Alvelestat An Oral Neutrophil Elastase (NE) Inhibitor In Alpha-1 Antitrypsin Deficiency (AATD): Results Of A Phase II Trial ("ASTRAEUS"; NCT03636347)

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Introduction

AATD is a genetic disorder that can lead to emphysema, driven by unopposed Neutrophil Elastase (NE) activity.

Desmosine and Aα-Val^{360} are biomarkers on the pathological pathway of AATD, associated with clinical disease activity and provide potential for assessing early indication of possible effects of an intervention.

Aα-Val^{360} is a neoepitope created on cleavage of fibrinogen and developed as a specific marker of NE activity. Desmosine is a breakdown fragment of mature elastin. Both biomarkers are elevated in AATD-associated lung disease (AATD-LD) and respond to AAT replacement therapy 'augmentation' (1,2).

Alvelestat, is a potent, selective, reversible, oral NE inhibitor with effective lung penetration (3) in development for AATD-LD. ASTRAEUS was a Ph II trial to assess dose, efficacy, safety and tolerability.

Aim

Primary objective : To evaluate the efficacy of alvelestat administered bid for 12 weeks on blood markers of NE and disease activity/severity.

Primary Endpoints	Secondary and Exploratory Endpoints
Within individual % change from baseline up to end of treatment within treatment arm and in comparison, to placebo at week 4, 8 & 12: Direct target engagement: ○ Blood NE activity Disease Activity/Severity biomarkers: ○ Aα-Val^{360} levels ○ Plasma desmosine levels	**Secondary** • Proportion NE Below Limit Quantitation • Safety and tolerability • Pharmacokinetics **Exploratory** • Spirometry, Exacerbations St. George's Respiratory Questionnaire • Lung damage and inflammation biomarkers

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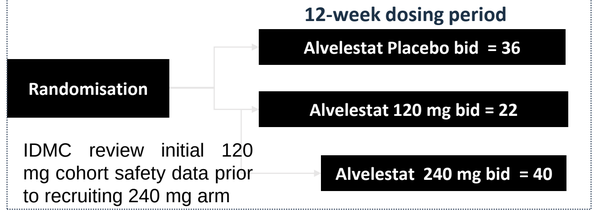
Methods

Multicentre, double-blind, randomised, dose-ascending, sequential group, placebo-controlled study.

Participants with severe AATD (PiZZ, null or other rare phenotype/genotype with blood alpha-1 antitrypsin [AAT] <11mU/L) and with lung disease (emphysema on CT) were enrolled in this proof-of-concept study powered to detect a mechanistic signal benchmarked to the effect of augmentation.

Two doses of alvelestat, 120 mg bid and 240 mg bid, were tested, designed for dose-ranging to achieve maximal NE inhibition over the dosing period (in ~ 50% and 90% of patients respectively).



Results

Baseline characteristics were comparable outside predominance of females in alvelestat arms, which was not expected to impact response. The efficacy analysis focussed on the per protocol 12-week completers.

	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)

Biomarkers Efficacy End Points

Results are point estimates of effect, using repeated measures model, with baseline value, FEV$_1$, smoking history, age, treatment arm and time as covariates in the model

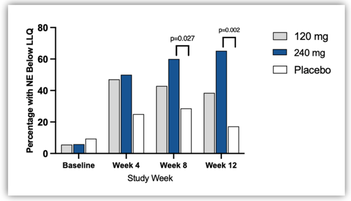
NE Inhibition: sustained >90% suppression at the 240mg dose at 12 weeks.

	NE inhibition : % Change from Baseline Least Squared Means					
Week	120 mg N=13	P value	240 mg N=23	P value	Placebo N=29	P value
12	-83.5%	0.023*	-93.3%	<0.001**	-18.1%	ns

*p=0.001, **p=<0.001 alvelestat versus placebo, ns = not significant

% Blood NE Below the Lower Limit of Quantitation (BLLQ)

NE BLLQ (<0.97 ng/ml) in 240mg dose (65.2%) at 12 weeks close to controls (74.4%)



Aα-Val^{360}: significant decrease from baseline (p=0.004) and compared to placebo (p=0.001) at the 240mg dose at week 12.

	Aα-Val360: % Change from Baseline Least Squared Means					
Week	120 mg N=13	P value	240 mg N=21	P value	Placebo N=27	P value
12	4.1%	ns	-22.7%	0.004#	11.7%	ns

#p=0.001 alvelestat versus placebo

Desmosine: statistically significant decrease from baseline and vs. placebo with 240mg dose.

	Desmosine: % Change from Baseline Least Squared Means					
Week	120 mg N=13	P value	240 mg N= 23	P value	Placebo N=30	P value
12	29.2 %	ns	-13.2 %	0.045*	18.1 %	ns

*p =0.041 alvelestat versus placebo

Safety: Headache was the most common reported AE, particularly in those with history of migraine, toleration on treatment was observed. There were no adverse trends on laboratory safety monitoring

	120 mg N=22	240 mg N=40	Placebo N=36
Patients with at least one Serious TEAE. 3 were events of headache +/- nausea/vomiting, 1 of gastroenteritis	1 (4.5)	3 (7.5)	0
Adverse Event of Special Interest (all fully resolved):	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

Discussion

- NE-inhibition with alvelestat 240 mg bid demonstrated statistically significant reduction in all three primary endpoint biomarkers relevant to AATD-associated lung disease by 12 weeks.
- Difference between effects 120 mg and 240 mg on disease activity/severity biomarkers Aα–val^{360} and desmosine) considered due to differences in predicted PK in lung/sputum.
- Effect size on Aα–val^{360} and desmosine is 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 (B22, Poster 107; 22nd May).
- Data support alvelestat safety in AATD, toleration (headache) to be addressed through dose-escalation.

Conclusion

The mechanistic efficacy responses and safety data support progression of development in AATD-LD, to include longer duration of dosing and clinical endpoints.

References

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