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Monte Carlo Simulations of BAL8557, a New Watersoluble Azole with Antifungal Activity

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Introduction:

BAL4815 is a new antifungal agent, which belongs to the azoles. BAL4815 is administered as the water-soluble pro-drug BAL8557 (figure 1). In vitro, BAL4815 showed broad-spectrum antifungal activity against Candida spp. (including fluconazole-resistant *C. albicans*), *Cryptococcus* spp., and various filamentous fungi including fluconazole-resistant strains. Monte Carlo Simulations (MCS) is a technique that can be used to determine the Probability of Target Attainment (PTA) for pharmacodynamic indices (PDI). Results from a single dose pharmacokinetic study were used to determine PTAs and, based on levels of BAL4815 evaluate the potential use of BAL8557 to treat fungal infections

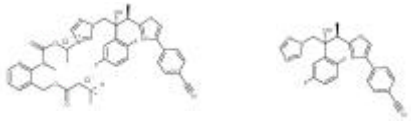

Figure 1

Pro-drug BAL8557 **Active drug BAL4815**

Aim:

Evaluate the potential use of BAL8557 to treat fungal infections using Monte Carlo simulations.

Methods:

Data from a single dose escalation study involving 3 groups of 6 subjects receiving 50, 100 and 200 mg were used (ECCMID, P1033). Protein binding in human serum was determined using the red blood cell partitioning method. Population PK parameters (including the covariance matrix) were estimated using NPEM2. MicLab232 was used to perform MCS for a 400 mg q24h dose to obtain PTAs at various *f*AUC/MIC ratio's in steady state.

Results:

Protein binding was 98%. A two-compartment model best fit the data, with Values (sd) of Vd =147.7 (47.7) L, Cl = 4.4 (1.9) L/h, k12 = 0.21 (0.11) 1/h and k21 = 0.11 (0.07) 1/h for the whole population. However, clearance was lower at higher doses, with 2.9 (0.61) L/h at a 200 mg dose. MCSs were therefore performed using the results of the 200 mg dose. Figure 1 shows a simulation of BAL4815 concentrations, steady state is obtained after 10-14 days. At steady state trough levels greater than 4 mg/L (total drug) are maintained.

MICs yielding probabilities of at least 100% target attainment at *f*AUC/MIC values of 25, 50 and 100 were 0.06, 0.03 and 0.015 mg/L, respectively (table 1).

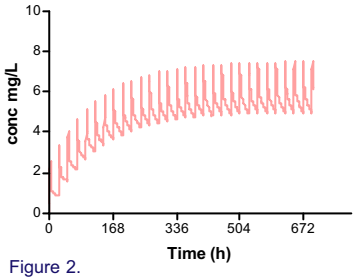

Figure 2.

Simulated concentration-time profile of BAL4815 (total drug)

	*f*AUC/MIC		
	25	50	100
MIC mg/L			
0.015			100
0.03		100	25
0.06	100	25	0
0.125	25	0	
0.25	0		
0.5			

Table 1

Probability of Target Attainment for a 400 mg dose BAL4815 in steady state (free drug)

Discussion:

The simulated plasma levels of BAL4815 clinical dosing regimens show that steady state concentrations are reached after 10-14 days, indicating the need for loading doses and/or more frequent administration during the first days of therapy. For instance, a 400 mg q12 h dosing regimen during the first 48 hours of therapy, as often used for itraconazole, would result in rapidly achieving active concentrations. Simulated concentrations after repeated administrations have been confirmed by the results multiple dose pharmacokinetics in humans (ICAAC04, A-37).The results indicate that patients with infections with Candida strains with a MIC up to 0.06 mg/L have a 100 % probability of attaining a target *f*AUC/MIC ratio of 25 mg.h/L. The MIC50 of *C. albicans* strains was 0.008 mg/L and for *C. glabrata* 0.032 mg/L in a pilot MIC distribution study (data on file), indicating that BAL8557 has the potential to be a clinical effective antifungal agent.

Conclusions:

- A 400 mg dose of BAL4815 yields probabilities of 100% at *f*AUC/MIC values of 25 and MICs of 0.06 mg/L in steady state, well above the MIC50 of *C. albicans*
- Simulation of a q24h dosing regimen shows that loading doses followed by maintenance doses will allow rapidly to achieve active concentrations

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