



Arrowhead and Takeda Announce Topline Results from SEQUOIA Phase 2 Study of Fazirsiran in Patients with Alpha-1 Antitrypsin Deficiency-Associated Liver Disease

January 9, 2023

- **Fibrosis regression observed in 50% of patients receiving fazirsiran**
- **Median reductions of 94% of Z-AAT accumulation in the liver and mean reduction of 68% in histologic globule burden**
- **Treatment emergent adverse events were generally well balanced between fazirsiran and placebo groups**
- **Results consistent with AROAAT-2002 open-label study previously published in *The New England Journal of Medicine***
- **Arrowhead to host webcast investor call today, January 9, 2023, at 8:30 a.m. ET**

OSAKA, Japan, CAMBRIDGE, Massachusetts, and Pasadena, CALIF., Jan. 9, 2023 – Takeda ([TSE:4502/NYSE:TAK](#)) and Arrowhead Pharmaceuticals Inc. (NASDAQ: ARWR) today announced topline 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 companies also provided an outline of a Phase 3 study that was co-developed by Takeda and Arrowhead and will be conducted by Takeda. Additional SEQUOIA study results are planned to be presented at a future medical meeting and submitted for publication. Arrowhead will host a webcast call for investors today, January 9, 2023, at 8:30 a.m. ET to review the Phase 2 data. To register for the webcast, visit the [Events and Presentations](#) page under the Investors section of www.arrowheadpharma.com.

"Currently there is no treatment for liver disease from alpha-1 antitrypsin deficiency. The results presented today from the SEQUOIA study are highly encouraging to physicians and patients in need of a safe and effective therapy for this rare genetic condition," said Virginia Clark, M.D., M.S., University of Florida, Division of Gastroenterology, Hepatology, and Nutrition. "We believe that the accumulation of misfolded protein in the liver is an important step in the development of liver disease, so therapies that block protein production may allow the liver to clear the toxic protein and potentially heal."

Key SEQUOIA Results

Patients receiving 25 mg, 100 mg, or 200 mg of fazirsiran who had baseline fibrosis (n=16) demonstrated a dose dependent mean reduction in serum mutant alpha-1 antitrypsin protein (Z-AAT) concentration at week 48 of 74%, 89%, and 94%, respectively. All three doses led to a dramatic reduction in total liver Z-AAT with a median reduction of 94% at the postbaseline liver biopsy visit. In addition, PAS-D globule burden, a histological measure of Z-AAT accumulation, was reduced from a baseline mean of 5.9 to a post baseline mean of 2.3 at the postbaseline liver biopsy visit. Improvement in portal inflammation was observed in 42% of patients while only 7% showed worsening. Lastly, 50% of patients achieved an improvement in fibrosis of at least one point by METAVIR stage.

In contrast, by week 48 patients receiving placebo who had baseline fibrosis (n=9) saw no meaningful changes from baseline in serum Z-AAT, a 26% increase in liver Z-AAT, no meaningful change in PAS-D globule burden, no placebo patients experienced an improvement in portal inflammation while 44% experienced worsening, and 22% of placebo patients experienced worsening while 38% experienced an improvement in fibrosis at the postbaseline liver biopsy visit. This finding highlights the known variability on histologic fibrosis assessment. With a larger sample size, like in the planned Phase 3 study, the rate of improvement in patients receiving placebo may more closely approximate results from natural history studies of untreated patients with AATD-LD.

Fazirsiran has been well tolerated with treatment emergent adverse events reported to date generally well balanced between fazirsiran and placebo groups. There were no treatment-emergent adverse events leading to drug discontinuation, dose interruptions, or premature study withdrawals in any study group. Compared with placebo, no dose-dependent or clinically meaningful changes were observed in pulmonary function tests over 1 year with fazirsiran.

These data are consistent with results from the Phase 2 AROAAT-2002 open-label study that were [previously published in *The New England Journal of Medicine*](#). Additional details on the SEQUOIA study will be provided at a future scientific meeting.

"Patients receiving fazirsiran showed dramatic and encouraging changes in several markers of disease during the treatment period, including fibrosis, Z-AAT accumulation in the liver, PAS-D globule burden, liver enzymes, and other important markers," said Javier San Martin, M.D., Chief Medical Officer at Arrowhead. "These consistent Phase 2 data give us additional confidence that fazirsiran has the potential in the future to provide physicians with the first therapeutic strategy to treat AATD associated liver disease in their patients. We would like to thank all of the patients and investigators who participated in the SEQUOIA study, and our valued partners at Takeda for their support and collaboration."

Advancing the Fazirsiran Phase 3 Study

This month Takeda plans to initiate TAK-999-3001, a randomized, double-blind, placebo-controlled, Phase 3 study to evaluate the efficacy and safety of fazirsiran in the treatment of alpha-1 antitrypsin deficiency-associated liver disease with METAVIR stage F2 to F4 fibrosis. Approximately 160 patients will be randomized 1:1 to receive fazirsiran or placebo. The primary endpoint of this 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.

"These compelling Phase 2 data confirm our belief that an RNAi therapy like fazirsiran has the potential to reverse liver disease associated with AATD," said Chinwe Ukomadu, M.D., Ph.D., Head, Gastroenterology Therapeutic Area Unit at Takeda. "We are now applying Takeda's deep expertise in gastroenterology to execute the Phase 3 study as we work with great purpose and efficiency to bring fazirsiran to patients."

About Fazirsiran

Fazirsiran is a potential first-in-class investigational RNA interference (RNAi) therapy designed to reduce the production of mutant alpha-1 antitrypsin protein (Z-AAT) as a potential treatment for the rare genetic liver disease associated with AATD. Z-AAT accumulation is believed to be the cause of progressive liver disease in patients with AATD. Reducing production of the inflammatory 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 (BTD) in July 2021 and Orphan Drug Designation in February 2018 for the treatment of AATD-LD from the US FDA.

About SEQUOIA Phase 2 Study

SEQUOIA ([NCT03945292](#)) is a placebo-controlled, multi-dose, Phase 2 study to determine the safety, tolerability, and pharmacodynamic effect of fazirsiran (TAK-999, ARO-AAT) in 42 patients with AATD-LD. Patients were enrolled in three cohorts to receive fazirsiran at doses of 25 mg (n=9), 100 mg (n=8), 200 mg (n=9), or matching placebo (n=14). All eligible participants received a pre-dose biopsy and those with baseline fibrosis (n=25) received a post-baseline biopsy at week 48. Treated participants were also offered the opportunity to continue treatment in an open-label extension (OLE).

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 Alpha-1 Antitrypsin Deficiency-Associated Liver Disease

Alpha-1 Antitrypsin Deficiency (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

Takeda is a global, values-based, R&D-driven biopharmaceutical leader headquartered in Japan, committed to discover and deliver life-transforming treatments, guided by our commitment to patients, our people and the planet. Takeda focuses its R&D efforts on four therapeutic areas: Oncology, Rare Genetics and Hematology, Neuroscience and Gastroenterology (GI), with expertise in immune and inflammatory diseases. We also make targeted R&D investments in Plasma-Derived Therapies and Vaccines. We are focusing on developing highly innovative medicines that contribute to making a difference in people's lives by advancing the frontier of new treatment options and leveraging our enhanced collaborative R&D engine and capabilities to create a robust, modality-diverse pipeline. Our employees are committed to improving quality of life for patients and to working with our partners in health care in approximately 80 countries and regions. For more information, visit <https://www.takeda.com>.

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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Takeda Forward-Looking Statements

This press release and any materials distributed in connection with this press release may contain forward-looking statements, beliefs or opinions regarding Takeda's future business, future position and results of operations, including estimates, forecasts, targets and plans for Takeda. Without limitation, forward-looking statements often include words such as "targets", "plans", "believes", "hopes", "continues", "expects", "aims", "intends", "ensures", "will", "may", "should", "would", "could" "anticipates", "estimates", "projects" or similar expressions or the negative thereof. These forward-looking statements are based on assumptions about many important factors, including the following, which could cause actual results to differ materially from those expressed or implied by the forward-looking statements: the economic circumstances surrounding Takeda's global business, including general economic conditions in Japan and the United States; competitive pressures and developments; changes to applicable laws and regulations, including global health care reforms; challenges inherent in new product development, including uncertainty of clinical success and decisions of regulatory authorities and the timing thereof; uncertainty of commercial success for new and existing products; manufacturing difficulties or delays; fluctuations in interest and currency exchange rates; claims or concerns regarding the safety or efficacy of marketed products or product candidates; the impact of health crises, like the novel coronavirus pandemic, on Takeda and its customers and suppliers, including foreign governments in countries in which Takeda operates, or on other facets of its business; the timing and impact of post-merger integration efforts with acquired companies; the ability to divest assets that are not core to Takeda's operations and the timing of any such divestment(s); and other factors identified in Takeda's most recent Annual Report on Form 20-F and Takeda's other reports filed with the U.S. Securities and Exchange Commission, available on Takeda's website at: <https://www.takeda.com/investors/sec-filings/> or at www.sec.gov. Takeda does not undertake to update any of the forward-looking statements contained in this press release or any other forward-looking statements it may make, except as required by law or stock exchange rule. Past performance is not an indicator of future results and the results or statements of Takeda in this press release may not be indicative of, and are not an estimate, forecast, guarantee or projection of Takeda's future results.

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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," or "continue" 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 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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References:

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Strnad P. Reduction of intra-hepatic Z-AAT synthesis by fazirsiran decreases globule burden and improves histological measures of liver disease in adults with alpha-1 antitrypsin deficiency. Poster presented at: The International Liver Congress; June 2022; London, UK