal decoding. With abnormal decoding (ala skips and playback problems), you get changes in proteins, enzymes and cells that can cause disease.

Perhaps the most studied area of epigenetics involves DNA methylation, which is the process of how methyl groups are added or removed from DNA and thus regulate the expression of various genes in our bodies. [16] Many studies have shown that genes become over- or under-methylated as we age, [17] , [18] , [19] thereby suggesting that the modulation of DNA methylation could enable the up- or down-regulation of specific genes and thus modulate the diseases of aging. The extent of DNA methylation can now be easily studied using Illumina analyzers, which quantify the percentage of methylation of over 850,000 specific “CpG probes” associated with various genes.

DNA is comprised of four nucleosides: adenine (A), cytosine (C), guanine (G) or thymine (T). DNA is a double helix where a C on one DNA strand is always coupled with a G on the other strand. When C is followed by a G on the same DNA strand, it creates a CpG [1] site. Various DNA methyltransferases can “methylate” the cytosine at a CpG site by adding a methyl group to form 5-methylcytosines. When DNA is methylated, the molecules responsible for decoding DNA may have trouble reading the underlying C. When enough misreading happens, biological consequences related to disease could arise – this is the biological equivalent to the laser not being able to read past the scratches and fingerprints, thereby resulting in skips and playback problems.

About BioVie

BioVie Inc. (NASDAQ: BIVI) is a clinical-stage company developing innovative drug therapies for the treatment of neurological and neurodegenerative disorders and advanced liver disease. In neurodegenerative disease, the Company’s drug candidate NE3107 inhibits inflammatory activation of ERK and NFkB (e.g., TNF signaling) that leads to neuroinflammation and insulin resistance, but not their homeostatic functions (e.g., insulin signaling and neuron growth and survival). Both are drivers of Alzheimer’s and Parkinson’s diseases. The Company is conducting a

potentially pivotal Phase 3 randomized, double-blind, placebo-controlled, parallel-group, multicenter study to evaluate NE3107 in patients who have mild to moderate probable Alzheimer's disease (NCT04669028). Results of a Phase 2 investigator-initiated trial (NCT05227820) showing NE3107-treated patients experienced improved cognition and biomarker levels were presented at the Clinical Trial in Alzheimer's Disease (CTAD) annual conference in December 2022. An estimated six million Americans suffer from Alzheimer's. A Phase 2 study of NE3107 in Parkinson's disease (NCT05083260) has completed, and data presented at the International Conference on Alzheimer's and Parkinson's Disease and Related Neurological Disorders conference in Gothenburg, Sweden in March 2023 showed significant improvements in "morning on" symptoms and clinically meaningful improvement in motor control in patients treated with a combination of NE3107 and levodopa vs. patients treated with levodopa alone, and no drug-related adverse events. In liver disease, the Company's Orphan drug candidate BIV201 (continuous infusion terlipressin), with FDA Fast Track status, is being evaluated in a US Phase 2b study for the treatment of refractory ascites due to liver cirrhosis. BIV201 is administered as a patent-pending liquid formulation. The active agent is approved in the U.S. and in about 40 countries for related complications of advanced liver cirrhosis. For more information, visit http://www.bioviepharma.com/.

Forward-Looking Statements

This press release contains forward-looking statements, including statements regarding the Company's strategy, plans and objectives, such as statements regarding the Company's anticipated timeline for announcing topline data readout for our NM101 product candidate. Forward-looking statements may generally be identified by words such as "expect," "look forward to," "anticipate" "intend," "plan," "believe," "seek," "estimate," "will," "project" or words of similar meaning. Although BioVie Inc. believes such forward-looking statements are based on reasonable assumptions, it can give no assurance that its expectations will be attained. Actual results may vary materially from those expressed or implied by the statements herein due risks associated with conducting and completing clinical trials, including our reliance on third parties to conduct our clinical trials, to successfully defend potential future litigation, our ability to raise capital when needed on reasonable terms, changes in local or national economic conditions as well as various additional risks, many of which are now unknown and generally out of the Company's control, and which are detailed from time to time in reports filed by the Company with the SEC, including quarterly reports on Form 10-Q, reports on Form 8-K and annual reports on Form 10-K. BioVie Inc. does not undertake any duty to update any statements contained herein (including any forward-looking statements), except as required by law.

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[1] Phosphate links any two nucleosides together

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