Athira PHARMA

ACT-AD: Fosgonimeton in Mild-to-Moderate Alzheimer's Disease—First Results of a Randomized, Placebo-Controlled, 26-Week, Phase 2 Proof-of-Concept Trial

This is a plain language summary of primary analyses from the ACT-AD study presented by Athira Chief Medical Officer, Dr. Hans J. Moebius, at the Alzheimer's Association International Conference (AAIC), July 31-August 4, 2022 in San Diego, California, and online.

DATE OF SUMMARY August 3, 2022 | **STUDY START DATE** November 23, 2020 | **STUDY END DATE** May 20, 2022

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1 WHY WAS THE ACT-AD STUDY DONE?

- In Alzheimer's disease (AD), the connections between brain cells break down over time. Alzheimer's disease gets worse the longer a person has it[1,2]
- People with AD slowly lose their memory and reasoning skills. They may not be able to do certain things without help and may not be able to carry out simple tasks[3]
- There is currently no cure for AD. Doctors and scientists continue to look for safe and effective treatments for AD, particularly for people with **mild-to-moderate AD**
  - **Mild AD**—people with mild AD can have limited memory loss. They can forget the location of an object or have a hard time coming up with the right word or name. They are still able to do most daily activities by themselves
  - **Moderate AD**—people with moderate AD have stronger signs of mental decline. They can forget facts about themselves or not know where they are or what day it is. They might behave differently than usual
- A **phase 1** study in people with AD looked at how safe an **investigational drug** called **fosgonimeton** was. The results showed that fosgonimeton was safe and that a test called **event-related potential (ERP) P300 latency** showed faster brain response speeds in participants who were given fosgonimeton[4]
  - **Phase 1**—the first step in testing whether a medication is safe to use in people. This phase can also include tests to figure out how the medication affects a person's symptoms
  - **Investigational drug**—a drug that has not been approved for use except in scientific studies
  - **Fosgonimeton**—a drug that can pass into the brain. It is thought to enhance natural processes that help in the maintenance and repair of brain cells and networks.[4-6] This is a different approach from current AD treatments
    - Other investigational drugs for AD are designed to break up amyloid plaques or tau tangles—two types of abnormal protein clumps seen in brains with AD
  - **ERP P300 latency**—a test of the amount of time it takes for the brain to react to a sound stimulus

The goals of the phase 2 ACT-AD study were to repeat and expand on the results of the phase 1 study and to inform the ongoing, larger LIFT-AD study of fosgonimeton in people living with mild-to-moderate AD

- **Phase 2**—after a safe dose is determined in a phase 1 study, a phase 2 study tests how a medication affects a person's symptoms. Any side effects of the medication are also looked at in this phase

References 1. Jackson J et al. *Front Neurosci.* 2019;13:735. 2. Forner S et al. *Trends Neurosci.* 2017;40:347-357. 3. McKhann GM et al. *Alzheimers Dement.* 2011;7(3):263-269. 4. Hua X et al. *J Alzheimers Dis.* 2022;86(3):1399-1413. 5. Reda S et al. Poster presented at: Alzheimer's Association International Conference; July 31-August 3, 2022; San Diego, CA. 6. Johnston J et al. Poster presented at: ASENT Annual Meeting; February 28-March 3, 2022; Virtual.

2 HOW, WHEN, AND WHERE WAS THE ACT-AD STUDY CARRIED OUT?

The ACT-AD study was a randomized, double-blind, placebo-controlled, parallel-group, phase 2 study to compare fosgonimeton with placebo treatment in people with AD[1,2]

- **Randomized**—participants were randomly split up into 3 treatment groups that were given a placebo, a 40-mg dose of fosgonimeton, or a 70-mg dose of fosgonimeton
- **Double-blind**—the participants and their doctors did not know whether the participant was receiving a placebo treatment or one of the fosgonimeton doses
- **Placebo-controlled**—one group was given a placebo, which is a harmless substance that looks like the drug but has no active ingredients
- **Parallel-group**—all three groups were treated at the same time
- **Phase 2**—after a safe dose is determined in a phase 1 study, a phase 2 study tests how a medication affects a person's symptoms. Any side effects of the medication are also looked at in this phase
- The ACT-AD study happened between November 23, 2020, and May 20, 2022, in the United States and in Australia[1]

References 1. ClinicalTrials.gov. Accessed July 22, 2022. https://clinicaltrials.gov/ct2/show/NCT04491006. 2. Moebius HJ et al. Presented at: Alzheimer's Association International Conference; July 31-August 4, 2022; San Diego, CA. Oral 61572.

3 WHO WAS INCLUDED IN THE ACT-AD STUDY?

The ACT-AD study enrolled 77 people with mild-to-moderate AD who were not taking AD medications or were on a stable dose of standard-of-care acetylcholinesterase inhibitor (AChEI)[1,2]

- **AD** is the most common cause of dementia. Dementia can appear as problems with memory, thinking, and/or language (reading, writing, and speaking)
  - **Mild AD**—people with mild AD can have limited memory loss. They can forget the location of an object or have a hard time coming up with the right word or name. They are still able to do most daily activities by themselves
  - **Moderate AD**—people with moderate AD have stronger signs of mental decline. They can forget facts about themselves or not know where they are or what day it is. They might behave differently than usual
- **AChEI**—a type of medication that is commonly used to treat symptoms of AD. Donepezil, galantamine, and rivastigmine are AChEIs

PARTICIPATING COUNTRIES: United States, Australia

AGES ELIGIBLE: 55-85 years

DIAGNOSIS OF AD: Mild AD, Moderate AD

BACKGROUND MEDICATION ALLOWED: Stable or no AChEI treatment

DISQUALIFIED: People with other causes of dementia or difficulty hearing or on the medication memantine

References 1. ClinicalTrials.gov. Accessed July 22, 2022. https://clinicaltrials.gov/ct2/show/NCT04491006. 2. Moebius HJ et al. Presented at: Alzheimer's Association International Conference; July 31-August 4, 2022; San Diego, CA. Oral 61572.

4 WHAT TREATMENTS WERE GIVEN IN THE ACT-AD STUDY?

Fosgonimeton is not approved and can only be used experimentally. Fosgonimeton is being investigated in ongoing clinical trials in people with mild-to-moderate AD, dementia with Lewy bodies, and Parkinson's disease dementia

- In the ACT-AD study, 53 people received **fosgonimeton** (40 mg or 70 mg) as their study treatment and 24 people received **placebo** as their study treatment[1,2]
  - **Fosgonimeton**—a drug that can pass into the brain. It is thought to enhance natural processes that help in the maintenance and repair of brain cells and networks.[3-5] This is a different approach from current AD treatments
    - Research has shown that parts of this repair system are not as active in the brains of people with AD (compared with the brains of people without AD)[6]
  - **Placebo**—a harmless substance that looks like the drug but has no active ingredients
- Fosgonimeton or placebo was given daily by an injection under the skin for a total of 26 weeks[1,2]

77 participants:
- 27 participants — FOSGONIMENTON 40 mg
- 26 participants — FOSGONIMENTON 70 mg
- 24 participants — PLACEBO

References 1. ClinicalTrials.gov. Accessed July 22, 2022. https://clinicaltrials.gov/ct2/show/NCT04491006. 2. Moebius HJ et al. Presented at: Alzheimer's Association International Conference; July 31-August 4, 2022; San Diego, CA. Oral 61572. 3. Hua X et al. *J Alzheimers Dis.* 2022;86(3):1399-1413. 4. Reda S et al. Poster presented at: Alzheimer's Association International Conference; July 31-August 3, 2022; San Diego, CA. 5. Johnston J et al. Poster presented at: ASENT Annual Meeting; February 28-March 3, 2022; Virtual. 6. Hamasaki et al. *Neuropathology.* 2014;34:284-290.

5 WHAT ACT-AD RESULTS WERE TALKED ABOUT AT AAIC 2022?

Effects[1,2]

- In ACT-AD, the effects of **fosgonimeton** were measured by use of several tests. Tests included the **event-related potential (ERP) P300 latency**, the **Alzheimer's Disease Assessment Scale–Cognitive Subscale (ADAS-Cog11)**, the **Alzheimer's Disease Cooperative Study–Activities of Daily Living (ADCS-ADL23)**, and **neurofilament light chain (NfL)** levels
  - **Fosgonimeton**—a drug that can pass into the brain. It is thought to enhance natural processes that help in the maintenance and repair of brain cells and networks.[3-5] This is a different approach from current AD treatments
  - **ERP P300 latency**—a test of the amount of time it takes for the brain to react to a sound stimulus
  - **ADAS-Cog11**—an exam to evaluate a person's memory, how well they communicate, and whether they can do simple tasks
  - **ADCS-ADL23**—an exam to evaluate how well people with AD can complete a range of daily activities such as eating, using the bathroom, doing chores, shopping, and traveling
  - **NfL**—a substance that can be measured from the blood. Its levels go up when damage occurs in the nervous system
- When looking at every study participant, compared with **placebo**, fosgonimeton did not appear to improve responses in most of the test results
  - **Placebo**—a harmless substance that looks like the drug but has no active ingredients
- However, there seemed to be some improvement in **ADCS-ADL23** scores and **NfL** levels after 26 weeks on fosgonimeton when compared with placebo
- Surprisingly, there appeared to be a difference between participants who received fosgonimeton only and participants who took fosgonimeton and standard-of-care **AChEIs**
  - Participants who received fosgonimeton only, without AChEI, had better scores on all of the mentioned tests (**ERP P300 latency**, **ADAS-Cog11**, **ADCS-ADL23**, and **NfL** levels)
  - **AChEI**—a type of medication that is commonly used to treat symptoms of AD. Donepezil, galantamine, and rivastigmine are AChEIs

Participants who were only taking fosgonimeton during the study (and did not take AChEI at the same time) showed some improvement in certain tests that measured AD symptoms

Safety[1]

- Safety was looked at in 24 participants who received placebo, 27 who received fosgonimeton 40 mg, and 26 who received fosgonimeton 70 mg
- Possible **side effects**, meaning any unwanted effect of a drug, were reported in
  - 71% of participants taking placebo,
  - 89% of participants taking fosgonimeton 40 mg, and
  - 100% of participants taking fosgonimeton 70 mg
- **Reaction at the injection site** was the most common side effect. The reactions were mild and were seen in
  - 4% of participants taking placebo,
  - 63% of participants taking fosgonimeton 40 mg, and
  - 81% of participants taking fosgonimeton 70 mg

Fosgonimeton was tolerated well and caused no serious side effects

References 1. Moebius HJ et al. Presented at: Alzheimer's Association International Conference; July 31-August 4, 2022; San Diego, CA, USA. Oral 61572. 2. Athira Pharma. Press release, August 3, 2022. Available at: https://www.athira.com/news/. Accessed: August 3, 2022. 3. Hua X et al. *J Alzheimers Dis.* 2022;86(3):1399-1413. 4. Reda S et al. Poster presented at: Alzheimer's Association International Conference; July 31-August 3, 2022; San Diego, CA. 5. Johnston J et al. Poster presented at: ASENT Annual Meeting; February 28-March 3, 2022; Virtual.

6 WHAT ARE THE OTHER STUDIES OF FOSGONIMETON?

- Other studies with fosgonimeton
  - In people with AD: **LIFT-AD** (NCT04488419) and the **ACT-AD/LIFT-AD Open-label Extension** (NCT04886063)
  - In people with Parkinson's disease dementia or dementia with Lewy bodies: **SHAPE** (NCT04831281)

7 WHERE CAN I ACCESS MORE INFORMATION ABOUT ACT-AD?

- You can visit ClinicalTrials.gov at the link here (NCT04491006)
- A recording of the presentation and other resources are available at https://www.athira.com/scientific-publications-aaic-2022/

8 DISCLOSURES

- The ACT-AD study was funded by Athira Pharma, Inc.
- The ACT-AD study is supported by a grant from the National Institute on Aging of the National Institutes of Health under Award Number R01AG06268. The information presented in this plain language summary is solely the responsibility of Athira and does not necessarily represent the official views of the National Institutes of Health
- This plain language summary was prepared by Katie Henderson, PhD, and Eileen McIver, PhD, of ApotheCom (San Francisco, CA, USA). Plain language services were funded by Athira Pharma, Inc.
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