RESULTS

Pharmacokinetic Studies

The single-dose pharmacokinetics of CD101 and anidulafungin were compared in CD-1 mice, Sprague-Dawley (SD) rats, beagle dogs, cynomolgus monkeys, and chimpanzees (Table 1). Animals (5-9/d) received CD101 or anidulafungin as an IV bolus (mouse and rat) or as an infusion (dog and primates). For each of these studies, whole blood samples (EDTA anticoagulant) were collected up to 72 h after dosing. The samples were centrifuged and plasma was stored at -70°C until analysis. CD101 and anidulafungin plasma concs were measured by LC/MS/MS.

Species Route Bodyweight (kg) Dose (mg/kg) Conc Volume per kg

CD-1 Mouse IV bolus 0.1 0.02 1 2.0

SD Dog IV (10-min) 2.8 0.14 2.2 140

Cynomolgus Monkey IV bolus 7.0 0.28 2.8 10

Chimpanzee IV bolus 88 1 0.77 1.3

Interspecies Scaling and Comparison

Plasma clearance (Cl) and volume of distribution (V) calculated from animal data were used to predict human Cl and V by allometric scaling. The allometric equation is as follows:

\[ y = \alpha \times \text{BW}^{\beta} \]

where \( y \) is \( \text{Cl} \) or \( V \), \( \alpha \) is the allometric coefficient, \( \text{BW} \) is the body weight, and \( \beta = 0.5 \) is the allometric exponent. McBride’s rule of exponents \( 0.55 < \beta < 1.0 \) was used where applicable. From these parameters, the half-life \( t_{1/2} \) in human was calculated. The predicted half-life was then retrospectively compared to the observed half-life following successful completion of Phase I clinical studies.

RESULTS (cont’d)

Chimpanzee as a Surrogate for Human PK

The pharmacokinetics of CD101 was superior to anidulafungin in the same study, especially in larger animal species (Table 4). From the chimpanzee PK study, the anticipated human \( t_{1/2} \) is at least 88 h.

Table 4. Pharmacokinetic parameters of CD101 and anidulafungin across different animal species; lower clearance of CD101 compared with anidulafungin determined from the same study.

Species Route Bodyweight (kg) Dose (mg/kg) Conc Volume per kg

CD101

Cl (mL/h/kg) 64 47 302 25.2

\( t_{1/2} \) (h) 22 12 8 30

Anidulafungin

Cl (mL/h/kg) 1.4 1.0 0.55 0.1

\( t_{1/2} \) (h) 3.0 2.0 1.0 0.5

Across all preclinical species studied, CD101 shows very low clearance and a longer half-life compared with previous echinocandins. The chimpanzee was a remarkable surrogate for the CD101 human PK profile.

REFERENCES

1. ICOAC 2014, Poster P1002
2. ICOAC 2014, Poster A003 and A048