Athira Pharma Announces Topline Results from Phase 2/3 LIFT-AD Clinical Trial of Fosgonimeton for Mild-to-Moderate Alzheimer's Disease

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LIFT-AD trial did not meet primary endpoint of GST and key secondary endpoints of cognition (ADAS-Cog11) and function (ADCS-ADL23)

In pre-specified subgroups of patients with moderate Alzheimer's disease or who are APOE4 carriers, fosgonimeton showed a numerically greater treatment effect

All biomarkers associated with Alzheimer's disease pathology showed changes with fosgonimeton treatment consistent with the broad neuroprotective mechanism of HGF modulation

Athira to host live webcast today at 4:30 PM Eastern time

BOTHELL, Wash., Sept. 03, 2024 (GLOBE NEWSWIRE) -- **Athira Pharma, Inc.** (NASDAQ: ATHA), a late clinical-stage biopharmaceutical company focused on developing small molecules to restore neuronal health and slow neurodegeneration, today announced topline results from its Phase 2/3 LIFT-AD clinical trial of fosgonimeton, a hepatocyte growth factor (HGF) positive modulator, in patients with mild-to-moderate Alzheimer's disease (AD).

The topline results showed that neither the trial's primary endpoint (the Global Statistical Test (GST), a combination of results from measures of cognition (ADAS-Cog11) and function (ADCS-ADL23)) nor its key secondary endpoints of ADAS-Cog11 and ADCS-ADL23 reached statistical significance compared with placebo at 26 weeks. However, both components of GST, cognition (ADAS-Cog11) and function (ADCS-ADL23), directionally favored fosgonimeton treatment, and in pre-specified subgroups characterized by more rapid disease progression (moderate AD and APOE4 carriers), cognition and function improved or stabilized in the fosgonimeton treated group. In addition, data across biomarkers of protein pathology (Aβ42/40, p-Tau181, and p-Tau217), inflammation (GFAP) and neurodegeneration (NfL) showed directional improvements with fosgonimeton treatment that are consistent with the broad neuroprotective mechanism of HGF modulation.

"These are not the results we hoped for, as the lack of clinical decline in the placebo group, combined with the short duration of the study, may have impacted the trial's ability to translate the effect of fosgonimeton treatment into meaningful clinical benefit," said Javier San Martin, M.D., Chief Medical Officer of Athira. "However, we believe the totality of the data continues to suggest that positive modulation of the HGF pathway has the potential to translate into improvement in parameters of neuronal health and may mitigate disease progression."

"While the trial did not meet its primary endpoint, the biomarker and subgroup data are intriguing and remarkably consistent not only across endpoints but also with our understanding of fosgonimeton's neuroprotective mechanism of action," added Anton P. Porsteinsson, M.D., Director of the University of Rochester Alzheimer's Disease Care, Research, and Education Program (AD-CARE) and a LIFT-AD investigator.

Phase 2/3 LIFT-AD Clinical Trial Design and Topline Results

LIFT-AD (NCT04488419) was a randomized, placebo-controlled, double-blind study that evaluated the efficacy and safety of once-daily subcutaneous injections of fosgonimeton (40 mg) in 312 mild-to-moderate AD patients not on acetylcholinesterase inhibitors (AChEIs) compared to placebo over a 26-week treatment period. The primary endpoint of LIFT-AD was the change from baseline after 26 weeks of treatment using the Global Statistical Test (GST), a combination of results from measures of cognition (ADAS-Cog11) and function (ADCS-ADL23). Secondary endpoints included cognition (ADAS-Cog11), function (ADCS-ADL23), and a plasma biomarker of neurodegeneration, neurofilament light chain (NfL). The trial explored additional plasma biomarkers including glial fibrillary acidic protein (GFAP), a marker of neuroinflammation, and both amyloid beta and phosphorylated tau (pTau), hallmark measures of AD pathology.

Primary Analysis Population
Topline results from the LIFT-AD study of fosgonimeton in mild-to-moderate AD patients after 26 weeks showed:

- A -0.08 change in GST favoring fosgonimeton that did not reach statistical significance (p=0.70)
- The change in cognition from baseline as assessed by ADAS-Cog11, for which a decrease from baseline represents improvement, was -0.39 for the placebo group and -1.09 for the fosgonimeton treated group, a difference of -0.70 (p=0.35) favoring fosgonimeton
- In the fosgonimeton treated group, there was an increase (improvement) of 0.65 in function as measured by ADCS-ADL23 versus a decline of -0.02 in placebo, although this difference did not meet statistical significance (p=0.61)

Prespecified Biomarker Analyses
Data from the plasma biomarkers of neurodegeneration (NfL), inflammation (GFAP), and protein pathology (p-Tau181, p-Tau217, and amyloid beta 42/40 ratio) showed consistent directional improvements favoring fosgonimeton versus placebo after 26 weeks. Notably, fosgonimeton treatment

reduced plasma levels of pTau217, a hallmark of AD, by -0.12 pg/mL compared to placebo (p<0.01).

Prespecified Subgroup Analyses
In a prespecified subgroup analyses of more advanced AD patients, a greater numerical treatment effect in clinical outcomes was observed in the fosgonimeton treatment group compared to placebo after 26 weeks:

- The change in cognition from baseline as assessed by ADAS-Cog11 in moderate AD patients, for which a decrease from baseline represents improvement, showed the fosgonimeton treatment group (n=61) improved compared to placebo (n=70), with a delta of -1.16 (p=0.39)
- For AD patients who are carriers of the APOE4 gene, the placebo group (n=74) declined in cognition as assessed by ADAS-Cog11 over the 26-week period as expected, whereas the fosgonimeton treatment group (n=74) remained stable, with a delta of -1.07 (p=0.33)

Post Hoc Subgroup Analyses
In a post hoc analyses by disease severity as defined by baseline ADAS-Cog11 (>30) and Clinical Dementia Rating (CDR) 2, fosgonimeton showed a larger effect size mainly driven by an improvement in cognition at week 26.

- Patients with the highest baseline ADAS-Cog11 (>30) who were treated with fosgonimeton (n=42) compared to placebo (n=52) showed a -2.51 improvement in cognition as assessed by ADAS-Cog11 (p=0.16), for which a lower number represents improvement
- A small subset of patients with a CDR 2 (moderate dementia) who were treated with fosgonimeton (n=20) compared to placebo (n=19) showed a -3.74 improvement in cognition as assessed by ADAS-Cog11 (p=0.21)

Safety and Tolerability
Fosgonimeton was generally well tolerated, with a favorable safety profile. Participants treated with fosgonimeton (40 mg) for 26 weeks showed a higher incidence of treatment emergent adverse events compared to placebo, mainly driven by injection site reactions. The incidence of serious adverse events (SAEs) was similar between treatment groups, with few treatment-related SAEs and no deaths observed in the study. The study had a 22 percent early termination rate.

“In addition to fosgonimeton, we have a pipeline of next-generation, orally delivered HGF modulators, with improved pharmacological properties, that we are currently evaluating in neurodegenerative diseases,” stated Mark Litton, Ph.D., President and Chief Executive Officer of Athira. “We want to express our sincere appreciation for the patients, caregivers, their families, and healthcare professionals who participated in the LIFT-AD trial. I also want to thank all Athira employees for their dedication and tireless contributions to advancing the science to benefit patients battling neurodegenerative diseases.”

Full analysis of these results is scheduled to be reviewed at the 17th Annual Clinical Trials on Alzheimer’s Disease (CTAD) taking place October 29 - November 1, 2024, in Madrid, Spain.

Athira continues to evaluate ATH-1105, a next-generation, orally administered, small molecule drug candidate in development for the potential treatment of amyotrophic lateral sclerosis (ALS), AD, and other neurodegenerative diseases. Athira is currently conducting a first-in-human, dose escalation Phase 1 clinical trial evaluating safety, tolerability and pharmacokinetics of ATH-1105 in up to 80 healthy volunteers. Athira completed the first cohort of healthy volunteers in June 2024 and expects trial completion by year-end 2024, with a goal to be in ALS patients in 2025. ATH-1105’s potential is supported by a growing body of preclinical evidence demonstrating improvements in nerve and motor function, biomarkers of inflammation and neurodegeneration, and survival in various models of ALS.

Live Webcast
Athira management will host a live webcast to discuss the LIFT-AD topline results at 4:30 PM Eastern time today, Tuesday, September 3, 2024. The live webcast can be accessed at Events and Presentations | Athira Pharma. The call can also be accessed by phone at 800-715-9871, conference ID: 4911242. A replay of the webcast will be available two hours after the call and will be archived on the Events for approximately 90 days.

About Athira Pharma, Inc.
Athira Pharma, Inc., headquartered in the Seattle, Washington area, is a late clinical-stage biopharmaceutical company focused on developing small molecules to restore neuronal health and slow neurodegeneration. Athira aims to alter the course of neurological diseases by advancing its pipeline of drug candidates that modulate the neurotrophic HGF system. For more information, visit www.athira.com. You can also follow Athira on Facebook, LinkedIn, X (formerly known as Twitter) and Instagram.

Forward-Looking Statements
This communication contains “forward-looking statements” within the meaning of Section 27A of the Securities Act of 1933, Section 21E of the Securities Exchange Act of 1934 and the Private Securities Litigation Reform Act of 1995. These forward-looking statements are not based on historical fact and include statements regarding: Athira’s drug candidates as potential treatments for Alzheimer’s disease, amyotrophic lateral sclerosis, and other neurodegenerative diseases; future development plans; the anticipated reporting of data; the potential learnings from preclinical studies and other nonclinical data, the LIFT-AD trial and the ongoing Phase 1 trial of ATH-1105 and their ability to inform and improve future clinical development plans; expectations regarding the potential efficacy and commercial potential of Athira’s drug candidates; and Athira’s ability to advance its drug candidates into later stages of development. Forward-looking statements generally include statements that are predictive in nature and depend upon or refer to future events or conditions, and include words such as “may,” “will,” “should,” “on track,” “would,” “expect,” “plan,” “believe,” “intend,” “pursue,” “continue,” “suggest,” “potential, target” and similar expressions. Any forward-looking statements are based on management’s current expectations of future events and are subject to a number of risks and uncertainties that could cause actual results to differ materially and adversely from those set forth in or implied by such forward-looking statements. These risks and uncertainties include, but are not limited to, the data from preclinical and clinical trials may not support the safety, efficacy and tolerability of Athira’s drug candidates; development of drug candidates may cease or be delayed; regulatory authorities could object to protocols, amendments and other submissions; future potential regulatory milestones for drug candidates, including those related to current and planned clinical studies, may be insufficient to support regulatory submissions or approval;

Athira may not be able to recruit sufficient patients for its clinical trials; the outcome of legal proceedings that have been or may in the future be instituted against Athira, its directors and officers; possible negative interactions of Athira's drug candidates with other treatments; Athira's assumptions regarding its financial condition and the sufficiency of its cash, cash equivalents and investments to fund its planned operations may be incorrect; adverse conditions in the general domestic and global economic markets; the impact of competition; the impact of expanded drug candidate development and clinical activities on operating expenses; the impact of new or changing laws and regulations; as well as the other risks detailed in Athira's filings with the Securities and Exchange Commission from time to time. These forward-looking statements speak only as of the date hereof and Athira undertakes no obligation to update forward-looking statements. Athira may not actually achieve the plans, intentions, or expectations disclosed in its forward-looking statements, and you should not place undue reliance on the forward-looking statements.

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