CD101 Lung Epithelial Lining Fluid (ELF) Concentrations Substantiate Its Use For Prophylaxis Treatment As Evident In Mouse Disseminated and Pulmonary Aspergillosis Models

V. Ong1, G. Hough1, S. Flanagan1, T. Sandison1, K. Bartizal1, A. Sattar2, A. Sharp2, P. Thommes2, T. Murphy3
1Cidara Therapeutics, San Diego, CA; 2Evotec, Manchester, UK; 3NeoSome Life Sciences, Lexington, MA

INTRODUCTION AND PURPOSE
Rezafungin (previously CD101) has demonstrated robust efficacy as prophylaxis and treatment in mouse antifungal models of aspergillosis. The distribution of rezafungin into lung ELF was studied to further substantiate the observed efficacy.

METHODS
Rezafungin (20 mg/kg IP; human equivalent dose) was administered to ICR mice. At 0, 1, 3, 6, 12, 24, 48, and 72 hours post-dose, 3 mice/timepoint were euthanized for plasma and bronchoalveolar lavage fluid (BALF) collection with 2x 0.5 mL flushes of saline. Urea levels for plasma/BALF normalization for lung ELF volume calculation were quantified using a spectrophotometry-based assay. Rezafungin concentrations in plasma/BALF samples were measured by LC-MS/MS.

Disseminated aspergillosis: ICR mice (6/grp) were rendered neutropenic by cyclophosphamide on days -3 (270 mg/kg), +1 and +4 (90 mg/kg). IV challenge with A. fumigatus ATCC 13073 (10⁴ CFU/mouse) was initiated on day 0 and rezafungin treatment was administered (2h post dose) as a single dose (2 mg/kg IV or IP) or daily (0.5 mg/kg BID for 5 days) dosing. Survival was monitored for ≥10 days. The same model was used for prophylaxis except rezafungin (5, 10, 20 mg/kg) was dosed on days -1, -3 or -5.

Pulmonary aspergillosis: ICR mice (10/grp) were made neutropenic by cyclophosphamide on day -4 (150 mg/kg), and cyclophosphamide/cortisone was given on day -1 (150/175 mg/kg). Intransal challenge with A. fumigatus AF293 (10⁴ CFU/mouse) was initiated on day 0 and prophylaxis with a single dose of rezafungin (IP; 5, 10, and 20 mg/kg) or posaconazole (PO; 2 and 10 mg/kg) was started 1 day prior to infection. Survival was monitored for 10 days.

RESULTS
Rezafungin ELF concentrations reached a maximum by 4h and were comparable between plasma and ELF beyond 24h post-dose in total-drug concentrations but much higher based on free-drug concentrations (99.2% plasma protein binding). the ELF/Plasma AUC ratio was 0.80 for total-drug and 100 based on free-drug exposures, respectively (fig. below).

In the more challenging pulmonary aspergillosis model, an increase in survival was also observed from a single prophylaxis rezafungin dose. The human dose (400 mg) equivalent of 20 mg/kg in mice showed 30% survival (fig. below). In the same study, posaconazole at its human equivalent dose of 2 mg/kg was not protective and only showed a significant increase in survival at 10 mg/kg (5x higher than human AUC).

For treatment of disseminated aspergillosis, rezafungin by IV or IP showed a significant increase in survival compared to vehicle. Survival was comparable with either a single 2 mg/kg dose or 0.2 mg/kg BID x 5d (fig. below), confirming that a single-dose, front-loading regimen was equally effective.

CONCLUSIONS
With a long plasma half-life in human (133 h) and extensive lung ELF exposures, these findings suggest that rezafungin could be a viable candidate for prophylaxis and treatment of aspergillosis.

REFERENCE