OBJECTIVE

The objective of this study was to determine if the frequency of CD101 administration and described effect on the shape of concentration-time curve influences efficacy in a neutropenic candidiasis mouse model.

METHODOLOGY

Pharmacodynamic Study

- Healthy female C3H mice weighing 22-23 g were given a single dose of CD101 via intraperitoneal (IP) injection.
- The following doses were studied: 1, 4, and 10 mg/kg.
- Plasma concentrations were determined at 0.1, 3, 12, 24, 48, 72, and 168 hours post-dose using a validated LC/MS assay with a lower limit of quantitation of 0.03 µg/mL.

Pharmacokinetic Study

- CD101 plasma concentrations were determined at 0.1, 3, 12, 24, 48, 72, 96, and 168 hours post-dose using a validated HPLC assay with a lower limit of quantitation of 0.2 µg/mL.

RESULTS

Pharmacodynamic Study

- CD101 exhibited PK over the dose range studied (1 to 14 mg/kg IP).
- Plasma concentrations were front loaded with the highest concentration observed early in therapy.
- The ratio of the area under the concentration-time curve (AUC) greatly influenced efficacy.

Pharmacokinetic-Pharmacodynamic Analysis

- Using data generated from PK and PD data, a model was developed in ADAPT/MCPEM.
- The developed PK model, concentration-time profiles and AUC, were used in one-colony growth study to determine the PK/PD relationship.
- The time profiles for each regimen were generated using a Monte Carlo Monte Carlo model.

CONCLUSIONS

- The magnitude of the PK/PD relationship in a neutropenic mouse model can inform the PK/PD relationship in humans.

REFERENCES

1. Ambrose PG, Drusano GL, Craig WA. In vitro activity of CD101, an echinocandin analog, against Aspergillus and Candida species, including –300 and –300-resistant isolates.
2. CD101 is a structural analog of amphotericin B, resulting in different physical and biological properties.
3. Reduced hepatotoxicity compared to amphotericin B.
4. Longer half-life, up to 130 hours in humans, approximately 75% of a dose, compared to aclacinomycin A - 20 hours in humans.
5. The ratio of the area under the concentration-time curve to the minimum inhibitory concentration (AUC/MIKC) ratio is the pharmacodynamic-pharmacokinetic parameter (PK/PD) index associated with CD101 efficacy.
6. CD101’s half-life, and the above-described PK/PD index associated with efficacy, provide the opportunity to evaluate PK/PD parameters for different dosing regimens.
7. Non-linear drug exposure has resulted in better efficacy for other long half-life antimicrobials.
8. Reduced hepatotoxicity compared to amphotericin B.
9. The model was validated by using data from a neutropenic model in which the total weekly dose was administered as a single dose, twice-weekly, or daily regimens.
10. Mice were sacrificed 148 hours (7 days) following the start of treatment.
11. Control arm mice were sacrificed 24, and 48 hours post-administration of vehicle.
12. Novel dosing regimens were tested for their ability to determine the fungal burden (CFU/g).
13. CD101 concentrations were front loaded with the highest concentration observed early in therapy.
14. The ratio of the area under the concentration-time curve (AUC) greatly influenced efficacy.
15. The magnitude of the PK/PD relationship in a neutropenic mouse model can inform the PK/PD relationship in humans.