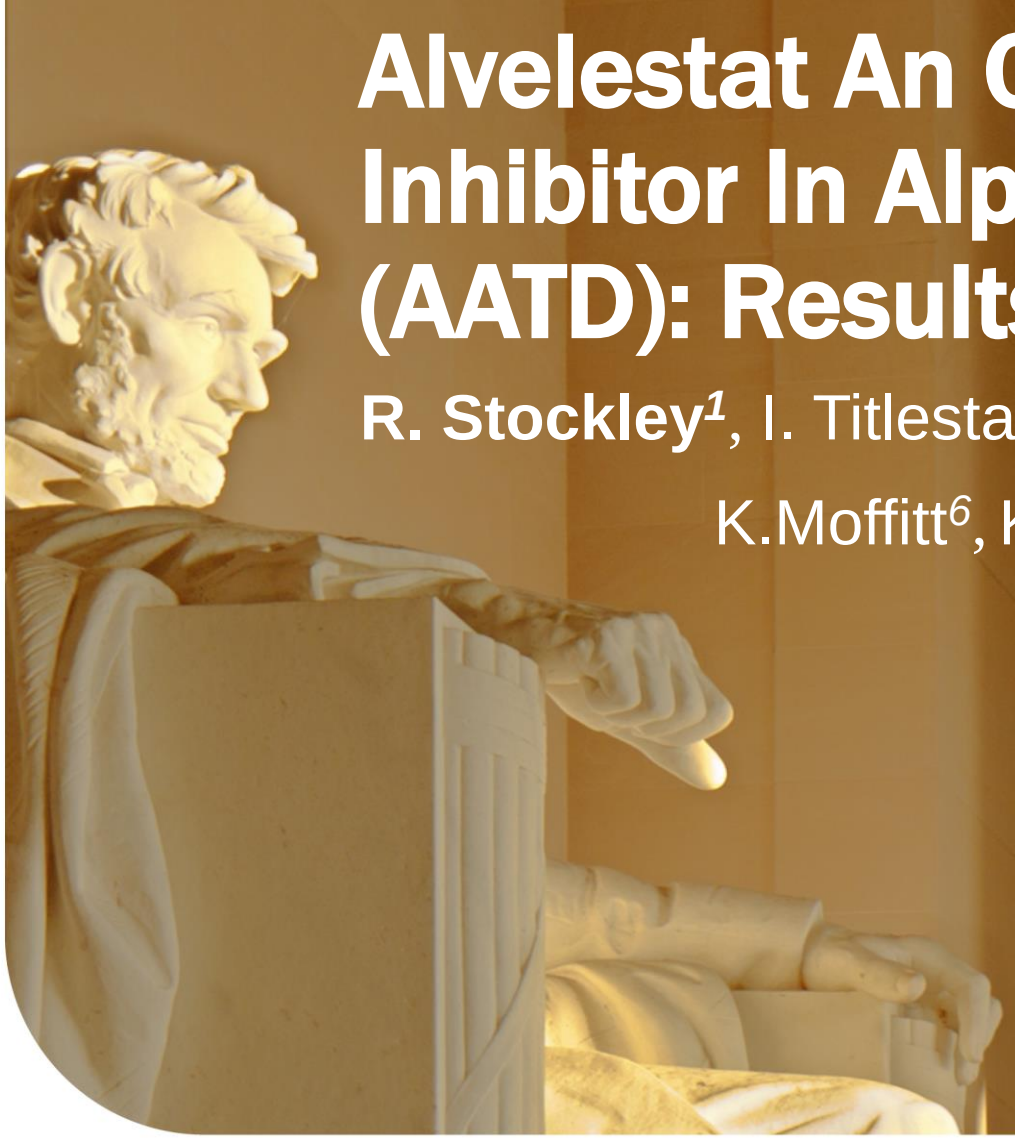

# Alvelestat An Oral Neutrophil Elastase Inhibitor In Alpha-1 Antitrypsin Deficiency (AATD): Results Of A Phase II Trial

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# Disclosure to Learners (R.A.S)

**Financial Relationships with “ineligible companies”:**

- CSL Behring; advisory board, investigator lead research grant funding
- InhibRx; advisory board
- Kamada; advisory board, DSMB
- Mereo Biopharma: advisory board; investigator lead research grant funding
- Takada; advisory board
- Vertex; advisory board
- Z Factor; advisory board

# Introduction:
# AATD-Associated Lung Disease (AATD-LD) and Alvelestat

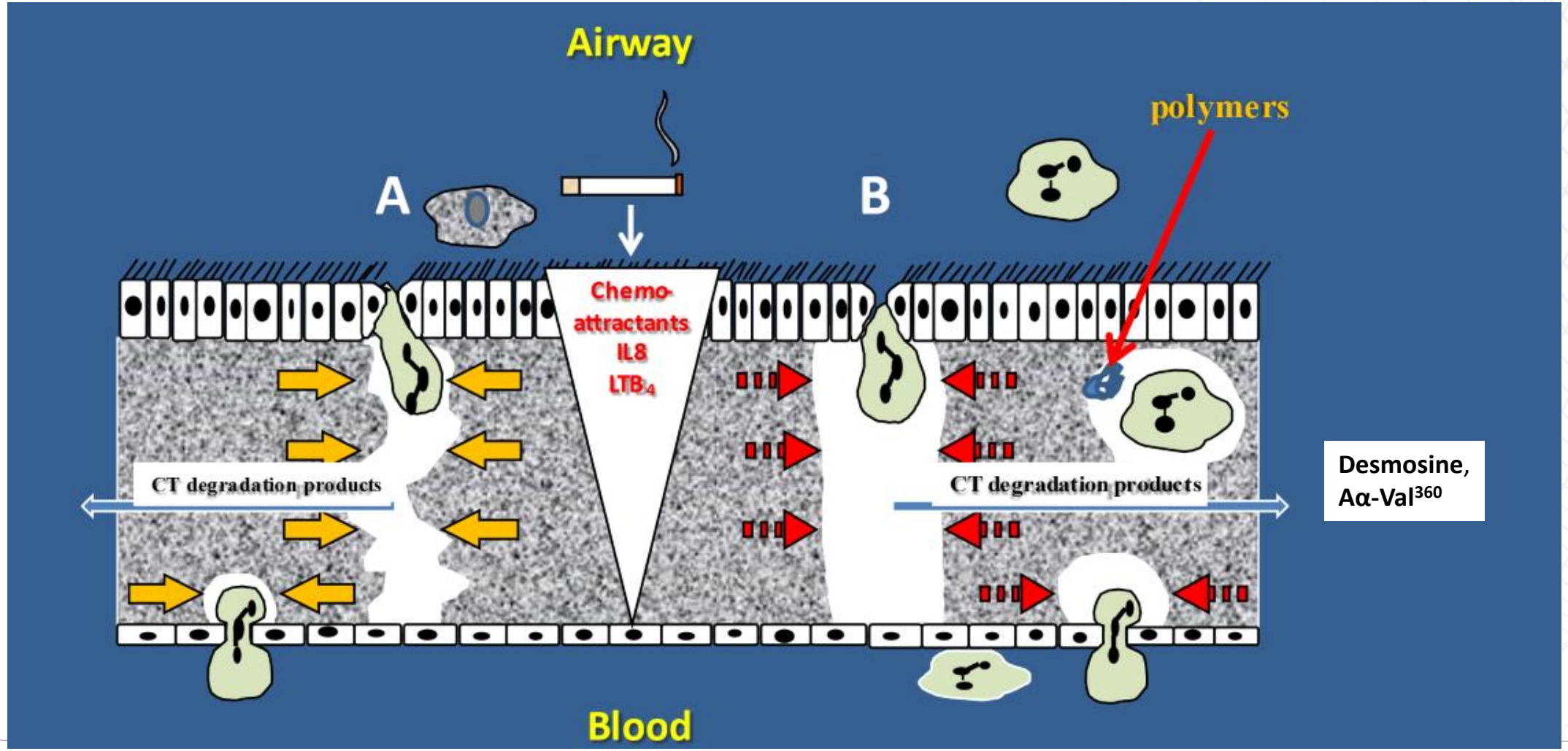
**AATD-LD - a genetic disorder due to deficiency Alpha-1 Antitrypsin (α1AT)**

- α1AT physiological inhibitor of **Neutrophil Elastase (NE)** , Proteinase 3 and Cathepsin G
- Unopposed proteases → inflammation, alveolar & structural damage → emphysema
- Approved therapy weekly IV plasma-derived α1AT ("augmentation")

**Alvelestat**

- **Oral**, selective NE inhibitor
- Association constant for NE similar to α1AT with potential advantages:
  - Effective lung penetration and resistant to oxidative inactivation
- Safety profile established in >1000 patients (COPD, bronchiectasis and cystic fibrosis)

# AATD-LD: Pathogenesis




Desmosine,
Aα-Val$^{360}$

# ASTRAEUS (NCT03636347) Study Overview

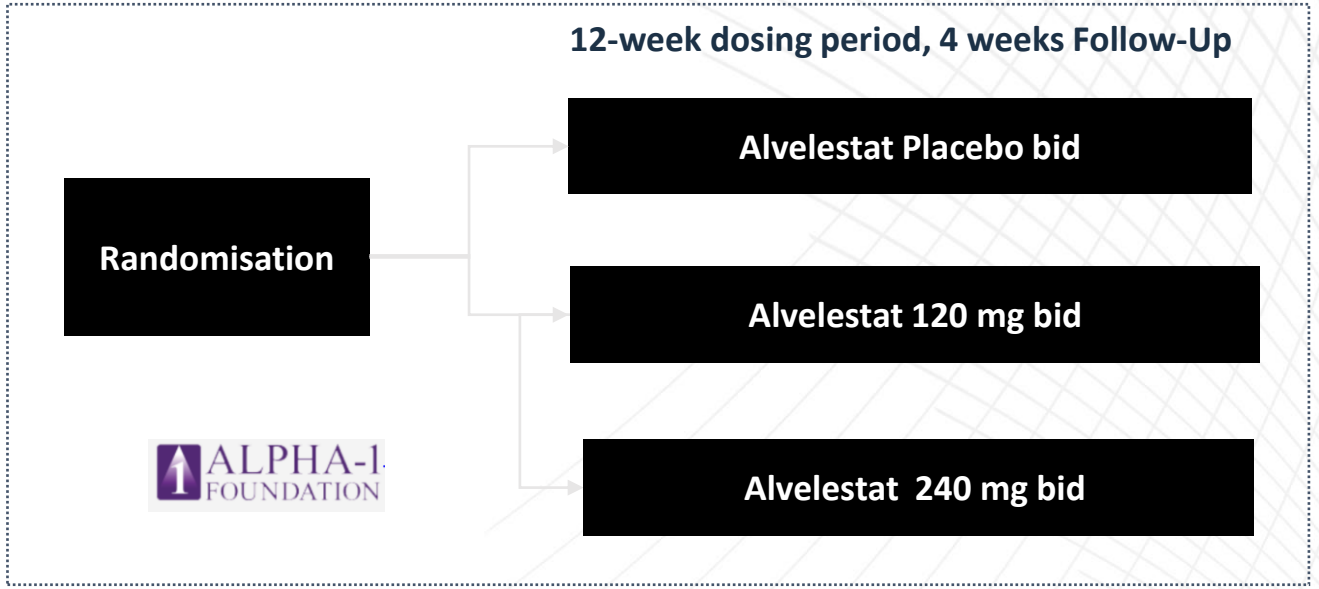
Clinical efficacy studies in AATD-LD require long duration, challenging in a rare disease.
The ASTRAEUS trial was designed to deliver feasible Proof of Concept and dose-decision.

**Aim:** Evaluate effect of alvelestat on biomarkers of AATD-LD over 12 weeks in AATD-LD

**Design:** Double-blind, randomisation to one of two active doses or placebo on top of Standard of Care for COPD (not receiving augmentation)

**Key Eligibility Criteria:**

- Age ≥18 and ≤80 years
- **Pi*ZZ**, Pi*Z Null, Pi*Null, other rare types with serum α1AT <11μM
- **Emphysema on CT scan, $FEV_1$ ≥20% predicted**




Dose-ranging based on targeting maximal NE inhibition throughout dosing period

# ASTRAEUS Endpoints

## Primary Endpoints

Within individual % change from baseline at weeks 4, 8 & 12 in blood biomarkers:

- **Direct target engagement:**
  - Blood Neutrophil Elastase (NE) activity
- **Disease Activity/Severity*:**
  - Aα-Val$^{360}$ (NE-specific)
  - Desmosine (elastin breakdown)

## Secondary and Exploratory Endpoints

**Secondary**

- Proportion NE Below Limit Quantitation
- Safety and tolerability
- Pharmacokinetics

**Exploratory**

- Spirometry, AECOPD, SGRQ,
- Inflammatory and lung damage biomarkers

*Correlation with $FEV_1$, gas transfer, CT densitometry, SGRQ in AATD-LD

# Analysis Populations

| | 120 mg | 240 mg | Placebo | TOTAL |
|---|---|---|---|---|
| Randomised and dosed (Safety Set) | 22 | 40 | 36 | 98 |
| Full Analysis Set (FAS)* | 20 | 39 | 35 | 94 |
| Per Protocol Set (PPS) completers to week 12# | 13 | 23 | 30 | 66 |

Actions as result of COVID-19 impact on recruitment and retention:

- Prioritised recruitment to 240 mg arm
- Trial stopped once adequate numbers for decision-making
- Efficacy analysis focus on 12-week completers for signal seeking

Discontinuations:

- 18 subjects in early study drop out, 12 < 5 weeks of treatment
- COVID-19 single most cause of discontinuation, followed by Adverse Event of headache

*Dosed and at least one post baseline primary biomarker (BM) result available

# No protocol violations/events known to affect efficacy biomarkers, subjects who were on study drug at week 12 assessment

# Demographics And Baseline AATD Characteristics

| | 120mg N=22 | 240mg N=40 | Placebo N=36 |
|---|---|---|---|
| Age years Mean (SD) | 55.5 (9.67) | 59.8 (9.25) | 55.3 (8.05) |
| Male Female | 15% 85% | 33% 67% | 60% 40% |
| $FEV_1$ % predicted Mean (SD) | 64.1 (17.28) | 57.0 (21.34) | 57.4 (21.9) |
| Past history smoking | 63.6% | 70.0% | 63.9% |
| α1AT µm Mean (SD) | 4.3 (1.4) | 3.8 (1.5) | 3.9 (1.5) |
| PiZZ (%) | 22 (100) | 40 (100) | 36 (100) |

- As expected for severe AATD population
- Predominance of females not expected to affect efficacy interpretation

# Primary Endpoint 1:
# Percentage change from baseline Blood NE Activity (PPS)

- Significant suppression from baseline and compared to placebo at both doses
- Sustained 90% suppression of blood neutrophil elastase activity at the 240mg dose

| | N | % Change from Baseline (LSM*) | P versus placebo |
|---|---|---|---|
| **Placebo** | **30** | **-18.1%** | |
| **120 mg** | **13** | **-83.5%** | **p=0.001** |
| **240 mg** | **23** | **-93.3%** | **p<0.001** |

**Secondary Endpoint: Proportion with NE below lower limit of quantitation (<0.97 ng/ml) at 12 weeks:**

- Placebo - 17.2%
- 120 mg - 38.5% (ns versus pbo)
- 240 mg - 65.2% (p<0.002 versus pbo)

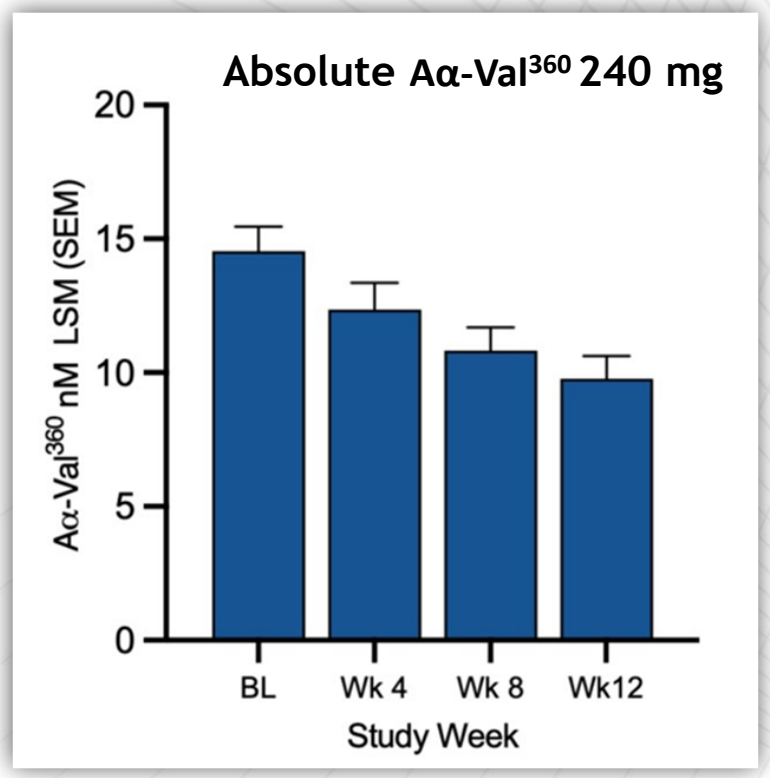
*Least Squared Means, point estimate, Repeated Measures Model

# Primary Endpoint 2: Percentage change from baseline Aα-Val$^{360}$ (PPS)

- Significant decrease in Aα-Val$^{360}$ from baseline and compared to placebo at 240mg dose by week 12

| | N | % Change from Baseline LSM (SE)* | P vs pbo |
|---|---|---|---|
| **Placebo** | **30** | **+11.7 (8.24) %** | |
| **120 mg** | **13** | **+4.1 (13.6) %** | **Not significant** |
| **240 mg** | **23** | **-22.7 (7.46) %** | **P=0.001** |

*Least Squared Mean (Standard Error)
Point estimates, Repeated Measures Model

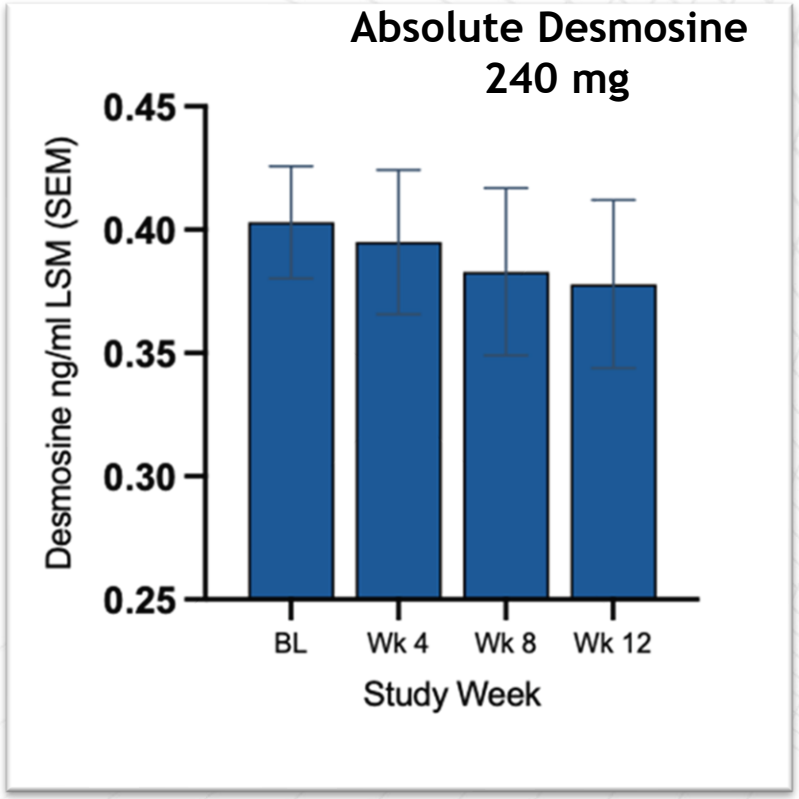


# Primary Endpoint 3:
# Percentage change from baseline desmosine (PPS)

- Statistically significant decrease desmosine from baseline and compared to placebo at 240mg dose by week 12

| | N | % Change from Baseline LSM (SE)* | P value vs pbo |
|---|---|---|---|
| **Placebo** | **30** | **+18.1 (6.64)%** | |
| **120 mg** | **13** | **+29.2 (11.59) %** | **Not significant** |
| **240 mg** | **23** | **-13.2 (7.42) %** | **P=0.041** |

*Least Squared Mean (Standard Error)
Point estimates, Repeated Measures Model



# Treatment-Emergent Adverse Events –All dosed subjects

| | 120 mg N=22 | 240 mg N=40 | Placebo N=36 |
|---|---|---|---|
| **Patients with at least one Serious TEAE*** | **1 (4.5)** | **3 (7.5)** | **0** |
| **Patients with Adverse Event of Special Interest:** | **5 (22.7)** | **11 (27.5)** | **7 (19.4)** |
| **Infection requiring antimicrobials** | **5 (22.7)** | **9 (22.5)** | **7 (19.4)** |
| **Specified liver function test** | **0** | **1 (2.5)** | **0** |
| **prolonged QTc** | **0** | **1 (2.5)** | **0** |

- *3 of 4 SAEs were headache, 2 with associated nausea/vomiting (medically important event), one SAE (240 mg) gastroenteritis
- Headache most common reported AE, especially in those with history of migraine, toleration on treatment was observed
- Lab monitoring – no safety signals of concern

# Exploratory Endpoints

- Numerical improvements at 240 mg in inflammatory and lung damage biomarkers, not statistically significant.
- No effect on spirometry or acute exacerbations at 12 weeks.
- Post-hoc analysis showed an association between reduction in Aα-Val$^{360}$ and desmosine with improvement in SGRQ-Activity Domain (B22, Poster 107; 22$^{nd}$ May).

# Summary and Conclusions

- NE-inhibition with alvelestat 240 mg bid demonstrated statistically significant reduction in all three primary endpoint biomarkers relevant to AATD-associated lung disease in at 12 weeks.
- Difference between effects 120 mg and 240 mg on disease activity biomarkers (A$\alpha$-val$^{360}$ and desmosine) considered due to differences in predicted PK in lung/sputum.
- Effect size on A$\alpha$-val$^{360}$ and desmosine similar to placebo-controlled trials of IV augmentation in AATD.
- Post-hoc association between suppression of biomarkers and improvement in SGRQ-Activity may reflect pathophysiology.
- Data support alvelestat safety in AATD, toleration (headache) to be addressed through dose-escalation.

# Acknowledgments


- ASTRAEUS investigators and patients:

| | |
|---|---|
| **Belgium** | **Spain** |
| **Canada** | **Sweden** |
| **Denmark** | **United Kingdom** |
| **Poland** | **USA** |

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# Q&A