Alvelestat (MPH966) for the Treatment of ALpha-1 ANTitrypsin Deficiency (ATALANTa): A Phase 2, multicenter, double-blind, randomized, placebo-controlled study to evaluate efficacy, safety, and tolerability of alvelestat in alpha-1 antitrypsin deficiency

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Rationale

- Alpha-1 antitrypsin deficiency (AATD) is the most common genetic cause of chronic obstructive pulmonary disease (COPD).
- AATD is characterized by low AAT levels; leading to excessive neutrophil elastase (NE) mediated lung destruction.
- Alvelestat (MPH966) is a potent, selective, and reversible, oral inhibitor of human NE.
- Suppression of NE is expected to reduce lung damage and may slow disease progression in AATD.
- This study is to establish proof of clinical concept by investigating the mechanistic effect and safety of alvelestat in AATD.

Methods

- Trial Design: Phase 2, multicenter, double-blind, randomized, placebo-controlled trial
- Patient Population: Pi*ZZ, Pi*SZ, or Pi*Null AATD
- Intervention: Alvelestat 120mg po bid or placebo
- Duration: 12-week
- The primary objectives:
  - safety and tolerability
  - blood markers of NE activity.
- Secondary endpoints (blood pharmacodynamics):
  - A-alpha-Val360
  - desmosine/isodesmosine
  - markers of lung tissue degradation and inflammation
- Exploratory endpoints:
  - lung function
  - respiratory symptoms
  - pharmacokinetics.
- Mixed-models for repeated measures were used for analyses

Figure 1. Study Schema

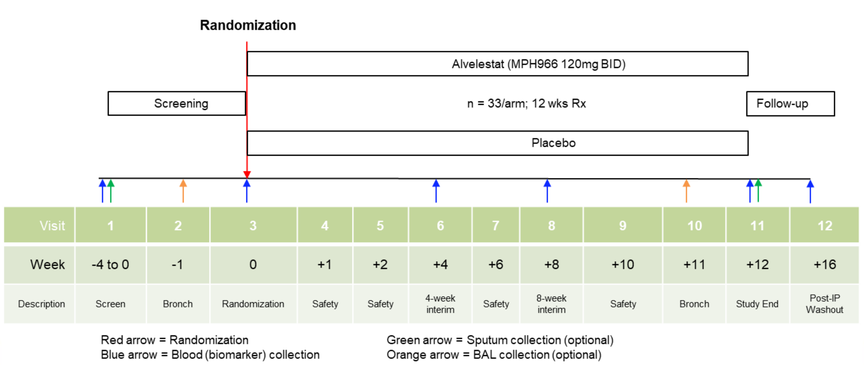


Figure 2. CONSORT Diagram

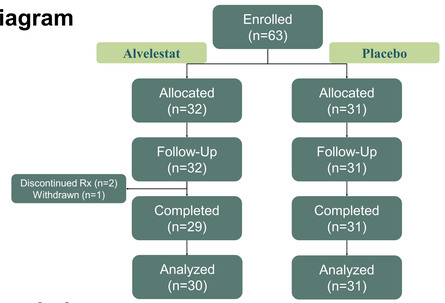


Table 1: Cohort Characteristics

	Alvelestat (n=30)	Placebo (n=31)	Total (n=61)
Age, years	52.4±14	54.6±11.9	53.5±12.9
Female Sex, n (%)	22 (73%)	22 (71%)	44 (72%)
White Race, n (%)	30 (100%)	31 (100%)	61 (100%)
Hispanic or Latino Ethnicity, n (%)	0 (0%)	1 (3%)	1 (1.6%)
Alpha-1 Antitrypsin Genotype, n (%) Pi*ZZ PI*SZ PI*Null	22 (73%) 6 (20%) 2 (7%)	24 (77%) 4 (13%) 3 (10%)	46 (75%) 10 (16%) 5 (8%)
Augmentation Therapy, n (%)	13 (43%)	15 (48%)	28 (46%)
COPD, n (%)	15 (50%)	20 (64%)	35 (57%)
ECOPD within prior year, n (%)	5 (17%)	9 (29%)	14 (23%)
AAT level, mg/dL	50±33	61±53	55±44

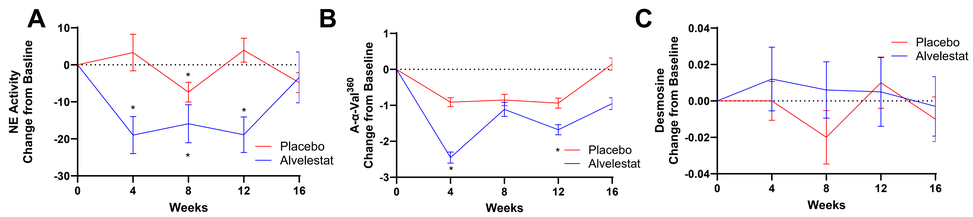
Table 2. Adverse Events

	Alvelestat (n=32) #events (#subjects)	Placebo (n=31) #events (#subjects)
AE	70 (25)	65 (23)
Deaths	0	0
SAE*	0	0
TEAE	70 (25)	64 (23)
AESI	**6 (5)**	**12 (11)****
Related TEAE	24 (15)	23 (10)
Serious Related TEAE	0	0
Withdrawal due to AEs	2 (2) – headache	0

*There were no serious adverse events, liver function abnormalities, ECG abnormalities, or neutropenia.
**Infections requiring antibiotics and COPD exacerbations were more common in the placebo group.

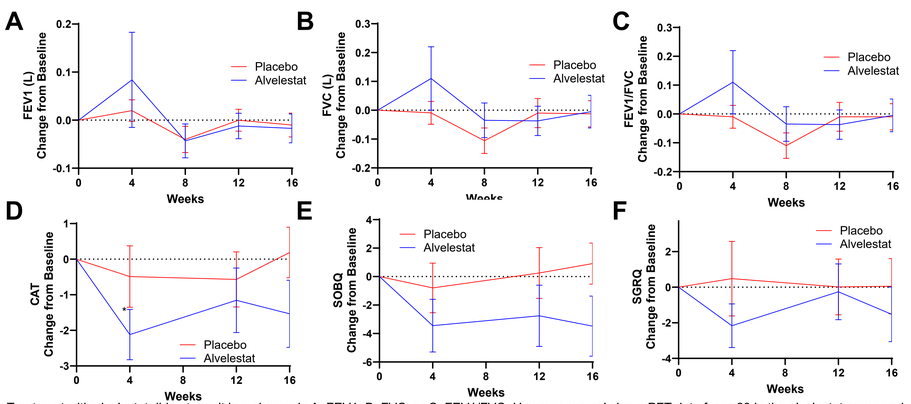
Results

Figure 3. Alvelestat Effects on NE Activity, A-alpha-Val360, and Desmosine



A. Treatment with alvelestat resulted in a significant reduction from baseline NE activity (-18.9±4.8ng/ml; -58.3%; p=0.0005) that also differed from placebo treatment (-15.0±5.2ng/ml; p=0.0059) at 12-weeks; B. There was a significant reduction from baseline A-α-Val^{360} in the alvelestat arm (-1.7±0.7nM; -13.4%; p=0.03) but not in the placebo arm (p=0.23); C. There were no within-subject or between-group changes in desmosine. There were no significant changes in other markers of inflammation (data not shown).

Figure 4. Alvelestat Effects on Lung Function and Respiratory Symptoms



Treatment with alvelestat did not result in a change in A. FEV1; B. FVC; or C. FEV1/FVC. However, we only have PFT data for n=23 in the alvelestat group and n=29 in the placebo group due to issues with aerosol generating procedures during the pandemic. Similarly, we did not observe sustained changes in D. COPD Assessment Test (CAT) score; E. San Diego Breathlessness Questionnaire (SOBQ) score; or F. St George's Respiratory Questionnaire (SGRQ) Score.

Conclusions

- The oral NE inhibitor alvelestat was safe, well-tolerated, and led to a significant and sustained reduction in NE activity and the NE-specific fibrinogen cleavage product A-alpha-Val360 at 120mg twice daily in AATD.
- These findings support further testing of alvelestat in severe AATD in Phase 3 clinical trials

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