No Infection Risk with Alvelestat in Patients with AATD in Two Phase 2 Trials

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Introduction

Background

- Alpha-1 antitrypsin deficiency-associated lung disease (AATD-LD) is a genetic disorder that can lead to emphysema, driven by disproportionate neutrophil elastase (NE) activity.
- Alvelestat, a potent, reversible, selective, oral inhibitor of NE, has been studied in two Phase 2 trials of severe AATD-LD.
- The effect of NE suppression on host defence was monitored by the reporting of infections requiring antimicrobial therapy and neutropenia as adverse events of special interest (AESI).

Aims

- To analyse the effects on NE suppression on the frequency of AESIs of infection in patients with AATD-LD receiving alvelestat compared to placebo.

Methods

- Two multicentre, double-blind, randomised, placebo-controlled Phase 2 trials of alvelestat in severe AATD-LD have been completed: ASTRAEUS (NCT03636347) and ATALANTa (NCT03679598).
- In the ASTRAEUS trial, two doses of alvelestat (120 mg BID [n=22] and 240 mg BID [n=40]) were tested against placebo (n=36) in patients not on augmentation, for 12 weeks. ASTRAEUS was performed across 26 sites in North America, EU and UK.
- In the ATALANTa trial, one dose of alvelestat (120 mg BID [n=32, 14 on augmentation]) was tested against placebo (n=31) for 12 weeks. ATALANTa was performed at 10 sites in the USA.
- AESIs of infection requiring anti-microbial therapy or neutropenia were required to be reported during the 12 weeks of active treatment and 4 weeks of safety follow-up.
- A consistent safety reporting and management process was used for both trials.

Results

- Across both trials, 94 patients received at least one dose of alvelestat, and 67 received placebo.
- There were no AESIs of neutropenia in either trial.
- AESIs of infection showed similar or lower frequency in the alvelestat groups compared to placebo (**Table 1**).
- All AESIs of infection were moderate or mild, except for one severe fungal infection in the placebo group. All resolved.
- The most frequently reported AESIs of infections were as follows: chronic obstructive airways disease (COPD) / infective exacerbation of COPD (13 events), and sinusitis/chronic sinusitis (4 events) (**Table 2**).
- Of the AESIs of COPD or infective exacerbation of COPD, the prevalence was lower in the alvelestat groups (4 of 94 subjects) compared to placebo (8 of 67 subjects).
- A total of 9 AESIs of infection involving the respiratory tract (upper, lower, unspecified) or pneumonia were reported, with no difference in prevalence between placebo (4 of 67 subjects treated) and alvelestat (5 of 94 subjects treated).
- Single events of other infections also occurred across the treatment groups (**Table 2**).

Conclusions

- The range of infections observed in these Phase 2 trials were as expected in the AATD-LD population.
- Consistent with studies in over 1000 patients with COPD, bronchiectasis and cystic fibrosis, selective inhibition of NE with alvelestat in patients with AATD-LD was not associated with an increased frequency or severity of infection over the course of 12 weeks, including at the 240 mg BID proposed Phase 3 AATD dose.

TABLES

Table 1: Prevalence of AESIs of Infection Requiring Antimicrobial Therapy

ATALANTA Alvelestat 120 mg (N = 32) n (%) [#AEs]	ASTRAEUS Alvelestat 120 mg (N = 22) n (%) [#AEs]	ASTRAEUS Alvelestat 240 mg (N = 40) n (%) [#AEs]	Placebo (ATALANTa + ASTRAEUS) (N = 67) n (%) [#AEs]
5 (15.6) [6]	5 (22.7) [6]	10 (25%) [11]	18 (26.9%) [20]

Table 2: AESIs by Preferred Term in Alvelestat Treatment Arms

ATALANTa Alvelestat 120 mg (N = 32)	ASTRAEUS Alvelestat 120 mg (N = 22)	ASTRAEUS Alvelestat 240 mg (N =40)	Combined Placebo N = 67
Chronic obstructive pulmonary disease (n=1)		Infective exacerbation of chronic obstructive airways disease (n=4)	Chronic obstructive pulmonary disease (n=7) Infective exacerbation of chronic obstructive airways disease (n=1)
-	Respiratory tract infection (n=1)	Respiratory tract infection (n=1)	-
-	Lower respiratory tract infection (n=1)	Upper respiratory tract infection (n=1)	Lower respiratory tract infection bacterial (n=1)
-	-	Pneumonia (n=1)	Pneumonia (n=3)
Urinary tract infection (n=1)	Urinary tract infection (n=1) Cystitis (n=1)	Urinary tract infection (n=1) Cystitis (n=1)	Urinary tract infection (n=3)
Sinusitis (n=2)	-	-	Sinusitis (n=1) Chronic sinusitis (n=1)
Diverticulitis (n=1) Otitis media (n=1)	Erysipelas (n=1) Oral candidiasis (n=1)	COVID-19 (n=1) Gastroenteritis bacterial (n=1)	COVID-19 (n=1) Fungal infection (n=1) Herpes zoster (n=1)

N=Number of subjects; n=Number of events.

References

Wells JM et al, American Thoracic Society. 2024; Poster A1211.
Stockley RA et al, Am J Respir Crit Care Med. 2023; 207: A4493.

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