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August 21, 2023
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CervoMed Inc.

(CRVO-NASDAQ)

CRVO: Initiating Coverage of CervoMed, Inc.; Phase 2b Trial in Dementia with Lewy Bodies Underway…

Based on our probability adjusted DCF model that takes into account potential future revenues for neflamapimod in DLB, CRVO is valued at $17.00/share. This model is highly dependent upon continued clinical success of neflamapimod and will be adjusted accordingly based upon future clinical results.

Current Price (08/21/23)	$5.88
Valuation	**$17.00**

OUTLOOK

We are initiating coverage of CervoMed Inc. (CRVO) with a valuation of $17.00. CervoMed is a clinical stage CNS therapeutics company that is developing treatments for acute and chronic neurodegenerative diseases. The company's lead development compound, neflamapimod, is currently being investigated in a Phase 2b clinical trial for the treatment of dementia with Lewy bodies (DLB) following positive results in a Phase 2a trial. DLB affects approximately 700,000 individuals each in the U.S. and E.U. and there are currently no approved treatment options. We anticipate results from the Phase 2b clinical trial, which is being fully supported by a $21 million grant from the National Institute on Aging (NIA), in the second half of 2024.

SUMMARY DATA

52-Week High	**$10.38**
52-Week Low	**$4.20**
One-Year Return (%)	**-41.05**
Beta	**1.78**
Average Daily Volume (sh)	**112,622**
Shares Outstanding (mil)	**6**
Market Capitalization ($mil)	**$34**
Short Interest Ratio (days)	**N/A**
Institutional Ownership (%)	**10**
Insider Ownership (%)	**2**
Annual Cash Dividend	**$0.00**
Dividend Yield (%)	**0.00**
5-Yr. Historical Growth Rates	
Sales (%)	**N/A**
Earnings Per Share (%)	**N/A**
Dividend (%)	**N/A**
P/E using TTM EPS	**N/A**
P/E using 2023 Estimate	**N/A**
P/E using 2024 Estimate	**N/A**

Risk Level	**Average**
Type of Stock	**Small-Value**
Industry	**N/A**

ZACKS ESTIMATES

Revenue
(in millions of $)

	Q1 (Mar)	Q2 (Jun)	Q3 (Sep)	Q4 (Dec)	Year (Dec)
2022	0 A	0 A	0 A	0 A	0 A
2023	0 A	0 A	0 E	0 E	0 E
2024					0 E
2025					0 E

Earnings per Share

	Q1 (Mar)	Q2 (Jun)	Q3 (Sep)	Q4 (Dec)	Year (Dec)
2022	-$2.22 A	-$2.06 A	-$1.37 A	-$2.00 A	-$7.65 A
2023	-$2.01 A	-$3.04 A	-$0.95 E	-$0.95 E	-$5.59 E
2024					-$2.67 E
2025					-$3.22 E

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WHAT'S NEW

Initiating Coverage



Source: CervoMed Inc.

We are initiating coverage of CervoMed Inc. (CRVO) with a valuation of $17.00. CervoMed is a biopharmaceutical company that is developing central nervous system (CNS) treatments for acute and chronic neurodegenerative diseases. The company's lead development compound is neflamapimod, which is being developed as a therapy for dementia with Lewy bodies (DLB). The compound targets and inhibits p38 mitogen-activated protein kinase (MAPK) alpha ("p38α"). Chronic activation of p38α is thought to impair how neurons in the brain communicate through synapses, which ultimately leads to synaptic dysfunction. Inhibition of p38α in the brain may improve neuroinflammation and improve cognitive and motor function that is seen in early-stage neurodegenerative diseases. Neflamapimod was previously tested in a Phase 2a clinical trial in DLB, with results showing a statistically significant improvement compared to placebo on measures of dementia severity and functional mobility.

Extensive Clinical Experience with Neflamapimod
Neflamapimod was in-licensed from Vertex Pharmaceuticals in 2014. It was discovered using Vertex's proprietary structure-based drug discovery program. The compound had completed both single- and multiple-dose Phase 1 trials in healthy volunteers as well as a Phase 2a clinical trial in rheumatoid arthritis. Post-licensing and prior to the Phase 2a clinical trial in DLB, neflamapimod was tested in two Phase 2a trials and one Phase 2b trial in Alzheimer's disease. Results from those trials showed that the drug was well tolerated, crosses the blood-brain barrier, and is pharmacologically active in the brain, with the demonstration of significant reduction, relative to placebo, of spinal fluid levels of markers of synaptic dysfunction and neurodegeneration.

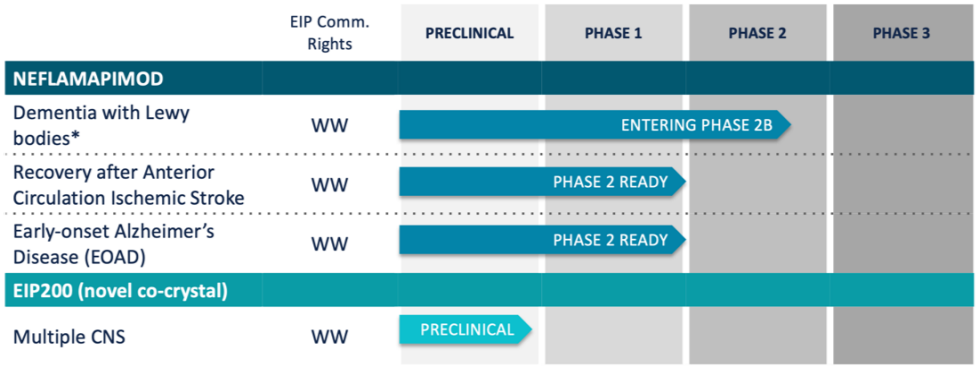
Phase 2b Clinical Trial Fully Funded by NIH/NIA
In January 2023, CervoMed was awarded a $21.0 million grant from the National Institute of Aging (NIA), which is estimated to fully fund the Phase 2b trial of neflamapimod in DLB. An initial disbursement of $6.9 million was made in February 2023, with an anticipated $8.1 million disbursement to be made in February 2024 and the remainder of the grant to be disbursed in February 2025.

Multiple Catalysts by the End of 2024
We anticipate a number of catalysts over the next 12-18 months, including the publication of additional Phase 2a data from the DLB study in the second half of 2023, completion of enrollment in the Phase 2b DLB trial in the first half of 2024, and topline data from the placebo controlled portion of the Phase 2b DLB trial in the second half of 2024.

Large Commercial Opportunity in DLB
DLB is the second most common neurodegenerative disorder after Alzheimer's disease and is more common than Parkinson's disease. There are an estimated 700,000 patients each in the U.S. and E.U. The only currently approved therapy is cholinesterase inhibition, which is only moderately effective. As screening techniques that distinguish DLB from other neurodegenerative disease become more sophisticated, the rate of diagnosis will likely increase which could lead to an expanded market opportunity.

INVESTMENT THESIS

CervoMed Inc. (CRVO), the surviving entity following a merger of Diffusion Pharmaceuticals and EIP Pharma, is a biopharmaceutical company that is developing therapies for acute and chronic neurodegenerative diseases, including dementia with Lewy bodies (DLB). The company's lead development compound, neflamapimod, is designed to bind to and inhibit p38 mitogen-activated protein kinase alpha (p38α). Chronic activation of p38α leads to impairment of neuronal communication (synaptic dysfunction) and ultimately to deterioration of cognitive and motor abilities. Without treatment, synaptic dysfunction can result in neuronal loss that leads to devastating disabilities, institutionalization, and ultimately death. In October 2020, EIP Pharma announced positive topline results from the Phase 2a AscenD-LB clinical trial. The trial results showed that neflamapimod significantly improved cognition and function in mild-to-moderate DLB. CervoMed recently initiated a Phase 2b clinical trial of neflamapimod in 160 patients with mild-to-moderate DLB. We anticipate topline results from this trial in the second half of 2024. Positive results from the Phase 2b clinical trial may put CervoMed in a position to conduct a single Phase 3 registration trial to support a new drug application (NDA), pending agreement with the FDA.



*Received FDA Fast Track designation

Source: CervoMed Inc.

Neflamapimod

Neflamapimod is an oral, highly selective, blood brain penetrant oral small molecule inhibitor of p38α. The compound was licensed from Vertex Pharmaceuticals (VRTX) in 2014. At the time of signing the license agreement, Vertex had already completed chronic repeat toxicology along with single- and multiple-dose Phase 1 trials in healthy volunteers and Phase 2 studies in Rheumatoid Arthritis. Inhibition of p38α reduces the effects of neuroinflammation on synaptic function, decreases tau phosphorylation, and modifies other mechanisms that underlie synaptic dysfunction in the cholinergic system.

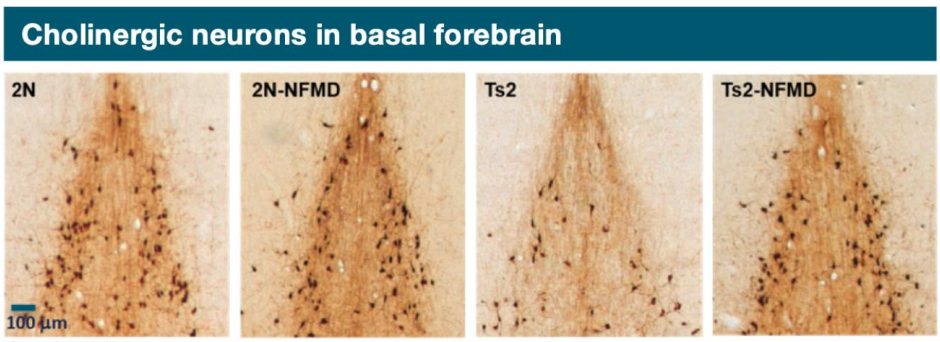
Improves Neurological Outcomes in Preclinical Studies

Neflamapimod has been evaluated in a number of preclinical studies:

Selective Brain-Targeted Antagonism of p38 MAPKα Reduces Hippocampal IL-1B Levels and Improves Morris Water Maze Performance in Aged Rats (Alam, 2015). This study evaluated the effect of neflamapimod (VX-745) in cognitively-impaired rats where the cognitive deficits were induced by inflammatory synaptic dysfunction. The results of the study showed that rats treated with neflamapimod showed a significantly improved performance in the Morris water maze (MWM) test (*P*=0.007) along with a significant reduction in hippocampal IL-1β protein levels.

Continuous Administration of a p38α Inhibitor During the Subacute Phase After Transient Ischemia-Induced Stroke in the Rat Promotes Dose-Dependent Functional Recovery Accompanied by Increase in Brain BDNF Protein Level (Alam *et al*., 2020). In this study, neflamapimod was evaluated as a potential subacute phase stroke treatment. Neflamapimod was administered to rats following transient middle cerebral artery occlusion at two dose levels for six weeks starting 48 hours after reperfusion. The results showed that treatment with neflamapimod led to multiple improved parameters of neurologic function compared to control (P<0.001 for each of global neurologic scores, motor-, and sensory-specific tests). These results support the hypothesis that neflamapimod can reverses synaptic damage as recovery from stroke is dependent upon neuronal and synaptic plasticity.

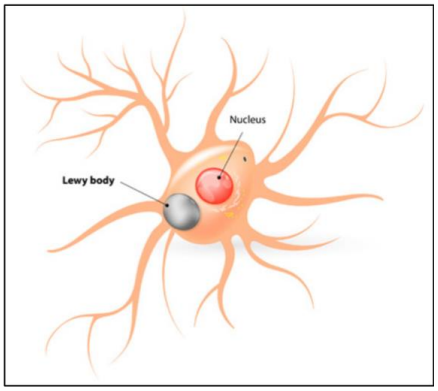
Preclinical and Randomized Clinical Evaluation of the p38a Kinase Inhibitor Neflamapimod for Basal Forebrain Cholinergic Degeneration (Jiang *et al*., 2022). In this study, Ts2 mice, which are a Down syndrome model that develop cholinergic degradation of the basal forebrain, were treated at approximately six months of age with either neflamapimod or placebo for 28 days. Results showed that neflamapimod reversed basal forebrain cholinergic neuron loss (as shown through a significant increase in the number of cholinergic neurons; see figure below) and restored cholinergic function (as shown through normalized performance in Open field and NOR behavioral tests).



Source: CervoMed Inc.

Dementia with Lewy Bodies

Dementia with Lewy bodies (DLB) is the second most common neurodegenerative dementia after Alzheimer's disease. It results from the accumulation of the protein α-synuclein into Lewy bodies, which accumulate in parts of the brain and nervous system and leads to neuronal cell death. Lewy bodies were first discovered in 1912 by Dr. Friedrich Lewy while he was studying the neuropathology of Parkinson's disease (PD) in the laboratory of Dr. Alois Alzheimer (Lewy *et al*., 1912). The constituent of Lewy bodies, α-synuclein, wasn't identified until the 1990's (Spillantini *et al*., 1997). While the function of α-synuclein isn't completely ascertained, it is thought to function in cell membrane remodeling at neuronal terminals (Varkey *et al*., 2010). The following cartoon shows that aggregates of misfolded, overexpressed α-synuclein accumulate as Lewy bodies in neurons.



Source: CervoMed Inc.

DLB is often misdiagnosed and underdiagnosed (Nelson *et al*., 2010). A diagnosis of DLB is largely based on an accurate clinical history, a thorough physical examination, cognitive testing (although early in the course of the disease there may be minimal deficits), and neuropsychiatric testing. The only way to make a definitive diagnosis is through postmortem autopsy, however even then overlapping pathology is often seen and complicates the primary diagnosis.

A diagnosis for DLB requires the presence of dementia that is significant enough to interfere with daily activities in addition to at least two of the following four core clinical features: fluctuating cognition, visual hallucinations, Parkinsonism, and REM behavioral sleep disorder. In addition to the core features of DLB, there are multiple supporting symptoms that may be suggestive of the diagnosis: visuospatial deficits, neuroleptic sensitivity, changes in mood, autonomic dysfunction, and recurrent falls.

DLB affects approximately 1.4 million people in the U.S. and E.U. combined. The largest risk factor for developing DLB is age, as the majority of cases are diagnosed after the age of 70. In addition, men have a higher risk of developing DLB than women. The under-diagnosis of DLB is exemplified by the contrast in its prevalence in clinical based studies (7.5% of all dementia cases; Vann Jones *et al*., 2014) compared to autopsy findings (20-25% of patients with a history of dementia; Galasko, 2017).

Treatment of DLB

There are currently no FDA approved, disease-modifying therapies available for treating DLB and the current standard of care is focused on treating symptoms. However, this is complicated by the fact that many medications may alleviate one symptom but worsen another.

Acetylcholinesterase inhibitors are utilized as they may delay cognition decline while having no adverse effect on motor symptoms. A meta-analysis showed that donepezil was the most effective, however there were higher rates of discontinuations due to adverse events when compared to placebo for all acetylcholinesterase inhibitors (Matsunaga *et al*., 2015). Memantine, an N-methyl-D-aspartate (NMDA) receptor antagonist, is used to improve cognition in Alzheimer's patients. However, studies in DLB patients have shown mixed results, with some studies showing improved cognition (Wesnes *et al*., 2015) and others showing no effects (Matsunaga *et al*., 2015).

Visual hallucinations can be a particularly troublesome symptom in DLB, however it is also difficult to treat. A number of studies have examined the effect of atypical and typical antipsychotics and their effects on visual hallucinations in DLB. Quetiapine was found to reduce delusions, hallucinations, and agitation in DLB patients, however 33% of study participants withdrew due to orthostatic hypotension or oversedation (Takahashi *et al*., 2003). One study of olanzapine showed moderate reductions in delusions and hallucinations (Cummings *et al*., 2002), while another did not show a similar effect due to a high dropout rate due to adverse effects (Walker *et al*., 1999).

Neflamapimod for Treating DLB

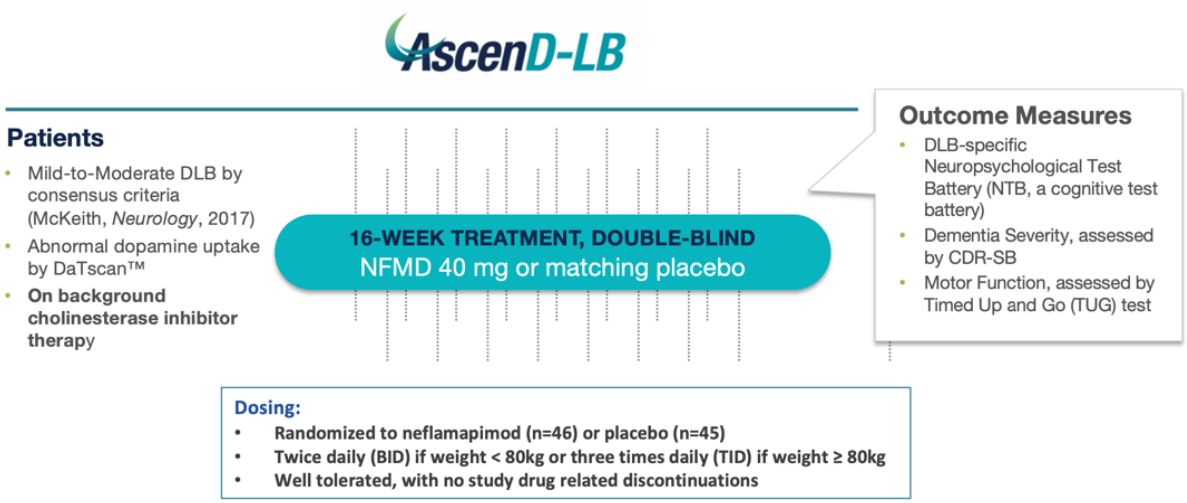
The development of neflamapimod began with the AscenD-LB Phase 2a clinical trial in October 2019 (NCT04001517). It was a randomized, double blind, placebo controlled study in 91 subjects with mild-to-moderate DLB. Subjects were treated for 16 weeks with either 40 mg neflamapimod or placebo. Dosing was based on weight, with study subjects weighing less than 80 kg receiving capsules twice daily ("BID") and those weighing greater than or equal to 80 kg receiving capsules three times a day ("TID"). All subjects were required to be on oral cholinesterase inhibitor therapy for at least three months (stable dose for > six weeks) and continued on that therapy during the trial.

The major clinical outcome measurements were:

- A six test Neuropsychological Test Battery ("NTB"). It measures the cognitive domains most impacted by DLB.

- Clinical Dementia Rating Sum of Boxes ("CDR-SB"), which is an assessment of dementia severity, measures three cognitive (memory, orientation, judgement and reasoning) and three functional domains (community affairs, home & hobbies, personal care).

- Timed Up and Go (TUG) test, which measures functional mobility, through the time in seconds that it takes a subject to rise from a chair, walk three meters, turn around 180 degrees, walk back to the chair, and sit down while turning 180 degrees.



Source: CervoMed Inc.

Results from the trial were published in 2022 (Jiang *et al.*, 2022). The following table shows the outcomes that were statistically significant for neflamapimod compared to placebo. In the modified intention-to-treat population that included all subjects with at least one on-treatment evaluation, neflamapimod showed improvement in dementia severity (evaluated by CDR-SB; *P*=0.023) and functional mobility (TUG test; *P*=0.044). For the patients at the highest dose (40 mg TID), a significant improvement on NTB was also evident (*P*=0.049). An encouraging positive trend was also seen on the 10-item Neuropsychiatric Inventory (NPI-10), particularly with regard to visual hallucinations, where a significant reduction in frequency relative to placebo was seen.

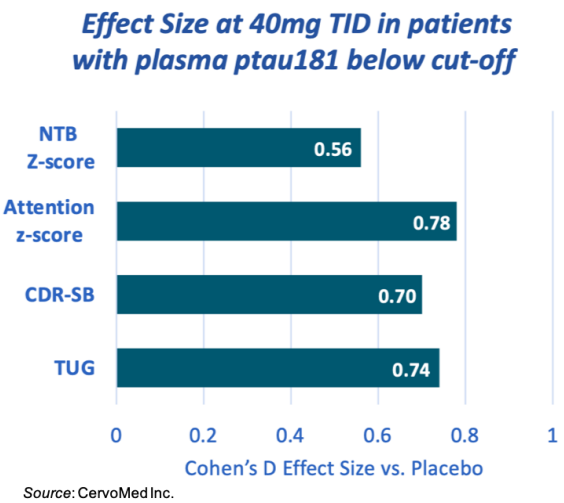
		40mg BID + 40mg TID			40mg TID		
Outcome	**Measure**	**Mean vs. placebo (95% CI)**	**p-value**		**Mean vs. placebo (95% CI)**	**p-value**	
Dementia Severity	Clinical Dementia Rating Sum of Boxes (CDR-SB)	-0.45 (-0.83, -0.06)	0.023	+	-0.56 (-0.96, -0.16)	0.007	+
Cognition	Neuropsychological Test Battery (NTB) Composite z-score	0.04 (-0.11, 0.19)	>0.2		0.17 (0.00, 0.35)	0.049	+
	Attention Composite z-score	0.14 (-0.06, 0.35)	0.17		0.28 (0.04, 0.51)	0.023	+
Motor Function	Timed and Go Test (TUG)	-1.4 (-2.7, -0.1)	0.044	+	-1.4 (-2.6, -0.2)	0.024	+

On-study (all time-points) results; change from baseline analysis utilizing Mixed Model for Repeated Measures (MMRM)

Number of participants: 41 for placebo, 20 each for 40mg BID and 40mg TID

Source: CervoMed Inc.

Recent publications have demonstrated that DLB patients with abnormally elevated plasma phospho - tau181 (ptau181) have Alzheimer's disease (AD) associated co-pathology (Hall *et al*., 2021). This is estimated to affect approximately 30-50% of DLB patients. In addition, DLB patients with elevated plasma ptau181 have more extensive neuronal loss, and would be expected to be less responsive to treatment. The following graph shows that in the 54% of DLB patients in the AscenD-LB trial that did not have biomarker evidence of AD (as determined by elevated plasma ptau181 levels), there was a statistically significant improvement in cognitive tests of attention, the CDR-SB, and the TUG test, with Cohen's d treatment effect size > 0.7 for all three endpoints.



Source: CervoMed Inc.

In summary, the following conclusions were drawn from the Phase 2a trial that will be applied to the Phase 2b study:

- The optimal dose is 40 mg three times a day.
- Clinical endpoints that can detect both cognitive and motor function endpoints (e.g., CDR-SB and TUG) perform better than endpoints that are purely focused on evaluating cognition. CDR-SB is an approvable endpoint for Alzheimer's disease trials.
- Patients with pure DLB appear to have a greater response to treatment than those with Alzheimer's co-pathology (e.g., elevated levels of ptau181).

DLB Phase 2b Clinical Trial

Based on the positive Phase 2a results, CervoMed initiated a randomized, double blind, placebo controlled Phase 2b clinical trial of neflamapimod in subjects with DLB in the second quarter of 2023. Trial participants will receive either 40 mg neflamapimod administered TID or matching placebo. Approximately 80 subjects will be enrolled into each group. Those with elevated ptau181 levels will be excluded. Dosing will continue for 16 weeks in the main, placebo controlled portion of the trial with a 36-week open label treatment extension for those completing the initial 16 weeks of the trial.

The primary outcome of the trial is improvement in dementia severity as assessed by change from baseline to week 16 in CDR-SB score. Secondary outcomes include effects on cognition (as assessed by DBL-specific cognitive test battery), motor function (as assessed by TUG test), and global rating of treatment effect (as assessed by the ADCS-Clinician Global Impression of Change). Tertiary outcomes include neuropsychiatric outcomes (as assessed by the NPI-12), effect on fluctuations in cognition (as assessed by the Dementia Cognitive Fluctuations Scale), impact on resting-state EEG, and (in a subset of patients) basal forebrain atrophy as assessed by structural MRI.

In January 2023, CervoMed was awarded a $21.0 million grant from the National Institute on Aging (NIA; a division of the NIH) that is expected to fully fund the Phase 2b trial. Funds from the grant will be

disbursed as costs are incurred. The first payment of $6.9 million was disbursed to the company in February 2023, with an additional $8.1 million anticipated to be disbursed in February 2024 and the remainder of the grant funds to be disbursed in February 2025. Future disbursements are contingent on Congress authorizing the NIH budget as well as "satisfactory" progress being demonstrated by CervoMed, as deemed by the NIA.

Neflamapimod for Treating Other Conditions

Recovery After Ischemic Stroke: Due to its ability to improve synaptic function, neflamapimod may be able to positively improve brain function following an acute neurological injury. The scientific rationale for evaluating neflamapimod derives from the fact that the basal forebrain cholinergic system is important for recovery following an ischemic stroke. Following a stroke, the basal forebrain cholinergic system is suppressed by residual inflammation. Neflamapimod would be expected to reverse the suppression of that system, which could lead to improved recovery of motor function. This is supported by the preclinical data described previously in which neflamapimod treatment led to substantial improvement on multiple parameters of neurologic function compared to vehicle controls in a rat ischemic stroke model. In addition, the TUG results from the AscenD-LB trial showed positive effects on basal forebrain mediated control of movement following neflamapimod treatment.

While the company has no immediate plans to initiate a clinical trial evaluating neflamapimod for the treatment of ischemic stroke, a proof-of-concept trial has been designed. It would be a 12-week placebo controlled Phase 2 trial that would enroll 120 subjects with uncomplicated acute moderate or moderate-to-severe ischemic stroke in the anterior circulation stroke (confirmed by MRI) and demonstrated motor deficits (hemiparesis or hemiplegia). Study subjects would be randomized 1:1 to receive either placebo or neflamapimod 40 mg TID for 12 weeks starting three to seven days after the acute stroke. The primary endpoint of the study would be the Fugl-Meyer motor scale at the end of three months of treatment. Secondary endpoints would include the TUG test, Montreal Cognitive Assessment, and the proportion of subjects with modified Rankin Scale score ≤ 2 (no to slight disability).

Early Onset Alzheimer's Disease: Early Onset Alzheimer's Disease (EOAD) is defined as AD dementia that begins prior to the age of 65. An estimated 200,000 individuals in the U.S. had EOAD in 2023 (The Alzheimer's Association). EOAD and Late Onset Alzheimer's Disease (LOAD) are distinct clinical entities, which was recently shown in a cross-sectional study using a large cohort (n=1750) of subjects with autopsy-confirmed sporadic AD. In this cohort, there was a clear distinction in the age of onset between EOAD (mean onset age of 57.2 ± 3.8) and LOAD (mean onset age of 76.7 ± 7.5). Subjects with EOAD were more likely than those with LOAD to present with noncognitive behavioral or motor symptoms and had more executive dysfunction but less language impairment. Individuals with EOAD also had faster cognitive and functional decline compared to those with LOAD. The latest research on EOAD indicates that the earliest, primary pathology is in the basal forebrain cholinergic system. Thus, neflamapimod has the greatest potential as a single agent therapy for EOAD. Positive results in the Phase 2b DLB clinical trial would likely warrant the pursuit of neflamapimod in EOAD, with an expected registrational trial requiring approximately 300-400 subjects and a 12-month duration.

Intellectual Property

CervoMed's intellectual property for neflamapimod is reflected in ten main patent families wholly owned by the company:

- The first patent family relates to methods of treating patients suffering from AD, as well as methods of reducing amyloid plaque burden. In this family, the company holds issued patents in the United States, Europe, Japan, China, Canada, Australia, and Hong Kong. These patents are set to expire in 2032

- The second patent family relates to the use of neflamapimod for improving cognition. In this family, the company holds issued patents in the United States, Europe, Japan, and a pending application in China. These patents are set to expire in 2035.

- The third patent family relates to co-crystals of neflamapimod. In this family, the company holds an issued patent in the United States. This patent is set to expire in 2038.

- The fourth patent family relates to methods for promoting recovery of function in patients who have suffered acute neurologic injuries, including those resulting from various forms of stroke. In this family, the company holds an issued patent in the United States, Europe, and Japan, and pending applications in Korea and Hong Kong. These patents are set to expire in 2035-2036.

- The fifth patent family relates to methods of treating patients suffering from dementia. In this family, the company has an issued patent in the United States for the treatment of patients with MCI to improve episodic memory and a pending application in Europe. Patents that issue in this family, if any, are expected to expire in 2037.

- The sixth patent family relates to formulations of neflamapimod, including pharmaceutical compositions for oral administration exhibiting desirable pharmacokinetics and processes for the manufacture thereof. In this family, the company has an issued patent in the United States that is set to expire in 2039.

- The seventh patent family relates to the treatment of DLB. In this family, the company has pending applications in the United States, Europe, Japan, China, Canada, and Hong Kong. Patents that issue in this family, if any, are expected to expire in 2040.

- The eighth patent family is co-owned by Boston University and relates to methods of treating prion disease. In this family, the company has a pending application in the United States. Patents that issue in this family, if any, are expected to expire in 2040

- The ninth patent family relates to treatment of gait dysfunction related to neurodegenerative disease. An International Application is pending. Patents that issue in this family, if any, are expected to expire in 2041.

- The tenth patent family relates to treatment of a subpopulation of patients having DLB but no substantial Alzheimer's like tau pathology. Patents that issue in this family, if any, are expected to expire in 2042.

The agreement with Vertex granted an exclusive license to patents owned by Vertex, including U.S. Patent No. 5,945,418, which relates to the composition of matter for neflamapimod. That patent expired in 2017.

Financials and Capital Structure

Based on unaudited pro forma combined financial statements for EIP Pharma and Diffusion Pharmaceuticals, as of June 30, 2023 the combined companies had approximately $13.0 million in cash and cash equivalents. The company has no long-term debt. We estimate the company has sufficient cash to fund operations through the end of 2024. Following the merger, CervoMed has approximately 5.7 million common shares outstanding.

Risks to Consider

In addition to the risks listed below, investors are encouraged to read the merger prospectus which discusses risks associated with the development of neflamapimod.

Development Risk: CervoMed does not have, and may never have, any products that generate significant revenues. The company's lead asset, neflamapimod, is currently in a Phase 2b clinical trial for the treatment of DLB. We currently estimate that enrollment in the trial will complete in the first half of 2024 and topline results will be available in the second half of 2024. However, there is no guarantee that those timelines will hold. In addition, there is no guarantee that this clinical trial or any future clinical trial will yield successful results that could lead to approval and commercialization.

Regulatory Risk: In August 2015, following a standard review of the long-term safety animal toxicity studies, the FDA placed a partial clinical hold on the Phase 2a AD study that limited administration of neflamapimod to doses that resulted in plasma drug levels which provide at least a 10-fold safety margin to the plasma drug levels in animals that in long-term animal toxicity studies had previously led to minimal or equivocal findings in the liver, bone marrow, and CNS. This partial clinical hold limits the dosing of neflamapimod to 40 mg TID in patients with a weight ≥ 60 kg (132 pounds). As of now, the company does not have plans to surpass this dose level. However, there is no guarantee that even at this dose level unexpected adverse events will not develop in future clinical trials.

Financial Risk: Following closing of the merger, we estimate that CervoMed will have approximately $13.0 million in cash and cash equivalents. While the company has a $21 million grant from NIA that is expected to cover the costs of the ongoing Phase 2b trial in DLB, the company will need additional funding to conduct a Phase 3 clinical trial in DLB. In addition, there is no guarantee that the company won't initiate additional clinical trials in other indications that could use up the company's financial resources.

MANAGEMENT PROFILES

John Alam, MD – Chief Executive Officer

John Alam is an industry leader in translational medicine and has over 30 years of experience in creating value to help build companies through clinical development success. Until May 2014, he was therapeutic area head for diseases of aging at Sanofi, where he led all discovery and development activities directed at Alzheimer's disease, as well as a number of other age-related diseases including sarcopenia/frailty, osteoarthritis, chronic pain and many others. From 1997 to 2008, he held positions of increasing responsibility at Vertex Pharmaceuticals, including Chief Medical Officer and Executive Vice President, Medicines Development. At Vertex, he played major roles in the development of novel innovative medicines for HIV, Hepatitis C and Cystic Fibrosis. Prior to Vertex, John led clinical development of Avonex (interferon beta-1a) for multiple sclerosis at Biogen from 1991 to 1997.

From 2014 to 2022, John was a member of the board of directors of the Alliance for Aging Research (AAR), a Washington, D.C. based non-profit organization dedicated to promoting innovation to address the healthcare needs of older Americans. He received a MD from Northwestern University School of Medicine and a SB in chemical engineering from the Massachusetts Institute of Technology. In addition, he completed an internal medicine residency at Brigham and Women's Hospital and a post-doctoral fellowship at Dana-Farber Cancer Institute.

Robert Cobuzzi, Jr., PhD – Chief Operating Officer

Robert Cobuzzi has over 25 years of cross-functional leadership experience in the pharmaceutical and biotechnology industries across the areas of Corporate Development, Research & Development, and Operations. He previously served as President, Chief Executive Officer, and Board Member of Diffusion Pharmaceuticals from September 2020 to August 2023. From 2005 until 2018 Dr. Cobuzzi held a variety of senior roles in Corporate Development, R&D and Operations at Endo International Plc, including most recently as President, Endo Ventures Limited in Dublin, Ireland from 2015 until 2018. Prior to Endo, he was with Adolor Corporation from 2001 until 2005. He began his career in 1995 at AstraMerck in clinical operations before joining Centocor (a subsidiary of Johnson & Johnson) in Worldwide Regulatory Affairs from 1999 to 2001.

William Tanner, PhD – Chief Financial Officer

William Tanner is a Managing Director at Danforth Advisors and has more than 25 years of experience in equity research, life science corporate development, capital raising and investment banking. He most recently served as Co-founder and CFO of ImmunoGenesis, a clinical stage immuno-oncology company formed around assets licensed from the MD Anderson Cancer Center. He previously spent 20 years as a biotech and biopharma research analyst for leading healthcare investment banks including Vector Securities, SG Cowen, Leerink Swann, Lazard Capital Markets and Guggenheim Securities. He has been involved in raising billions of dollars for public and private life science companies. Bill holds a PhD in physiology from Texas A&M University and completed post-doctoral training in Washington University School of Medicine's Department of Cell Biology and in the Center for Immunology.

Kelly Blackburn – Senior Vice President, Clinical Development

Kelly Blackburn has more than 30 years of experience in clinical development operations, most recently as Vice President, Clinical Affairs at aTyr Pharma and as Vice President, Clinical Development Operations at Vertex. Of note, she held the senior global clinical operational responsibility for three major novel therapeutics: Kalydeco® for the treatment of cystic fibrosis, Incivek® for hepatitis C, and Velcade® for multiple myeloma. Kelly is an active board member of the Hildebrand Family Self-Help Center, Cambridge MA; and long-standing long-standing volunteer case reviewer and emergency foster care mother for the Department of Children and Families in Massachusetts. She has an MHA degree from Quinnipiac University and a BS degree in biochemistry from the University of New Hampshire.

William Elder – General Counsel and Corporate Secretary

William Elder is an attorney with nearly a decade of experience advising public and private companies in a variety of corporate, securities, governance, regulatory, and general commercial matters. He served as General Counsel for Diffusion Pharmaceuticals from September 2020 to August 2023. He also previously served as a consultant to Diffusion from July 2020 to September 2020. Prior to joining Diffusion, he spent eight years as an associate at the law firm of Dechert LLP, counseling clients in a broad range of transactions and other matters, including serving as outside counsel to Diffusion in connection with the Company's reverse merger in 2016 and several subsequent financings. Bill received a JD from the University of Pennsylvania School in Law, a MSF (Master of Science in Finance) from Villanova University, and a BA in Economics from Tufts University. Bill is licensed to practice law in the Commonwealth of Pennsylvania.

Sylvie Grégoire, Pharm D – Chair of the Board

Sylvie Grégoire is an industry veteran with 30 years of industry experience. Dr. Grégoire currently serves on the board of directors of Novo Nordisk A/S (NYSE: NVO), a global pharmaceutical company, and on the board of directors of Revvity Inc (NASDAQ: RVTY) (previously PerkinElmer,Inc. (NYSE: PKI)), a publicly traded company and a provider of products, services and solutions for the diagnostics, life sciences and applied markets. In addition, Dr Grégoire serves on the board of F2G Ltd, a privately held company developing treatments for severe rare mold infections where she is also the chair of the Commercial Committee. Previously, Dr. Grégoire served as chair of the board of directors of Corvidia Therapeutics, Inc., from 2016 to 2020, a private company focused on treatments for cardiorenal diseases. Corvidia was sold to NovoNordisk in 2020. She is the former president of Human Genetic Therapies at Shire Pharmaceuticals, a position she held from 2007 to 2013. Previously, she was executive chairman of IDM Pharma Inc., and president and chief executive officer of GlycoFi Inc. From 1995 until 2003, Sylvie held various leadership positions at Biogen most recently as executive vice president of Technical Operations. Prior to Biogen, she was at Merck and Co, in clinical research and regulatory affairs for a period of 8 years. Dr. Grégoire received a bachelor's degree in Pharmacy from Laval University and a doctoral degree in Pharmacy from the State University of New York at Buffalo.

VALUATION

We are initiating coverage of CervoMed Inc. (CRVO) with a valuation of $17.00. CervoMed, the surviving entity following a merger of Diffusion Pharmaceuticals and EIP Pharma, is a biopharmaceutical company that is developing therapies for acute and chronic neurodegenerative diseases, including dementia with Lewy bodies (DLB). The company's lead development compound, neflamapimod, is designed to bind to and inhibit p38 mitogen-activated protein kinase alpha (p38α). Chronic activation of p38α leads to impairment of neuronal communication (synaptic dysfunction) and ultimately to deterioration of cognitive and motor abilities. Without treatment, synaptic dysfunction can result in neuronal loss that leads to devastating disabilities, institutionalization, and ultimately death. In October 2020, EIP Pharma announced positive topline results from the Phase 2a AscenD-LB clinical trial. The trial results showed that neflamapimod significantly improved cognition and function in mild-to-moderate DLB. CervoMed recently initiated a Phase 2b clinical trial of neflamapimod in 160 patients with mild-to-moderate DLB. We anticipate topline results from this trial in the second half of 2024. Positive results from the Phase 2b clinical trial may put CervoMed in a position to conduct a single Phase 3 registration trial to support a new drug application (NDA), pending agreement with the FDA.

Neflamapimod

Neflamapimod is an oral, highly selective, blood brain penetrant oral small molecule inhibitor of p38α. The compound was licensed from Vertex Pharmaceuticals (VRTX) in 2014. At the time of signing the license agreement, Vertex had already completed chronic repeat toxicology along with single- and multiple-dose Phase 1 trials in healthy volunteers and Phase 2 studies in Rheumatoid Arthritis. Inhibition of p38α reduces the effects of neuroinflammation on synaptic function, decreases tau phosphorylation, and modifies other mechanisms that underlie synaptic dysfunction in the cholinergic system.

CervoMed is developing neflamapimod for the treatment of Dementia with Lewy bodies (DLB). DLB is the second most common neurodegenerative dementia after Alzheimer's disease. It results from the accumulation of the protein α-synuclein into Lewy bodies, which accumulate in parts of the brain and nervous system and leads to neuronal cell death. DLB affects approximately 1.4 million people in the U.S. and E.U. combined.

In June 2022, results from the Phase 2a AscenD-LB trial were published. In the modified intention-to-treat population that included all subjects with at least one on-treatment evaluation, neflamapimod showed improvement in dementia severity (evaluated by CDR-SB; *P*=0.023) and functional mobility (TUG test; *P*=0.044). For the patients at the highest dose (40 mg TID), a significant improvement on NTB was also evident (*P*=0.049). An encouraging positive trend was also seen on the 10-item Neuropsychiatric Inventory (NPI-10), particularly with regard to visual hallucinations, where a significant reduction in frequency relative to placebo was seen.

Based on the results of the Phase 2a trial, CervoMed recently imitated a Phase 2b clinical trial of neflamapimod in patients with DLB. The primary outcome of the trial is improvement in dementia severity as assessed by change from baseline to week 16 in CDR-SB score. Secondary outcomes include effects on cognition (as assessed by DBL-specific cognitive test battery), motor function (as assessed by TUG test), and global rating of treatment effect (as assessed by the ADCS-Clinician Global Impression of Change). In January 2023, CervoMed was awarded a $21.0 million grant from the National Institute on Aging (NIA; a division of the NIH) that is expected to fully fund the Phase 2b trial. We anticipate enrollment in the trial completing in the first half of 2024 and topline results for the placebo controlled portion of the study being announced in the second half of 2024.

Valuation

We value CervoMed using a probability-adjusted discounted cash flow model that takes into account potential future revenues of neflamapimod for the treatment of DLB in the U.S. and the E.U. The company has indicated that it may pursue additional indications for neflamapimod in the future, but for now we only consider DLB for modeling purposes. Additional indications for neflamapimod represents potential upside to our valuation. We model for CervoMed to enter into commercialization partnerships and to receive 15% royalties on net sales of neflamapimod for the treatment of DLB in both the U.S. and E.U.

The following assumptions were made for generating our model: 1) A Phase 3 trial will initiate in 2025 followed by an NDA filing in 2027 and approval in the U.S. in 2028; 2) An MAA filing in the E.U. will occur in 2028 and approval in the E.U. will occur in 2029; 3) the list price for neflamapimod will be $30,000 in the U.S. and $15,000 in the E.U. upon launch, with a 3% yearly increase in price; 4) peak sales in the U.S. of approximately $2.4 billion and in the E.U. of approximately $1.2 billion seven and six years after launch in each jurisdiction, respectively; 5) a 15% gross-to-net adjustment; 6) patent exclusivity loss in 2035 with a subsequent 50% drop in revenues the following year.

Using a 15% discount rate and a 33% probability of approval leads to a net present value for neflamapimod in DLB of $134.5 million. We combine this with the company's estimated cash balance following the merger ($13 million) to derive a net present value for CervoMed of $147.5 million. Dividing by the current share count (5.7 million) plus an estimated 3.0 million shares for future dilution leads to a valuation of $17 per share.

PROJECTED FINANCIALS

CervoMed, Inc.	2022 A	Q1 A	Q2 A	Q3 E	Q4 E	2023 E	2024 E	2025 E
Neflamapimod	$0	$0	$0	$0	$0	$0	$0	$0
Grants & Collaborative Revenue	$0	$0	$0	$0	$0	$0	$0	$0
Total Revenues	**$0**	**$0**	**$0**	**$0**	**$0**	**$0**	**$0**	**$0**
Cost of Sales	$0	$0	$0	$0	$0	$0	$0	$0
Product Gross Margin	-	-	-	-	-	-	-	-
Research & Development	$7.2	$1.3	$1.4	$1.4	$1.4	$5.5	$6.0	$17.0
General & Administrative	$8.7	$3.0	$5.2	$4.0	$4.0	$16.1	$10.0	$12.0
Operating Income	($16.0)	($4.3)	($6.6)	($5.4)	($5.4)	($21.6)	($16.0)	($29.0)
Operating Margin	-	-	-	-	-	-	-	-
Non-Operating Expenses (Net)	$0.4	$0.2	$0.4	$0.0	$0.0	$0.0	$0.0	$0.0
Pre-Tax Income	($15.6)	($4.09)	($6.2)	($5.4)	($5.4)	($21.6)	($16.0)	($29.0)
Income Taxes	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0
Net Income	**($15.6)**	**($4.1)**	**($6.2)**	**($5.4)**	**($5.4)**	**($21.6)**	**($16.0)**	**($29.0)**
Net Margin	-	-	-	-	-	-	-	-
Reported EPS	**($7.65)**	**($2.01)**	**($3.04)**	**($0.95)**	**($0.95)**	**($5.59)**	**($2.67)**	**($3.22)**
YOY Growth	-	-	-	-	-	-	-	-
Basic Shares Outstanding	2.0	2.0	2.0	5.7	5.7	3.9	6.0	9.0

Source: Zacks Investment Research, Inc. *David Bautz, PhD*

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