



Results from Phase 2 Study of Fazirsiran in Patients with Alpha-1 Antitrypsin Deficiency Published in New England Journal of Medicine

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- Fibrosis regression observed in 58% (7 of 12) of patients receiving 200 mg fazirsiran
- Median reduction of 83% of Z-AAT accumulation in the liver
- Reduction of 69% in histologic globule burden
- Substantial and sustained improvements in clinically relevant biomarkers of liver health

Osaka, JAPAN, and Pasadena, CALIF., June 27, 2022 – Takeda ([TSE:4502/NYSE:TAK](#)) (“Takeda”) and Arrowhead Pharmaceuticals Inc. (NASDAQ: ARWR) today announced that results from a Phase 2 clinical study (AROAT-2002) of investigational fazirsiran (TAK-999/ARO-AAT) for the treatment of liver disease associated with alpha-1 antitrypsin deficiency (AATD) were recently published in the New England Journal of Medicine (NEJM) and presented in an oral presentation at The International Liver Congress™ 2022 - The Annual Meeting of the European Association for the Study of the Liver (EASL). [The NEJM article was published online ahead of print](#) and is titled, “Fazirsiran for Liver Disease Associated with Alpha-1 Antitrypsin Deficiency.” The EASL presentation was titled, “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.”

“There is currently no specific treatment for liver disease associated with AATD. The results from the AROAT-2002 study provide multiple lines of evidence that preexisting liver damage in these patients may be meaningfully improved following treatment with fazirsiran,” said Pavel Strnad, M.D., Professor at University Hospital RWTH Aachen and principal investigator of the AROAT-2002 study who presented the data at EASL. “Specifically, the improvements in histological globule burden, reduction in histological signs of portal inflammation, normalization of elevated liver enzymes, and improvement in liver fibrosis are all encouraging indicators that fazirsiran may rapidly ameliorate liver injury. It also speaks to the exciting innovation going on in the field, that an siRNA therapeutic specifically targeted into the liver has the potential to address a previously untreatable liver disease”

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 from the US FDA.

“The exciting data on fazirsiran treatment from the open label AROAT-2002 Phase 2 study in patients with AATD liver disease suggest a treatment effect and the potential to improve multiple downstream markers of liver health. We are also nearing completion of the Phase 2 SEQUOIA study and we look forward to further assessing the potential of fazirsiran in this larger placebo-controlled study,” said Javier San Martin, M.D., Chief Medical Officer at Arrowhead. “Fazirsiran has shown a high level of activity across all patients studied and is representative of how the RNA interference pathway can be leveraged to reliably and consistently silence gene expression and potentially have a positive impact on patients with various genetic diseases.”

“These early results demonstrate the potential for an RNAi therapy like fazirsiran to reverse liver disease in patients with AATD liver disease and we are hopeful fazirsiran will one day help patients avoid the need to undergo liver transplantation,” said Chinwe Ukomadu, M.D., Ph.D., Head, Gastroenterology Therapeutic Area Unit at Takeda. “We look forward to continuing our successful collaboration with Arrowhead and applying Takeda’s long history of innovation in gastroenterology to initiate a Phase 3 study of fazirsiran.”

About The Phase 2 AROAT-2002 Study

AROAT-2002 ([NCT03946449](#)) is a pilot open-label, multi-dose, Phase 2 study to assess the response to fazirsiran in 16 patients with AATD associated liver disease and baseline liver fibrosis. Patients were enrolled in three cohorts. All eligible participants received a pre-dose biopsy and an end of study biopsy. Treated participants were also offered the opportunity to continue treatment in an open-label extension (OLE). Including the OLE, interim assessments were made after 6 months and 18 months (cohorts 1, 1b), and 12 months and 24 months (cohort 2) of treatment with fazirsiran.

Efficacy Results

All patients (n=16) had reductions in accumulated total mutant AAT protein (Z-AAT) in the liver (median percentage change at week 24 or 48, -83.3%; 95% confidence interval, -89.7 to -76.4). A substantial mean reduction from baseline in serum Z-AAT concentration was observed in all cohorts, with a nadir of -90±5% in the 200-mg cohort and -87±6% in the 100-mg cohort at week 6. Reductions in liver Z-AAT concentrations were associated with histologic improvements in inflammation.

Most patients had a high histologic PAS-D globule burden at baseline (mean score, 7.4; scores range from 0 to 9, with higher scores indicating a greater globule burden). After treatment, all patients had a decreased globule burden, with the mean score decreasing to 2.3 at week 24 or 48 (69% reduction).

Biomarkers of liver injury were also reduced. At baseline, mean ALT concentrations were above the upper limit of the normal range in all cohorts. After treatment, ALT concentrations decreased in all cohorts from week 16 through week 52. All 12 patients with ALT concentrations above the upper limit of the normal range at baseline had reductions to normal concentrations at week 52.

Regression of fibrosis of at least 1 stage occurred in 7 of 12 patients receiving the 200-mg dose (cohorts 1 and 2), including 2 patients with cirrhosis, and in none of 3 patients with evaluable biopsies who received the 100-mg dose (cohort 1b). Two patients in cohort 2 had progression of fibrosis from

baseline to week 48 (both from F2 to F3), although both had profound reductions in PAS-D globule burden (scores of 9 and 4 at baseline and 0 for both at week 48) and reduced ALT and γ -glutamyltransferase concentrations with treatment.

Safety Results

Fazirsiran was generally well tolerated. Over a period of 1.5 years, there were no deaths, discontinuations of treatment with fazirsiran, or dose interruptions. The most common adverse events that emerged or worsened after the first administration of fazirsiran were arthralgia and increased concentrations of blood creatinine kinase. There were no apparent dose dependent increases in the frequency or severity of adverse events. Four serious adverse events, all moderate in severity, were reported in cohorts 1 and 2, all of which resolved with all four patients continuing to receive fazirsiran treatment in the extension period.

So far, there have been no major pulmonary adverse events resulting in drug or trial discontinuations. Four of the six patients who entered the trial while receiving AAT augmentation therapy had a history of emphysema, and none reported exacerbations.

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-Associated Deficiency

Alpha-1 Antitrypsin-Associated 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. 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 Pharmaceutical Company Limited

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). 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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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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References:

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Srnad 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