



Arrowhead Presents Updated Data from Phase 2 SEQUOIA Study of Investigational RNAi Therapy Fazirsiran in Patients with Alpha-1 Antitrypsin Deficiency Liver Disease

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- Data Presented During Oral Session at EASL 2023 Demonstrate Fazirsiran's Promising Impact on Key Markers of Liver Disease
- AATD-LD is a Rare Genetic Disease Affecting Children and Adults with no Approved Treatments
- Takeda and Arrowhead are Advancing Fazirsiran and Actively Enrolling in 160 patient [Phase 3 REDWOOD Study](#)

PASADENA, Calif.--(BUSINESS WIRE)--Jun. 24, 2023-- Arrowhead Pharmaceuticals Inc. (NASDAQ: ARWR) today presented updated results from the Phase 2 SEQUOIA clinical study of investigational fazirsiran (TAK-999/ARO-AAT) for the treatment of liver disease associated with alpha-1 antitrypsin deficiency (AATD-LD). The SEQUOIA Phase 2 data are consistent with the promising results from an open-label Phase 2 trial of fazirsiran (AROAT2002) that were published in [The New England Journal of Medicine](#). Takeda (TSE:4502/NYSE:TAK) and Arrowhead are further investigating fazirsiran in the ongoing pivotal [Phase 3 REDWOOD](#) clinical study which is actively recruiting a total of 160 patients.

The updated Phase 2 clinical data were presented at the European Association for the Study of the Liver (EASL) Congress 2023 in an oral presentation titled, "Fazirsiran reduces liver Z-alpha-1 antitrypsin synthesis, decreases globule burden and improves histological measures of liver disease in adults with alpha-1 antitrypsin deficiency: a randomized placebo-controlled phase 2 study," which may be accessed on the [Events and Presentations](#) page under the Investors section of the Arrowhead website.

"The clinical results from the Phase 2 SEQUOIA study of fazirsiran were clear and compelling. Fazirsiran treatment demonstrated a substantial effect on several key markers of liver disease," said Javier San Martin, M.D., chief medical officer at Arrowhead. "Together with our partners at Takeda, we are now conducting the Phase 3 REDWOOD study to further investigate fazirsiran's potential in patients with AATD-LD and F2 to F4 liver fibrosis."

Key findings from the SEQUOIA study include the following:

- Fazirsiran reduced serum Z-AAT concentration in a dose-dependent manner
 - At week 48, patients receiving 25, 100, or 200 mg fazirsiran (n=16) achieved serum Z-AAT reductions of 74%, 89%, and 94%, respectively, versus an increase of 9% observed in patients receiving placebo (n=9)
- Fazirsiran significantly reduced liver Z-AAT
 - Patients receiving 200 mg fazirsiran achieved a least-squares mean percentage difference (95% CI) versus placebo at post-dose biopsy of -14.1% (p = 0.0004)
- Fazirsiran consistently reduced hepatic globule burden
 - 100% of patients in the pooled fazirsiran treatment group achieved at least a 1-point improvement in PASD-positive globule burden
- Fazirsiran treatment reduced histological signs of hepatic inflammation
 - 42% of patients in the pooled fazirsiran treatment group achieved at least a 1-point improvement in portal inflammation versus 0% in the placebo group
 - 67% of patients in the pooled fazirsiran treatment group achieved at least a 1-point improvement in interface hepatitis versus 0% in the placebo group
- 50% of the pooled fazirsiran treated patients showed at least a 1-point improvement in METAVIR liver fibrosis versus 38% in the placebo group
- Fazirsiran has been well tolerated to date
 - No treatment-emergent adverse events related to study drug causing discontinuation, dose interruptions or premature study withdrawals
 - Treatment emergent adverse events reported to date generally well balanced between fazirsiran and placebo groups
- Pulmonary function test results (FEV1 and DLCO) for both fazirsiran and placebo were stable over time with no apparent dose-dependent effects

About Fazirsiran

Fazirsiran (TAK-999/ARO-AAT) is an investigational RNA interference (RNAi) therapy designed to reduce the production of mutant alpha-1 antitrypsin protein (Z-AAT) as the first potential treatment for AATD-LD, a rare genetic disease. Z-AAT accumulation is believed to be the cause of progressive liver disease in patients with alpha-1 antitrypsin deficiency (AATD). Reducing production of the mutant Z-AAT protein is expected to halt the progression of liver disease and potentially allow the liver to regenerate and repair. Fazirsiran was granted Breakthrough Therapy Designation in July 2021 and Orphan Drug Designation in February 2018 for the treatment of AATD-LD from the U.S. Food and Drug Administration.

About the Phase 3 REDWOOD Clinical Trial

The REDWOOD (TAK-999-3001) clinical study ([NCT05677971](#)) is a randomized, double-blind, placebo-controlled, Phase 3 trial to evaluate the efficacy and safety of fazirsiran in the treatment of AATD-LD. Approximately 160 adult patients with METAVIR stage F2 to F4 fibrosis will be randomized 1:1 to receive fazirsiran or placebo. The primary endpoint of the study is a decrease from baseline of at least 1 stage of histologic fibrosis METAVIR staging in the centrally read liver biopsy done at Week 106 in patients with METAVIR stage F2 and F3 fibrosis. The REDWOOD study is now recruiting across several sites in the U.S., additional information can be found at <https://theredwoodliverstudy.com/>.

About Alpha-1 Antitrypsin Deficiency-Associated Liver Disease

AATD is a rare genetic disorder associated with liver disease in children and adults and pulmonary disease in adults. AATD is estimated to affect 1 per 3,000-5,000 people in the United States and 1 per 2,500 in Europe, of which 35% may develop liver disease. The protein AAT is primarily synthesized and secreted by liver hepatocytes. Its function is to inhibit enzymes that can break down normal connective tissue. The most common disease variant, the Z mutant, has a single amino acid substitution that results in improper folding of the protein. The mutant protein cannot be effectively secreted and accumulates in globules inside the hepatocytes. This triggers continuous hepatocyte injury, leading to fibrosis, cirrhosis, and increased risk of hepatocellular carcinoma.

Individuals with the homozygous PiZZ genotype have severe deficiency of functional AAT that may lead to pulmonary disease and liver disease. Lung disease is frequently treated with AAT augmentation therapy. However, augmentation therapy does nothing to treat liver disease, and there is no specific therapy for hepatic manifestations. There is a significant unmet need as liver transplant, with its attendant morbidity and mortality, is currently the only available cure.

About Takeda and Arrowhead Collaboration and License Agreement

In October 2020, Arrowhead and Takeda announced a collaboration and licensing agreement to develop fazirsiran. Under the terms of the agreement, Arrowhead and Takeda will co-develop fazirsiran, which, if approved, will be co-commercialized in the U.S. under a 50/50 profit-sharing structure. Outside the U.S., Takeda will lead the global commercialization strategy and receive an exclusive license to commercialize fazirsiran with Arrowhead eligible to receive tiered royalties of 20-25% on net sales. Arrowhead received an upfront payment of \$300 million and is eligible to receive potential development, regulatory and commercial milestones up to \$740 million.

About Arrowhead Pharmaceuticals

Arrowhead Pharmaceuticals develops medicines that treat intractable diseases by silencing the genes that cause them. Using a broad portfolio of RNA chemistries and efficient modes of delivery, Arrowhead therapies trigger the RNA interference mechanism to induce rapid, deep, and durable knockdown of target genes. RNA interference, or RNAi, is a mechanism present in living cells that inhibits the expression of a specific gene, thereby affecting the production of a specific protein. Arrowhead's RNAi-based therapeutics leverage this natural pathway of gene silencing.

For more information, please visit www.arrowheadpharma.com, or follow us on Twitter [@ArrowheadPharma](https://twitter.com/ArrowheadPharma). To be added to the Company's email list and receive news directly, please visit <http://ir.arrowheadpharma.com/email-alerts>.

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This news release contains forward-looking statements within the meaning of the "safe harbor" provisions of the Private Securities Litigation Reform Act of 1995. Any statements contained in this release except for historical information may be deemed to be forward-looking statements. Without limiting the generality of the foregoing, words such as "may," "will," "expect," "believe," "anticipate," "hope," "intend," "plan," "project," "could," "estimate," "continue," "target," "forecast" or "continue" or the negative of these words or other variations thereof or comparable terminology are intended to identify such forward-looking statements. In addition, any statements that refer to projections of our future financial performance, trends in our business, expectations for our product pipeline or product candidates, including anticipated regulatory submissions and clinical program results, prospects, or benefits of our collaborations with other companies, or other characterizations of future events or circumstances are forward-looking statements. These forward-looking statements include, but are not limited to, statements about the initiation, timing, progress and results of our preclinical studies and clinical trials, and our research and development programs; our expectations regarding the potential benefits of the partnership, licensing and/or collaboration arrangements and other strategic arrangements and transactions we have entered into or may enter into in the future; our beliefs and expectations regarding milestone, royalty or other payments that could be due to or from third parties under existing agreements; and our estimates regarding future revenues, research and development expenses, capital requirements and payments to third parties. These statements are based upon our current expectations and speak only as of the date hereof. Our actual results may differ materially and adversely from those expressed in any forward-looking statements as a result of numerous factors and uncertainties, including the impact of the ongoing COVID-19 pandemic on our business, the safety and efficacy of our product candidates, decisions of regulatory authorities and the timing thereof, the duration and impact of regulatory delays in our clinical programs, our ability to finance our operations, the likelihood and timing of the receipt of future milestone and licensing fees, the future success of our scientific studies, our ability to successfully develop and commercialize drug candidates, the timing for starting and completing clinical trials, rapid technological change in our markets, the enforcement of our intellectual property rights, and the other risks and uncertainties described in our most recent Annual Report on Form 10-K, subsequent Quarterly Reports on Form 10-Q and other documents filed with the Securities and Exchange Commission from time to time. We assume no obligation to update or revise forward-looking statements to reflect new events or circumstances.

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