Introduction/Aim

PC945 is a novel inhaled antifungal agent\(^1\)-\(^2\), whose profile maximises the likelihood of clearing a pulmonary Aspergillus infection, while minimising the risk of either direct toxicity or toxicity/medical complications arising from unwanted drug-drug interactions. Since the target of PC945 is pulmonary Aspergillus infections, attempts to develop a useful pharmacokinetic (PK): pharmacodynamic (PD) model to aid clinical development have focused on exploring the relationship between local concentrations of PC945 in the lung and antifungal effects.

Methods

AJ mice (males, 5 weeks old) were dosed with hydrocortisone (125 mg/kg, sc.) on days 3, 2 and 1 before infection, and with cyclophosphamide (250 mg/kg, ip) 2 days before infection to induce temporary neutropenia. On day 0, animals were infected intranasally with 30 μL of the spore suspension of Aspergillus fumigatus (A. fumigatus) (ATCC 13073) at a concentration of 1.67 × 10\(^{5}\) spores/mL in physiological saline. PC945 (0.016 mg/mL) was treated intranasally on days 7-10 to Day 1-10 (2 days), and animals were culled on day 3 post Aspergillus fumigatus intranasal inoculation. Bronchoalveolar lavage fluid (BALF), lung and plasma were collected 24 or 72 hrs post the last dose (post infection) for biomarker and PK analysis. BAL cell pellet (alveolar cells) and BALF supernatant were collected separately after centrifugation of BALF samples (Figure 1).

Figure 1. Treatment schedule

Results

Intranasally dosed PC945 showed much stronger antifungal effects (CFU in lung, galactomannan (GM) in BALF and plasma) with 8 days rather than 3 days of prophylaxis (Figure 2).

Figure 2. Summary of pharmacodynamics of extended prophylaxis treatment with PC945 in A. fumigatus infected immunocompromised AJ mice

PC945 was not detectable in plasma at either 24hrs or 72hrs post the last dose, and much higher levels of PC945 were detected in the lung at 24hrs post the last dose after 8 days (709±126 ng/lung) than after 2 days prophylaxis (301±56 ng/lung). Interestingly, little or no PC945 was detected in BAL supernatant (<10 ng/mL) but significantly higher levels were detected in BAL cell pellets (Figure 3). The concentrations in alveolar cell pellets show an impressive correlation with anti-fungal activity in the lung (Figure 4, Table 1).

Figure 3. Summary of pharmacokinetics of extended prophylaxis treatment with PC945 in A. fumigatus infected immunocompromised AJ mice

Figure 4. PK (BAL cell)-PD analysis : Better correlation with PK [24h]

Table 1. Correlation between PK (BAL cell)-PD analysis

Conclusion

Intranasally dosed PC945 accumulated in alveolar cells. These observations will be pursued, and it is intended that BAL cell concentrations of PC945 be measured in the future clinical study rather than standard BALF measurement.

References