BIOWORLD™ TODAY
THE DAILY BIOPHARMACEUTICAL NEWS SOURCE
BIOTECH'S MOST RESPECTED NEWS SOURCE FOR MORE THAN 20 YEARS
MARCH 12, 2015
VOLUME 26, NO. 48
SPECIAL REPRINT

Agenebio's AGB101 enroute to phase III on back of aMCI phase II

By Jennifer Boggs, Managing Editor

Trying to translate discovery research and early clinical data into phase III success has proved the bane for drug developers working in Alzheimer's disease. But executives at Agenebio Inc., which is gearing up to start a phase III study in the second half of this year with lead product AGB101, think their approach will be up to the task.

For one, rather than targeting the frequently debated amyloid beta or tau tangles, considered the hallmarks of Alzheimer's disease, Agenebio's approach involves reducing activity in the hippocampus, a brain structure key to memory formation. Work by founder and Johns Hopkins scientist Michela Gallagher, who also serves the firm's chief scientific officer, found that patients with amnestic mild cognitive impairment (aMCI) showed hyperactivity in functional magnetic resonance imaging (MRI) studies. In fact, the higher the activity, Gallagher's research showed, the greater the memory loss. (See *BioWorld Today*, May 20, 2010.)

Second, by targeting specifically aMCI, considered the pre-dementia stage of Alzheimer's, Agenebio's approach aims to preserve memory and cognition, potentially delaying the onset of Alzheimer's by intervening before patients suffer too much neuronal damage. One of the going theories in Alzheimer's drug development is that later-stage approaches have failed simply because the disease had progressed too far for therapeutic intervention.

Third, phase II data recently published in *NeuroImage: Clinical* showed that lead product AGB101 restored brain network function and significantly improved memory in elderly patients with aMCI. Agenebio CEO Jerry McLaughlin described those findings as "an exquisite translation from animal data to human data, which has been very difficult in the Alzheimer's field, so it gives us a ton of confidence going into phase III."

Preclinical data showed that AGB101, a low-dose version of anti-epileptic drug levetiracetam (marketed by UCB SA as Keppra), could reduce excess neural activity in the CA3 region of the hippocampus in male Long-Evans rats with memory impairment, according to Cortellis Competitive Intelligence. Clinical results published in *Neuron* in 2012 showed that treatment with levetiracetam reduced the level of hippocampal activity so that it was no longer different than controls, as measured by MRI, though memory improvements were not observed, a fact attributed to the short duration of treatment. (See *BioWorld Today*, May 15, 2012.)

In the newly published data, however, AGB101 soundly hit both of those marks. The double-blind study with subject crossover enrolled 69 patients – 54 with aMCI and 17 control patients – and used functional MRI BOLD activation, or blood-oxygen-level dependent contrast imaging, to measure the effects of drug treatment. The point of the control patients was to provide a comparison against which investigators could measure the effect of AGB101.

"You want to see what normal brain function looks like, so once you understand that you have a good target for where you want to return brain activity," McLaughlin said. Results showed that, when dosed at 125 mg or 250 mg once daily, ABG101 reduced excess hippocampal activity to a normal range.

"By restoring [hippocampal activity] to pre-disease levels, we can preserve memory and cognition and potentially slow disease progression and delay the onset of Alzheimer's," he told *BioWorld Today*.

Treatment with AGB101 also significantly improved memory performance in phase II, an outcome Agenebio hopes will be mirrored in the upcoming phase III trial, which, if successful, should allow the firm to file for approval under the accelerated 505(b)(2) pathway.

The company already had meetings with the FDA, and the agency has signed off on the primary endpoint, which will measure change in the Clinical Dementia Rating – Sum of Boxes.

The key secondary endpoint will involve MRI measurements of change in entorhinal cortex thickness. Additional outcomes measures include CDR (global, memory box), MMSE (Mini-Mental Status Exam), Alzheimer's Disease Assessment Scale-cognitive subscale 13, Wechsler Logical Memory I and II and other MRI measures. The precise dosage has not yet been disclosed, but McLaughlin said it will be roughly one-15th the typical dosage used for epilepsy. As an anti-epileptic, levetiracetam is approved for dosing at 3,000 mg per day.

The phase III will enroll about 500 patients – all will be diagnosed using PET scans with florbetapir F18 injection – randomized into two groups of 250 to receive either AGB101 or placebo for two years, with a possible interim analysis at one year. Agenebio is estimating the study will take a full year to enroll, "so we're looking at three years from start to finish," McLaughlin said.

SECURING A PARTNER

Right now, the privately held biotech is looking for a partnership or funding, or both, for the phase III trial. "We're now exploring those strategic options," he said. "We're in the process of talking to potential partners and other alternative sources of financing."

McLaughlin, who came on board in July, brings to the table capital-raising and business development experience, having most recently served as senior vice president and chief commercial officer at Nupathe Inc., the developer of migraine patch Zecuity (sumatriptan iontophoretic transdermal system), bought last year by Teva Pharmaceuticals Industries Ltd. for $144 million up front.

To date, Baltimore-based Agenebio has operated on relatively little. All told, it's raised about $15 million, McLaughlin said, with that money coming from high-net worth individuals and grants from the NIH and the Alzheimer's Drug Discovery Foundation. The latter recently awarded a second grant, totaling $900,000, in January.

The company is not backed by any venture capital. "We're really proud of the fact that we're facing phase III" while having been capital-efficient, he said.

When asked whether the firm would consider going to the currently robust capital markets, McLaughlin said he doesn't "rule anything out," but added that the primary goal is "securing a good partner."

Since it is designed to tackle the pre-dementia stage of Alzheimer's, AGB101 doesn't compete with the amyloid beta- and tau-targeting drugs in development. MCI patients comprise about 5.6 million in the U.S. and an estimated 25 million worldwide. About 10 percent to 15 percent of aMCI patients progress to Alzheimer's dementia each year.

"There's nothing approved for this population," McLaughlin said. "There's nothing available off-label that has proven to be effective. We're able to intercept potentially at a stage that precedes dementia and [AGB101] can potentially be the first treatment for patients with amnestic mild cognitive impairment.

"We're the only company to target the underlying cause [of aMCI], which is hippocampal overactivity," he added.

Agenebio has intellectual property around use of AGB101 in combination with other Alzheimer's drugs such as Aricept (donepezil, Pfizer Inc.). There's also a possibility that the drug could work well in other neurological diseases.

Beyond AGB101, Agenebio has a late-stage discovery program targeting GABAA alpha5, which has the potential to address several diseases, including aMCI but also schizophrenia and even autism. "We're very thrilled about the prospects" of that program, which has been funded in part by the NIH, McLaughlin said.

The company anticipates submitting an investigational new drug application for the first GABAA alpha 5 small molecule in the first half of 2016. //