Efficacy of Alvelestat on SGRQ in Patients with AATD and Mild Airflow Limitation: A Pooled Analysis from two Phase 2 Studies

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Introduction

- Alpha-1 antitrypsin deficiency (AATD) patients with GOLD Grade 1 airflow limitation (FEV_1≥80%) have not been regularly included in AATD studies.
- Entrance criteria in RAPID study of augmentation was ≤70% FEV_1% predicted with a mean baseline of 43%.[1]
- In the 12-week ATALANTa study, in a younger treatment-naïve subpopulation with mild airflow limitation, alvelestat showed SGRQ improvements in the Total and Activity scores.
- SGRQ scores are impaired early in AATD patients and before patients meet spirometry criteria for COPD.[2]

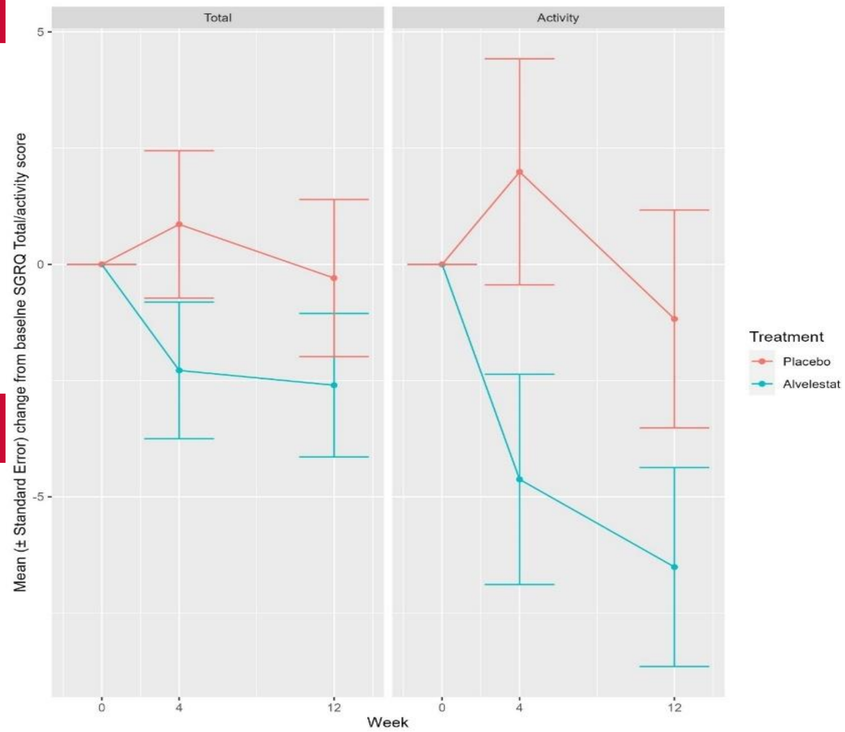
Methods

- A pooled analysis of two Phase 2 AATD studies of alvelestat (ASTRAEUS [NCT03636347] and ATALANTa [NCT03679598]) to determine the effect of 12 weeks of alvelestat treatment in patients with GOLD 1 airflow limitation at baseline on SGRQ Total and SGRQ Activity domain scores.
- Both 120 mg BID and 240 mg BID doses of alvelestat were included in the alvelestat group.
- Within-group and between-group effects on SGRQ were analysed using a mixed model repeated measures approach.

Results

- The pooled population included 39 patients (22 on alvelestat, 17 on placebo).
- Baseline demographics of the population are detailed in **Table 1**.
- A complete case analysis was performed whereby baseline and week 12 measurements were required (36 patients included: 20 alvelestat, 16 placebo).

Figure 1: Change from Baseline of SGRQ Total and SGRQ Activity Domain



- After 12 weeks of alvelestat treatment, there was a mean change from baseline of:
  - SGRQ Total domain score: -2.6 (95% CI: -5.76, 0.56; p=0.1).
  - SGRQ Activity domain score: -6.5 (95% CI: -10.87, -2.15; p=0.005).
- No changes observed for placebo (SGRQ Total: -0.29, SGRQ Activity: -1.17).
- Between group changes for both scores were numerically superior with alvelestat vs. placebo but not statistically significant (SGRQ Total -2.31, SGRQ Activity -5.34).
- A responder analysis of the proportion of patients achieving a clinically meaningful response using a threshold of 4 for SGRQ Total (validated in COPD) and 7.1 for SGRQ Activity (literature estimate in COPD[3]) is presented in **Table 2**. Changes were not significant between groups.

Table 1: Baseline Demographics

	ATALANTa N=22		ASTRAEUS N=17		Overall N=39	
Mean (SD)	Placebo N=10	Alvelestat N=12	Placebo N=7	Alvelestat N=10	Placebo N=17	Alvelestat N=22
Age	48.7 (11.1)	42.1 (12.4)	53.6 (8.14)	54.8 (7.90)	50.7 (10.0)	47.9 (12.2)
FEV_1 % predicted	100.5 (11.4)	97.0 (13.7)	92.5 (8.9)	90.8 (5.6)	91.5 (6.92)	98.6 (12.5)
Total SGRQ score	10.2 (8.9)	20.4 (17.5)	16.5 (13.2)	20.6 (21.6)	12.8 (11.0)	20.5 (19.0)
Activity domain SGRQ	13.7 (13.8)	27.1 (23.0)	19.3 (18.7)	31.7 (29.9)	16.0 (15.7)	29.2 (25.8)
N (%) Female	10 (100%)	11 (91.7%)	3 (42.9%)	8 (80.0%)	13 (76.5%)	19 (86.4%)

Table 2: Responder Analysis of SGRQ Total and Activity Scores for Clinically Meaningful Differences

	Placebo n/N (%)	Alvelestat n/N (%)
SGRQ Total Responder	5/16 (31.3%)	9/20 (45%)
SGRQ Activity Responder	4/16 (25%)	11/20 (55%)

Conclusions

- This was a pooled analysis of AATD patients with mild or no airflow limitation; patients not previously studied in RCTs.
- They still have elevated SGRQ scores compared with the controls in ECLIPSE.[4]
- Despite their mild disease, approximately half of patients achieved a clinically meaningful SGRQ response with alvelestat.
- Baseline imbalances across both studies mean that there may also have been a regression to the mean effect. The finding will seek to be confirmed in a planned Phase 3 study for alvelestat in AATD with:
  - Broad inclusion criteria to include patients with mild airflow disease and emphysema.
  - SGRQ Total score as primary endpoint for the US.

References

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2. Stockley J et al. Eur Respir J 2017; 49: 1602055.
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