BIOCENTURY

PRODUCT DEVELOPMENT | REPRINT FROM NOV. 18, 2024

An understudied dementia soon to get a pair of Phase II readouts

BY SELINA KOCH, EXECUTIVE EDITOR

BIOCENTURY & GETTY IMAGES

Ask a dementia expert what the most common neurodegenerative disease is that people have never heard of and the answer will be dementia with Lewy bodies. Affecting an estimated 1.4 million people in the U.S. alone, the condition ranks second only to Alzheimer's among dementias, and third, after Alzheimer's and Parkinson's, among neurodegenerative diseases.

Despite its prevalence, dementia with Lewy bodies (DLB) remains underdiagnosed and less understood than other neurodegenerative disorders. No drugs have been approved to treat the condition.

Now, two programs, both from small biotechs, are nearing Phase II proof of concept: p38α kinase inhibitor neflamapimod from CervoMed Inc. (NASDAQ:CRVO) and sigma-2 receptor modulator CT1812 from Cognition Therapeutics Inc. (NASDAQ:CGTX). Readouts from both trials are expected by year-end.

Successful or not, these studies will inform a field in desperate need of any data that offer clues about how to intervene in disease biology or better design trials. Neither program is directly targeting α-synuclein, the primary component of the Lewy body pathology that defines DLB.

Both are small caps that have had some setbacks and may need positive data to raise additional funds. Outside their programs, the DLB pipeline holds little else.

Tangled web of pathologies

Part of the challenge for drug developers is that dementia with Lewy bodies can share clinical and pathological features with Alzheimer's and Parkinson's. On the symptom side, these include cognitive impairment and movement symptoms. On the pathology side, Lewy bodies — α-synuclein-containing protein aggregates — are also a hallmark of Parkinson's and other "synucleinopathies" and can sometimes be seen in the brains of patients with Alzheimer's. Conversely, β-amyloid and tau pathology can found in some DLB patients.

Clinical characteristics that set DLB apart include pronounced fluctuations in attention, visual hallucinations, and a behavior disorder in which patients act out their dreams while in rapid eye movement (REM) sleep.

Diagnostic challenges are compounded by a lack of simple, reliable biomarkers, with a probable DLB diagnosis confirmed after death by the presence of Lewy bodies predominantly in neurons, rather than gial cells, and in certain parts of the brain. Other synucleinopathies are characterized by different patterns of Lewy bodies.

Based on learnings from its Phase IIa study, CervoMed is aiming to isolate "pure" DLB from DLB with concomitant Alzheimer's disease in its Phase IIb trial population using plasma p-tau181 as biomarker of Alzheimer's pathology. Low p-tau181 can also be considered indicative of early-stage DLB given that many patients eventually do develop tau pathology. CervoMed has powered its Phase IIb RewinD-LB trial for significance on the primary efficacy endpoint of CDR-SB (change in clinical dementia rating scale – sum of boxes), and hopes to start Phase III testing next year.

In contrast, the goal of Cognition Therapeutics' Phase II SHIMMER study is signal-finding; it is not powered for significance. The company believes the mechanism of its therapy should apply to DLB with or without Alzheimer's pathology, but has prespecified subgroup analyses by baseline levels of α-synuclein, β-amyloid and tau. It is enrolling a mild-to-moderate DLB population.

Both programs are also measuring indicators neuroinflammation and neurodegeneration as they test their different therapeutic hypotheses.

CervoMed's program is centered on the idea that p38α inhibition can restore function to the cholinergic neurons affected early in the disease, thereby mitigating symptoms and possibly delaying subsequent neurodegeneration. Cognition believes blocking the sigma-2 receptor will protect synapses from misfolded α-synuclein and β-amyloid.

CervoMed: multiple mechanisms, one therapy

CervoMed's candidate, neflamapimod, originated at Vertex Pharmaceuticals Inc. (NASDAQ:VRTX), where it was developed for immunology applications such as rheumatoid arthritis. CervoMed CEO John Alam had spent a decade at Vertex, before a stint as therapeutic area head for diseases of aging at Sanofi (Euronext:SAN; NASDAQ:SNY). He then founded CervoMed predecessor company EIP Pharma Inc.

Neflamapimod, a CNS-penetrant molecule, targets the MAPK family member p38α. Considered a stress kinase, p38α induces a proinflammatory response to various damage or stress signals. Hence, mitigating chronic neuroinflammation in the CNS is one mechanism by which neflamapimod is hypothesized to confer benefit in neurodegenerative diseases. Another is through reining in over-activation of RAB5, a key regulator of endocytosis and endosomal function. Studies

"IF THERE IS ONE DISEASE THAT'S WORSE THAN ALZHEIMER'S, IT MIGHT BE LEWY BODY DEMENTIA. YOU HAVE ALL THE SYMPTOMS OF ALZHEIMER'S PLUS PARKINSON'S DISEASE."

RAYMOND TURNER, GEORGETOWN UNIVERSITY

in preclinical models suggest dysregulation of the endo-lysosomal system can impair neurotransmitter receptor trafficking and synaptic function; neurotrophic factor signaling; and various protein pathologies such as uptake by neurons of misfolded α-synuclein.

Intervening early to push neurons and glial cells back toward homeostasis along these various axes should alleviate symptoms and delay disease progression, Alam told BioCentury early this year. "Only in neurodegeneration do we assume that that disease modification and symptom treatment are different, that you can't test both."

Although neflamapimod failed to show efficacy on memory tests in a Phase II Alzheimer's study, Alam said, "we now know the dose was too low." The Alzheimer's study tested 40 mg twice-daily; whereas the company's Phase IIa AscenD-LB trial in DLB found that treating three times per day led to differences from placebo on CDR-SB and a movement test called Timed Up and Go. Further analysis of the results suggested those benefits were specific to a subgroup of patients with low p-tau181 baseline. Based on learnings from AscenD-LB, CervoMed is focusing on DLB and running a Phase IIb trial in a 160-patient low p-tau181 population.

Alam believes CervoMed will be able to show symptomatic benefit by 16 weeks in the DLB population; whereas Alzheimer's trials tend to be longer. Moreover, less neuronal death occurs prior to symptom onset in DLB than in Alzheimer's, which may render the early symptomatic DLB population more amenable to treatment. "DLB in its purest form is a disease of synaptic dysfunction; there's not significant neuronal loss at symptom onset," he told BioCentury.

The synaptic dysfunction that occurs early in DLB is largely in cholinergic neurons, which project to many parts of the brain and play roles in cognition, attention and other DLB-relevant symptom domains. To get determine whether neflamapimod is indeed improving the functional connectivity of cholinergic

neurons, the Phase IIb RewinD-LB study will also measure EEG and MRI indicators of cholinergic circuit activity.

CervoMed, which has a market cap of $86 million, said it has a cash runway through year-end 2025. Its pipeline contains one other, preclinical asset.

Cognition: ejecting synuclein from synapses

Cognition Therapeutics is also focusing on synapses and is testing its therapy, sigma-2 receptor modulator CT1812, in DLB and Alzheimer's. The company's hypothesis is that sigma-2 forms a complex with a synaptic receptor that binds various prion-like proteins, including α-synuclein and β-amyloid. Binding of CT1812 to sigma-2 changes the conformation of the receptor, displacing the problematic proteins.

Given the frequency of multiple protein pathologies in neurodegenerative disease patients, and the widespread belief that still-soluble small oligomers of α-synuclein and β-amyloid mediate toxic effects on synapses, the hope is that the molecule will be useful for a broad range patients.

But like neflamapimod's Phase II Alzheimer's study, the Phase II SHIINE study of CT1812 did not yield statistically significant results on its cognitive endpoints. The molecule did, however, show trends in the right direction, and a subsequent an analysis of the data by baseline levels of p-tau217 suggested the therapy may benefit patients who have not yet accumulated much tau pathology.

In its 3Q24 earnings report, Cognition said it had cash runway into 2Q25. Before then, it is seeking an end-of-Phase-II meeting with FDA in Alzheimer's and awaiting DLB data from its Phase II SHIMMER study.

The 130-patient SHIMMER trial is testing 100 mg and 300 mg once-daily doses of CT1812 against placebo. Safety is the primary objective, with several tests of cognition and motor function serving as exploratory endpoints.

The DLB pipeline

In another parallel with Alzheimer's disease, cholinesterase inhibitors are the standard of care in DLB, underscoring loss of cholinergic synaptic transmission as a feature of both diseases. But blocking break down of acetylcholine outside of cells only works as long as neurons are releasing the neurotransmitter, and does not slow the process that leads to cholinergic neuron dysfunction and death.

The little drug development undertaken in DLB has not made much progress in identifying effective therapeutic mechanisms. For example, in 2022, Eisai Co. Ltd. (Tokyo:4523) found PDE-9 modulator E2027 did not improve scores on the Montreal Cognitive Assessment scale. In February 2023, now-defunct Aptinyx Inc. reported that NYX-458, an NMDA receptor positive allosteric modulator, failed to meet its endpoints in a Phase II trial to treat DLB and Parkinson's with mild dementia. Then in December 2023, Athira Pharma Inc. (NASDAQ:ATHA) said fosgonimeton, a positive modulator of HGF/c-MET signaling, did not meet its primary objective in a small Phase II study in DLB and Parkinson's dementia.

Apart from a handful of academic trials, the DLB pipeline is bare. Georgetown University spinout KeifeRx LLC in-licensed several tyrosine kinase inhibitors for development in neurodegenerative diseases including IND-stage KFRX05, which the company's website says targets c-KIT mutants and LRRK2 and is in development for dementia associated with Parkinson's.

At this year's Clinical Trials on Alzheimer's Disease (CTAD) meeting, Georgetown professor Raymond Turner noted that the university has been working to reposition TKIs for neurodegenerative diseases including DLB. "If there is one disease that's worse than Alzheimer's, it might be Lewy body dementia. You have all the symptoms of Alzheimer's plus Parkinson's disease," Turner said.

Turner presented findings from a small Phase II study testing a 200 mg dose nilotinib in DLB patients. Nilotinib is approved under the brand name Tasigna for chronic myelogenous leukemia, and a version of the molecule has become KeifeRx's lead program, which is in Phase III testing for Alzheimer's.

Georgetown's Phase II DLB study found changes in several biomarkers and clinical and cognitive measures that were either significant or trending in the right direction. Turner suggested the nilotinib or another multikinase inhibitor may represent "broad-spectrum anti-neurodegenerative" therapies with potential benefits across Alzheimer's, Parkinson's and DLB.

Nilotinib binds several TKIs, with BRC-ABL its proposed target in CML. In response to the CTAD presentation, CervoMed's Alam, who was in the audience, noted that nilotinib has "an IC50 that's equivalent or very similar for p38 MAP kinase as it does for ABL."

CervoMed's results are expected in December, and Cognition's by year-end.

BIOCENTURY

BIOCENTURY INC.

BioCentury's mission is to provide value-added business intelligence & analysis for life science companies, investors, academia and government on the strategic issues essential to the formation, development and sustainability of life science ventures.

NEWSROOM
news@biocentury.com

SAN CARLOS, CA
+1 650-595-5333; Fax: +1 650-595-5589

CHICAGO
+1 312-755-0798; Fax: +1 650-595-5589

WASHINGTON, DC
+1 202-462-9582; Fax: +1 202-667-2922

UNITED KINGDOM
+44 (0)1865-512184; Fax: +1 650-595-5589