Transcript Details

This is a transcript of an educational program. Details about the program and additional media formats for the program are accessible by visiting: https://reachmd.com/programs/cme/exploring-autophagy-through-sigma-1-receptor-activation-innovative-therapeutics-for-alzheimers-disease-beyond-amyloid-pathways/26516/

ReachMD
www.reachmd.com
info@reachmd.com
(866) 423-7849

Exploring Autophagy through Sigma-1 Receptor Activation: Innovative Therapeutics for Alzheimer's Disease Beyond Amyloid Pathways

Announcer:
Welcome to ReachMD. This activity, titled “Exploring Autophagy through Sigma-1 Receptor Activation: Innovative Therapeutics for Alzheimer's Disease Beyond Amyloid Pathways” is provided by Total CME, LLC.

Dr. Sabbagh:
Hello. I'm Marwan Noel Sabbagh. I'm a cognitive geriatric neurologist on ReachMD. Today, we are going to discuss exploring autophagy through sigma-1 receptor activation, innovative therapeutics for Alzheimer's disease [AD] beyond amyloid pathways.

As you all know, AD is a complex and highly heterogeneous disease. It is influenced by environment, genotype, cognitive reserve, and a range of demographic factors. Some people think that there is an intersection between amyloid clearance, tau mechanisms, and multiple biological pathways contributing to AD presentation.

One possible potential solution is an activation of an upstream endogenous pathway for clearing protein aggregates.

[Video plays: Alzheimer’s is a biologically complex disease. Blarcamesine is an orally once-daily small molecule with evidence of efficacy in early Alzheimer's disease patients. It binds to sigma-1 receptors, increasing free endogenous sigma-1, restoring the impaired protein clearing mechanism. Blarcamesine has demonstrated in vivo ability to improve elderly immune systems by making cells more able to clear out their waste in a process called autophagy enhancement, also demonstrating neural protection, reducing neural inflammation and maintaining cellular function. Blarcamesine plays a crucial role in restoring neuronal homeostasis by reducing cell stress upstream through clearing misfolded proteins, including A beta and tau, by enhancing the autophagy process.]

So let me walk you through this slide for a minute. And if we go from left to right and bottom to top, you see that the protein aggregates of amyloid and tau cause cellular stress, and in so doing, they have maturation and formation and maturation of vesicles, which ultimately interact with lysosomes, which cause a lysosomal dysfunction, and subsequently you have accumulation of protein aggregation. This leads to neurotoxicity. Blarcamesine activates the sigma-1 receptor, and in so doing, it allows functional lysosomes to occur, which allows docking of the autolysosomal pathway to be engaged, which causes degradation, ultimately leading to recycling, which triggers a neuroprotection.

When we look at this in a broader therapeutic perspective, we feel that this approach might be complementary to the monoclonal antibodies. I want to direct you to the bottom of this slide. You see that the monoclonal antibodies trigger microglial phagocytosis and remove amyloid A beta plaques downstream. In a complementary way, blarcamesine would trigger sigma-1 receptors and activate sigma-1 receptors, which subsequently leads to autophagy, which has neuroprotective properties, specifically upstream neuroprotection, including removal, repair, regenerate, and resilience, and it would operate in a complementary way, reducing neurotoxicity and enhancing cellular survival.

When we look at the blarcamesine proof of concept, both in the preclinical and the phase 2a trials, you see that in a dose-dependent manner, blarcamesine inhibits amyloid-beta peptide 1 to 42 and it inhibits tau hyperphosphorylation in a dose-dependent manner, and it works to stabilize in the highest dose or slightly stabilize cognitive decline, as seen on the right-hand side.

When we look at the phase 2b/3 trial in early Alzheimer's disease, you see that it's a 3-arm study, low dose, high dose, and placebo, approximately 170 participants per arm. All of them were treated for 48 weeks. All of them met NIA-AA [National Institute on Aging - Alzheimer’s Association] criteria for Alzheimer's disease or mild cognitive impairment due to Alzheimer's disease, with biomarker

confirmation, age range 60 to 85, Mini Mental 20 to 28, with the primary outcome measures of ADAS-Cog 13 [13-item cognitive subscale of the Alzheimer Disease Assessment Scale], ADCS-ADL [AD Cooperative Study-Activities of Daily Living Scale], and a key secondary endpoint of CDR [Clinical Dementia Rating] sum of the boxes, and other structural endpoints, including structural MRI, functional MRI, A beta 42/40 ratio, p-tau181, p-tau231, neurofilament light, and a blinded clinician impression called the CGI [clinical global impression] looking at it. And we have an open-label extension called the ATTENTION-AD study with some data to be read out in the near future on the blinded study.

When we take a sneak peek at some of these data, we point out to this audience that blarcamesine treatment may reduce neurodegeneration by decreasing brain atrophy, and it showed that after 48 weeks slowed the rate of atrophy and slowed the rate of neurodegeneration in a statistically significant manner, suggesting that it could have effects on neurodegeneration.

In summary, blarcamesine offers an oral route of administration for user convenience. It targets the sigma-1 receptor to restore cellular homeostasis effectively. This therapeutic approach is designed to complement existing anti-amyloid treatments. It can be used to reduce a neurodegeneration as a critical aspect of its therapeutic effect.

Thank you for listening.

Announcer:
You have been listening to ReachMD. This activity is provided by Total CME, LLC. To download this activity, go to ReachMD.com/CME. Thank you for listening.