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Poster 4455

LONG-TERM SAFETY AND EFFICACY OF FAZIRSIRAN IN PATIENTS WITH ALPHA-1 ANTITRYPSIN DEFICIENCY-ASSOCIATED LIVER DISEASE ENROLLED IN THE PHASE 2 PLACEBO-CONTROLLED SEQUOIA TRIAL

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INTRODUCTION

- Alpha-1 antitrypsin deficiency (AATD) is a rare genetic disease that may lead to the development of liver and/or lung disease.[1]
- The most severe AATD phenotypes are associated with the protease inhibitor (Pi)*ZZ genotype, which causes the accumulation of misfolded alpha-1 antitrypsin (Z-AAT) in hepatocytes and increased risk of developing liver disease.[1]
- Currently, there are no approved pharmacological therapies available for AATD-associated liver disease; consequently, liver transplantation is recommended in patients with AATD and advanced liver cirrhosis or failure.[2]
- Fazirsiran is an investigational, small interfering RNA therapy undergoing phase 3 development in patients with AATD-associated liver disease.[3,4]
- In a previous analysis of the phase 2, double-blind, randomized SEQUOIA trial (NCT03945292), fazirsiran reduced serum and liver concentrations of Z-AAT in a dose-dependent manner and reduced hepatic globule burden compared with placebo.[4]

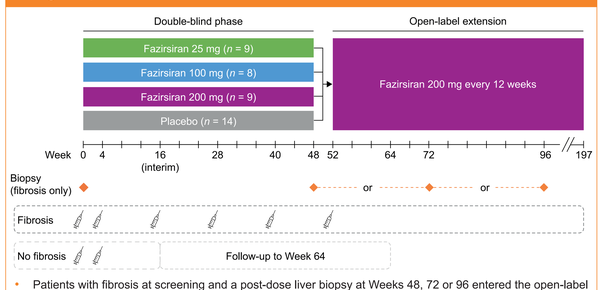
AIM

- To evaluate the long-term (up to 197 weeks) safety and efficacy of fazirsiran in patients enrolled in the open-label extension of the SEQUOIA trial.

METHOD

Figure 1. Study design

The SEQUOIA trial enrolled 40 adults with a Pi*ZZ genotype who were randomized to receive fazirsiran 25, 100 or 200 mg or placebo during the double-blind phase and fazirsiran 200 mg during the open-label extension



- Patients with fibrosis at screening and a post-dose liver biopsy at Weeks 48, 72 or 96 entered the open-label extension phase and received fazirsiran 200 mg every 12 weeks for a total treatment period of ≤ 197 weeks.
  - Additional methodological detail has been described previously.[4]
- Endpoints measured from baseline (last measurement before the first dose of open-label fazirsiran) to the end of the open-label extension (end of study) included serum Z-AAT levels, laboratory measures of liver health, safety outcomes and pulmonary function.

Figure adapted from Clark *et al.*[4] End of study was the last visit in the study for any patient who did not discontinue early.

RESULTS

Table 1. Characteristics of patients who entered the open-label extension[a]

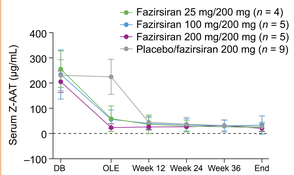
Overall, 23 patients received ≥ 1 dose of fazirsiran 200 mg during the open-label extension. During the double-blind phase, these patients had previously received fazirsiran 25 mg (*n* = 4), 100 mg (*n* = 5), 200 mg (*n* = 5) or placebo (*n* = 9)

Characteristic	Fazirsiran 25 mg/ 200 mg (*n* = 4)	Fazirsiran 100 mg/ 200 mg (*n* = 5)	Fazirsiran 200 mg/ 200 mg (*n* = 5)	Fazirsiran pooled[b] (*n* = 14)	Placebo/ fazirsiran 200 mg (*n* = 9)
Age, years, mean (SD)	65.5 (6.0)	41.2 (10.2)	55.4 (5.4)	53.2 (12.4)	58.3 (9.6)
Male, *n* (%)	2 (50.0)	2 (40.0)	2 (40.0)	6 (42.9)	8 (88.9)
BMI, kg/m², mean (SD)	27.8 (3.7)	32.5 (9.0)	29.0 (6.8)	29.9 (6.8)	31.6 (8.0)
Fibrosis at screening (local read), *n* (%)	4 (100.0)	5 (100.0)	5 (100.0)	14 (100.0)	9 (100.0)
Adjudicated METAVIR fibrosis stage (central read), *n* (%)					
F0	1 (25.0)	0	0	1 (7.1)	1 (11.1)
F1	0	3 (60.0)	3 (60.0)	6 (42.9)	3 (33.3)
F2	3 (75.0)	1 (20.0)	1 (20.0)	5 (35.7)	5 (55.6)
F3	0	1 (20.0)	1 (20.0)	2 (14.3)	0
F4	0	0	0	0	0
ppFEV$_1$,%, post-bronchodilation, mean (SD)	96.1 (11.5)	98.2 (5.6)	95.4 (18.1)	96.4 (12.7)	91.4 (11.2)
AAT augmentation therapy, *n* (%)	3 (75.0)	0	2 (40.0)	5 (35.7)	2 (22.2)
Treatment duration, weeks, median (range)					
Open-label extension	24.4 (23.0–36.0)	35.1 (34.0–46.0)	35.1 (23.0–38.0)	35.1 (23.0–46.0)	35.3 (0–41.0)
Total (double-blind phase and open-label extension)	117.5 (101.0–136.0)	113.3 (101.0–161.0)	126.0 (66.0–183.0)	118.1 (66.0–183.0)	111.1 (98.0–197.0)

[a]Patient characteristics were recorded at the start of the double-blind phase baseline. [b]Pooled group of patients from the fazirsiran 25 mg/200 mg, fazirsiran 100 mg/200 mg and fazirsiran 200 mg/200 mg groups.

Figure 2. Change in serum Z-AAT levels over time

Serum Z-AAT levels in the placebo/fazirsiran 200 mg group decreased by 85.5% from the open-label extension baseline to the end of the study

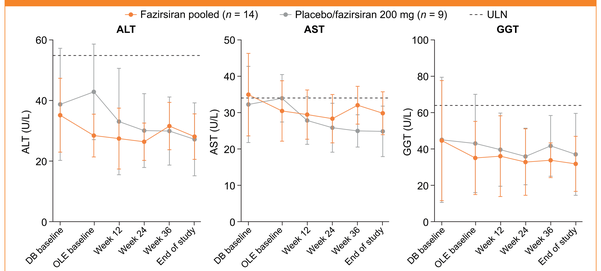


Serum Z-AAT (µg/mL)	Open-label extension baseline, mean (SD)	End of study, mean (SD)	Percentage change from open-label extension baseline to end of study, mean (SD)
Fazirsiran 25 mg/ 200 mg (*n* = 4)	59.0 (50.4)	23.7 (16.9)	−55.1 (24.1)
Fazirsiran 100 mg/ 200 mg (*n* = 5)	56.2 (37.7)	33.4 (36.3)	−49.1 (26.7)
Fazirsiran 200 mg/ 200 mg (*n* = 5)	23.7 (15.4)	20.3 (11.7)	−8.5 (33.3)
Fazirsiran pooled (*n* = 14)	45.4 (37.1)	25.9 (23.4)	−36.3 (34.1)
Placebo/fazirsiran 200 mg (*n* = 9)	224.7 (69.9)	26.7 (18.6)	−85.5 (13.1)

- Extended use of fazirsiran 200 mg every 12 weeks throughout the open-label extension resulted in sustained reductions in serum Z-AAT in the fazirsiran 200 mg/200 mg group and further reductions of serum Z-AAT in the fazirsiran 25 mg/200 mg and 100 mg/200 mg groups.

Figure 3. Changes in laboratory measures of liver health over time

ALT, AST and GGT levels improved in the placebo/fazirsiran 200 mg group during the open-label extension



Laboratory measure, U/L, mean (SD)	Fazirsiran pooled (*n* = 14)		Placebo/fazirsiran 200 mg (*n* = 9)	
	Open-label extension baseline	Change from baseline to end of study	Open-label extension baseline	Change from baseline to end of study
ALT	*n* = 14 28.4 (7.1)	*n* = 12 −0.2 (8.1)	*n* = 9 42.9 (15.9)	*n* = 7 −15.7 (12.2)
AST	*n* = 14 30.5 (8.4)	*n* = 13 0.7 (7.1)	*n* = 9 34.0 (6.6)	*n* = 7 −8.6 (9.8)
GGT	*n* = 14 35.0 (20.2)	*n* = 13 −3.2 (10.6)	*n* = 9 43.0 (27.2)	*n* = 7 −8.0 (9.1)

Error bars show ± standard deviation.

Table 2. Safety outcomes

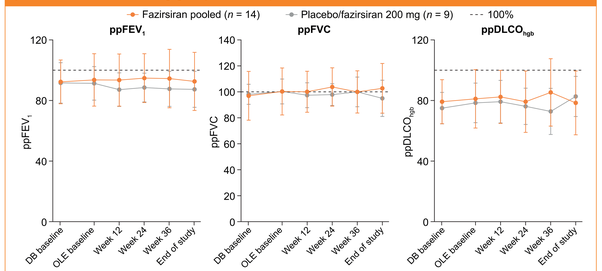
Overall, 20 patients reported a treatment-emergent adverse event during the open-label extension; of those, most were mild or moderate and one led to study withdrawal

TEAEs, *n* (%)	Fazirsiran pooled (*n* = 14)	Placebo/fazirsiran 200 mg (*n* = 9)
TEAEs	11 (78.6)	9 (100.0)
TEAEs experienced by at least 2 patients		
COVID-19	2 (14.3)	2 (22.2)
Nausea	2 (14.3)	1 (11.1)
Diarrhea	1 (7.1)	1 (11.1)
Dyspnea (exertional)	0	2 (22.2)
Fatigue	2 (14.3)	0
Headache	2 (14.3)	0
Nasopharyngitis	2 (14.3)	0
Treatment-related TEAEs	6 (42.9)	2 (22.2)
Serious TEAEs	3 (21.4)	1 (11.1)
TEAEs that led to treatment discontinuation, dose interruptions or study discontinuation	0	1 (11.1)[a]
TEAEs that caused deaths	0	0

[a]A 72-year-old male with liver fibrosis (centrally adjudicated as F1 at baseline and F2 at the Week 72 post-dose liver biopsy during the double-blind phase) in the placebo/fazirsiran 200 mg group withdrew from the study during the open-label extension. Relevant medical history included AATD with mild cylindrical bronchiectasis, as well as hepatic involvement, migraines, sinus bradycardia, gastroesophageal reflux disease and pancreatitis. After one dose of fazirsiran 200 mg in the open-label extension, the patient had four TEAEs that led to treatment discontinuation; these TEAEs included moderate chest pain, moderate chest discomfort, moderate left atrial enlargement (none of these TEAEs were reported in any other patient) and mild dizziness (reported in one other patient in the fazirsiran 25 mg/200 mg group). All TEAEs that led to treatment discontinuation were nonserious and assessed as possibly related to treatment.

Figure 4. Changes in pulmonary function tests over time

Mean percent predicted pulmonary function remained stable in the fazirsiran pooled and placebo/fazirsiran 200 mg groups in the open-label extension



Endpoint, mean (SD)	Fazirsiran pooled (*n* = 14)		Placebo/fazirsiran 200 mg (*n* = 9)	
	Open-label extension baseline	Change from baseline to end of study	Open-label extension baseline	Change from baseline to end of study
ppFEV$_1$	*n* = 14 94.1 (17.6)	*n* = 14 −0.9 (6.0)	*n* = 9 91.8 (11.2)	*n* = 8 −3.8 (9.4)
ppFVC	*n* = 12 100.8 (18.4)	*n* = 12 2.4 (5.5)	*n* = 8 100.9 (9.7)	*n* = 7 −2.7 (10.8)
ppDLCO$_{hgb}$	*n* = 14 79.8 (18.6)	*n* = 12 0 (9.2)	*n* = 9 77.8 (14.2)	*n* = 7 −2.8 (6.1)

Error bars show ± standard deviation.

CONCLUSIONS

- Fazirsiran showed sustained improvements in serum Z-AAT levels and laboratory measures, and long-term safety in patients with AATD-associated liver disease during the open-label extension.
- Extended use of fazirsiran 200 mg every 12 weeks throughout the open-label extension resulted in sustained reductions in serum Z-AAT levels in the fazirsiran 200 mg/200 mg group, further reductions in the fazirsiran 25 mg/200 mg and fazirsiran 100 mg/200 mg groups, and an 85.5% mean reduction in the placebo/fazirsiran 200 mg group.
- In the fazirsiran 200 mg open-label extension, there was a trend towards improved laboratory measures of liver health, stable pulmonary function and a safety profile that supports further clinical development of fazirsiran in patients with AATD-associated liver disease.

ABBREVIATIONS

AAT, alpha-1 antitrypsin; AATD, alpha-1 antitrypsin deficiency; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; DB, double-blind; GGT, gamma-glutamyl transferase; METAVIR, Meta-analysis of Histological Data in Viral Hepatitis; OLE, open-label extension; Pi, protease inhibitor; ppDLCO$_{hgb}$, percent predicted diffusing capacity of the lung for carbon monoxide adjusted for hemoglobin; ppFEV$_1$, percent predicted forced expiratory volume in 1 second; ppFVC, percent predicted forced vital capacity; SD, standard deviation; TEAE, treatment-emergent adverse event; ULN, upper limit of normal; Z-AAT, misfolded alpha-1 antitrypsin.

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