Abstract #: 8383

Association of Biomarker Suppression with SGRQ and CAT in Patients with AATD Treated with Alvelestat: Results from the Treatment of Alpha-1-ANTitrypsin Deficiency (ATALANTa) Study

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Rationale

- Alvelestat is an oral inhibitor of human neutrophil elastase in development for AATD-associated lung disease.
- In an earlier Phase 2 study in Pi*ZZ AATD patients (ASTRAEUS; NCT03636347), an association was found between the extent of disease activity biomarker responses to alvelestat (including the elastin breakdown biomarker, desmosine) and improvement in the Saint Georges' Respiratory Questionnaire (SGRQ)-Activity Domain.[1]
- Alvelestat was further explored in the ATALANTa Phase 2 trial, which investigated alvelestat in a broader patient population, including Pi*SZ and by augmentation status.
- In patients not receiving augmentation, who were generally earlier in disease, trends to improvement in SGRQ-Total and significance for the Activity Domain were observed with alvelestat.
- The relationship of the SGRQ response to alvelestat was further explored in ATALANTa and extended to the COPD Assessment Test (CAT), which was not studied in ASTRAEUS.

Methods

- ATALANTa was a double-blind, placebo-controlled study evaluating the safety, tolerability and mechanistic effect of 120 mg bid alvelestat in patients with Pi*ZZ, Pi*SZ, or Pi*Null AATD (NCT03679598).
- ATALANTa was performed at 10 sites in USA, led by the University of Alabama (Birmingham) in collaboration with Mereo BioPharma plc.
- 63 participants (31 placebo; 32 alvelestat) enrolled; 46% on augmentation. 60 participants completed the 12-week study (31 placebo; 29 alvelestat).
- SGRQ and CAT assessed in the study. Biomarker responders defined as any reduction (>0%), or >5% reduction of desmosine from baseline.
- In a planned post-hoc analysis, the association of SGRQ-Total score (and the domain scores: Activity, Symptoms, Impacts) and CAT score with biomarker response was examined by fitting a linear mixed effects model, with change in SGRQ and CAT score as the outcome, and visit, treatment arm, biomarker responder status, and their interactions as covariates, as well as baseline score and a random effect for subject.

Acknowledgments

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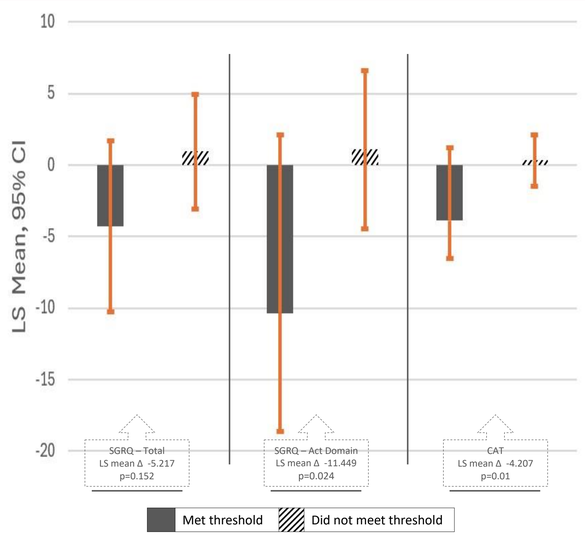
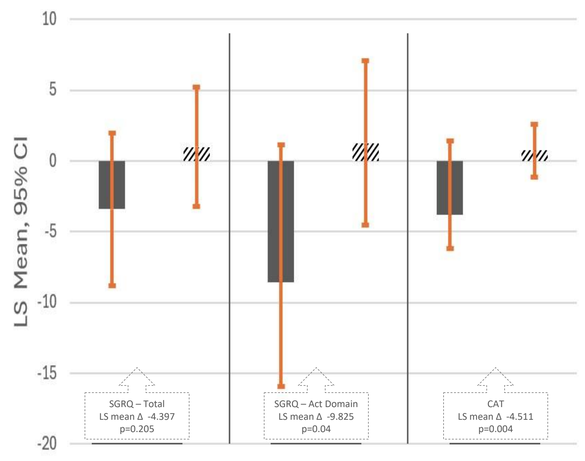
Alvelestat patients with >5% desmosine response Week 12



Alvelestat patients with >0% desmosine response Week 12



Results

- Main results from ATALANTa presented separately at this meeting.
- Similar baseline SGRQ/CAT scores and desmosine levels in alvelestat and placebo groups.
- Alvelestat group: 11/29 showed >0% and 9/29 a >5% reduction in desmosine at Week 12. Placebo group: 10/29 showed >0% and 8/29 a >5% reduction in desmosine.
- Association between extent of desmosine response and improvement in SGRQ-Total observed. Significance for the SGRQ-Activity domain met at both thresholds with a greater effect in those with >5% reduction. No relationship between biomarker response and SGRQ in placebo group.
- Same relationship demonstrated for the CAT; significance met at both thresholds of desmosine reduction. No relationship observed on placebo.
- Reductions also observed for alvelestat biomarker responders for SGRQ Symptoms and Impacts domains (not statistically significant).

Conclusions

- Association of extent of desmosine reduction with alvelestat to improvement in SGRQ response in the ASTRAEUS study further substantiated by ATALANTa data.
- No association between biomarker change and SGRQ/CAT was observed in placebo, supporting a mechanistic effect of alvelestat.
- Size of response in those with a desmosine reduction on alvelestat is greater than the validated minimally clinically important difference in COPD for SGRQ-Total score (4), CAT score (2), and published estimates for SGRQ-Activity domain (-7.1).[2]
- Progressive decrease in desmosine was observed over time in ASTRAEUS, as with augmentation[3], supporting that improvements are expected to continue with more prolonged alvelestat treatment
- Confirmatory Phase 3 alvelestat study planned in AATD, with a primary endpoint for the US of change in SGRQ-Total score.

References

1. Parkin et al. Analysis from Phase II Clinical Trial, Alvelestat NE (Neutrophil Elastase) Inhibitor in AATD-LD Correlation Between Biomarker Response (Desmosine and Aα-val360) and Clinical Outcome (SGRQ). Am J Respir Crit Care Med. 2023;207:A2844.
2. Jenkins et al. Baseline dependent minimally important differences for clinical outcomes of pulmonary rehabilitation in people with COPD, Pulmonology 2023.
3. Ma et al. The Effect of Alpha-1 Proteinase Inhibitor on Biomarkers of Elastin Degradation in Alpha-1 Antitrypsin Deficiency: An Analysis of the RAPID/RAPID Extension Trials. Chronic Obstr Pulm Dis. 2017;4(1):34-44.