Belcesiran was Well Tolerated and Reduced Serum AAT Levels in Healthy Volunteers (Phase 1 Interim Results)

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BACKGROUND

Alpha-1 antitrypsin (AAT) is a 52-kilodalton soluble plasma protein synthesized and secreted primarily by hepatocytes. Its main function is to protect normal body tissue from damage by neutrophil proteolytic enzymes, which can degrade lung elastin and damage bronchial and alveolar wall integrity.

Alpha-1 antitrypsin deficiency (AATD) is caused by inherited autosomal mutations in the *SERPINA1* gene resulting in a mutant AAT that is prone to misfolding and aggregation in hepatocytes. The impaired degradation of the aggregated protein leads to a toxic accumulation in the liver, predisposing patients to AATD-associated liver disease (AATLD). Patients with AATLD can progress to liver fibrosis, cirrhosis, or hepatocellular carcinoma. Whereas the pulmonary complications of AATD can be treated with infusion of human plasma-derived AAT from healthy donors to supplement circulating AAT concentrations (augmentation therapy), the only potential treatment available for AATLD is liver transplantation.

Belcesiran is an *N*-acetyl-galactosamine (GalNAc)-conjugated oligonucleotide, which enables specific delivery to the liver after subcutaneous administration and is intended to reduce levels of AAT accumulation in hepatocytes of patients with AATLD. This Phase 1 clinical study of belcesiran evaluated the safety, tolerability, and effect on serum AAT concentrations in healthy adults.

STUDY DESIGN AND METHODS

This is a first-in-human, placebo-controlled (2:1 active vs. placebo), single ascending-dose study in healthy volunteers (HVs). A validated, standard-of-care quantitative nephelometry assay was used to measure serum AAT levels. Repeat measurements of spirometry and diffusing capacity of the lungs for carbon monoxide (DLCO) were performed in every HV to monitor pulmonary function.

Key Inclusion Criteria:

- Overtly healthy males or females, 18-55 years, non-smoking, serum AAT >100 mg/dL and forced expiratory volume in 1 second (FEV1) ≥85% of predicted with FEV1/FVC (forced vital capacity) ≥ 0.7

Key Exclusion Criteria:

- Presence of any condition/comorbidities that would interfere with study compliance, data interpretation, or affect participant safety
- Alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma glutamyl transferase (GGT), total bilirubin, or alkaline phosphatase (ALP) levels outside of the normal reference range

RESULTS

Thirty HVs in 5 cohorts (0.1, 1.0, 3.0, 6.0, 12.0 mg/kg; 4 active: 2 placebo in each cohort) were dosed and completed their treatment period (EOT; Day 57). All 16 HVs in the ≥ 1.0 mg/kg cohorts who received belcesiran entered and will remain in a conditional follow-up period after EOT until their AAT concentrations normalize or return to ≥ 80% of baseline.

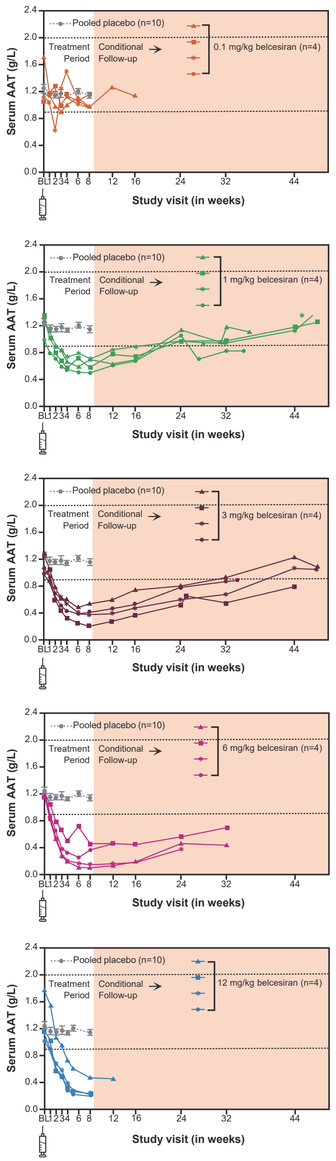
Table 1: Baseline Characteristics

Baseline characteristics of HVs demonstrate similar lung function and serum AAT levels. (Table 1)

Baseline Characteristic	Cohort 1 (0.1 mg/kg) n=4	Cohort 2 (1.0 mg/kg) n=4	Cohort 3 (3.0 mg/kg) n=4	Cohort 4 (6.0 mg/kg) n=4	Cohort 5 (12.0 mg/kg) n=4	Placebo n=10	Total n=30
Age (years), (min-max)	44.8 (38-51)	33.3 (23-52)	37.8 (28-53)	34.8 (18-54)	40.3 (29-51)	33.8 (22-44)	36.7 (18-54)
Sex (Male : Female)	4:0	3:1	3:1	4:0	3:1	10:0	27:3
Race (White : Asian : Other)	4:0:0	3:1:0	1:0:3	2:1:1	4:0:0	5:3:2	19:5:6
Weight (kg)	84.2	75.7	73.6	82.7	83.5	74.4	78.1
Body mass index (kg/m^2)	25.3	26.3	24.7	26.2	26.3	24.2	25.2
% Predicted FEV1 (%)	96.99	108.35	99.42	108.42	104.99	104.20	103.82
% Predicted FVC (%)	102.22	105.31	102.96	108.41	104.77	107.08	105.51
FEV1/FVC Ratio	0.75	0.86	0.79	0.83	0.81	0.80	0.81
% Predicted DLCO (%)	107.97	115.34	113.92	105.16	109.00	112.40	110.98
Serum AAT level (g/L)	1.20	1.20	1.14	1.20	1.28	1.17	1.19

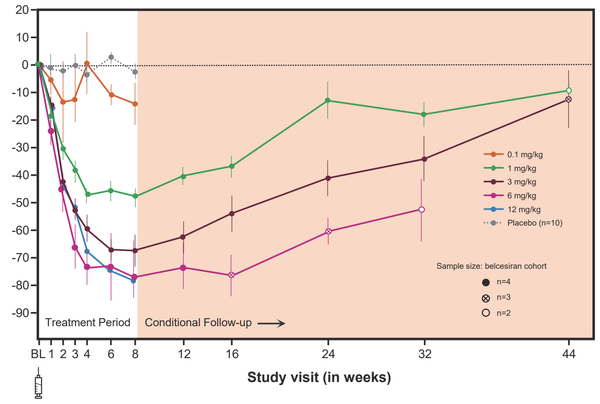
All measurements are expressed as means unless stated otherwise.

Figure 1: Individual Serum AAT Across Cohorts



Abbreviations: BL: baseline.
Conditional follow-up period shown in orange. Placebo expressed as mean±SE.

Figure 2: Mean Percent Reduction in Serum AAT Across Cohorts



Only timepoints with at least 2 observations were included.

- Single doses of belcesiran resulted in robust and dose-dependent reduction of serum AAT up to 6 mg/kg (Figure 1)
- Similar reductions were observed with the 6 mg/kg and 12 mg/kg doses
- At doses ≥ 1.0 mg/kg, the mean maximum reduction occurred ~8 weeks post dose (EOT; Figure 2)
- The % mean reduction from baseline at EOT was 14%, 48%, 67%, 77%, and 78% for 0.1, 1, 3, 6, and 12 mg/kg doses, respectively
- Two HVs had a maximum serum AAT reduction of ~90%; both received 6 mg/kg doses

Table 2: Safety Data

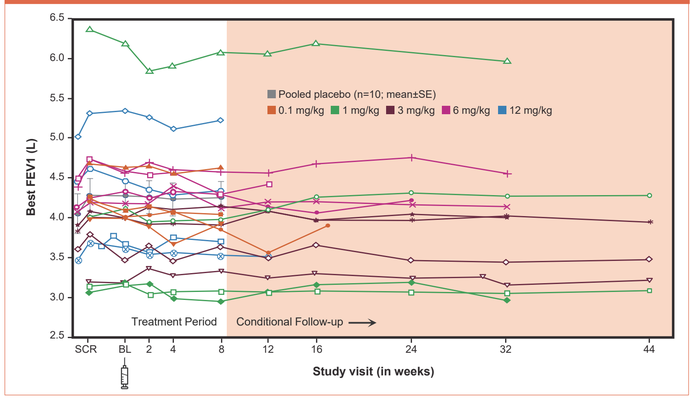
- No treatment-emergent SAEs were observed (Table 2)
- 42 TEAEs occurred in 23 HVs
- 39 TEAEs were graded as "mild" and 3 as "moderate" in 2 participants (common cold, gastroenteritis, and staphylococcal folliculitis) – all deemed "Not Related" and "Resolved"
- No dose-dependent increases in frequency or severity of TEAEs, or abnormalities in safety labs, ECGs, physical exams, or vital signs were observed

	Cohort 1 (0.1 mg/kg) n=4	Cohort 2 (1.0 mg/kg) n=4	Cohort 3 (3.0 mg/kg) n=4	Cohort 4 (6.0 mg/kg) n=4	Cohort 5 (12.0 mg/kg) n=4	Placebo n=10	Total n=30
Number (%) of HVs reporting ≥ 1 occurrence:							
Any TEAE	4 (100.0)	3 (75.0)	4 (100.0)	4 (100.0)	3 (75.0)	5 (50.0)	23 (76.7)
Mild TEAEs (Grade 1)	4 (100.0)	3 (75.0)	4 (100.0)	4 (100.0)	3 (75.0)	5 (50.0)	23 (76.7)
Moderate TEAEs (Grade 2)	1 (25.0)	0	0	1 (25.0)	0	0	2 (6.7)
Severe TEAEs (Grade ≥3)	0	0	0	0	0	0	0
Treatment-emergent SAEs	0	0	0	0	0	0	0
Drug-related TEAE*	2 (50.0)	3 (75.0)	2 (50.0)	3 (75.0)	2 (50.0)	1 (10.0)	13 (43.3)
HVs with protocol defined ISRs†	1 (25.0)	1 (25.0)	0	2 (50.0)	0	0	4 (13.3)

Abbreviations: ISR, injection site reaction; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

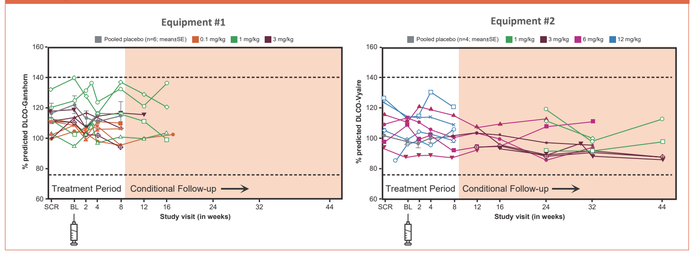
Note: TEAEs are defined as those adverse events (AEs) satisfying one of the following: have a start date on or after the administration of study drug; or occur prior to the administration of study drug and worsen in severity/grade or relationship to investigational medication after the administration of study drug.
*Drug-related TEAE is defined as any TEAE that is at least possibly related to study treatment (possibly related, probably related, and definitely related).
†Protocol defined ISRs = onset ≥ 4 hours postdose.

Figure 3: Individual Forced Expiratory Volume in 1 Second (FEV1) by Spirometry



SCR: screening; One HV in the lowest dose cohort had an AE of "common cold" in February 2020 coinciding with transient decline in FEV1 and was followed until resolution.

Figure 4: Individual Diffusing Capacity of the Lungs for Carbon Monoxide (DLCO) Stratified by Diagnostic Equipment



Observations were initially collected using the PowerCube Body+/Diff-FRC (Ganshorn Medizin Electronic GmbH) and later using the Vyntus One DL (Vyaire Medical). Some participants therefore have their DLCO measurements using the Ganshorn equipment during the early treatment period and the Vyaire equipment during the late treatment or conditional follow-up period. Horizontal dotted lines are the reference high and low for % predicted DLCO. The DLCO reference range is based on Modi P, Cascella M. Diffusing Capacity Of The Lungs For Carbon Monoxide. In: *StatPearls*. Treasure Island (FL): StatPearls Publishing; March 24, 2021.

- No clinically significant changes in lung function were noted on spirometry or DLCO (Figure 3, 4)
- No dose-dependent changes were noted in repeat measurements of any spirometry parameter
- All Percent Predicted DLCO repeat measurements remained within normal limits across all cohorts
- There were no clinically significant abnormalities in safety laboratory tests, including liver function tests
  - Four HVs had transient ALT elevations < 2 x ULN (upper limit of normal), and 1 HV in the 6 mg/kg cohort had a self-resolving ALT increase of up to 2.3 x ULN; all 5 HVs were asymptomatic
  - One HV (1 mg/kg) had transient AST elevations starting at the week 24 conditional follow-up visit that peaked at 4.7x ULN with normal total bilirubin and elevated C-reactive protein, after taking several medications for "flu-like illness"
  - In the highest dose cohort (12 mg/kg), there were no ALT or AST elevations above ULN
  - All HVs maintained normal liver synthetic and excretory function throughout follow-up

CONCLUSIONS

- In this interim analysis of the Phase 1 study (NCT04174118):
  - Single ascending doses of belcesiran in healthy volunteers (up to and including 12 mg/kg) appear to be safe and well tolerated
  - Normal lung function was maintained, based on repeat measurements of spirometry and DLCO
  - There were no clinically significant or apparent dose-dependent elevations in AST or ALT
  - Belcesiran demonstrated proof of mechanism with robust, dose-dependent reductions in serum AAT in up to the 6 mg/kg dose level, with a maximum individual reduction of 91%
- A Phase 2 study evaluating the safety and efficacy of belcesiran in individuals with alpha-1 antitrypsin deficiency-associated liver disease is ongoing (NCT04764448)

DISCLOSURES

EG is an advisor and/or speaker for AbbVie, Aligos, Arbutus, Arrowhead, Assembly, Avalia, Clear B Therapeutics, Dicerna, DrugFarm, Enanta, Finch Therapeutics, Gilead Sciences, GlaxoSmithKline, Janssen, Merck, Novartis, Roche and Vir Bio. FS and CS declare no conflict.

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