O0943 Efficacy of APX001 in treatment of Candida endophthalmitis and haematogenous meningoencephalitis in experimental non-neutropenic rabbit model

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Background: Candida endophthalmitis is a serious sight-threatening complication of candidemia that may occur before or during antifungal therapy. Hematogenous Candida meningoencephalitis (HCME) also is a serious manifestation of disseminated candidiasis in premature infants, immuno suppressed children, and immunocompromised adults. HCME has been associated with a high rate of mortality and severe neurodevelopmental abnormalities. APX001 is a novel isoxazolyl-bis-pyridine antifungal agent which is highly active in vitro and in vivo against Candida spp., Aspergillus spp., and other fungal pathogens. It has a novel mechanism of action, consisting of inhibition of an early step in fungal glycosyl-phosphatidyl-inositol biosynthesis. Little is known, however, about the activity of APX001 against Candida endophthalmitis or HCME. We therefore studied the activity of APX001 in the rabbit model of Candida endophthalmitis and HCME.

Materials/methods: Non-neutropenic catheterized New Zealand White rabbits weighing 2.6–3.3 kg were used in all experiments. Six rabbits per dosage group received APX001 at 25 (APX25), 50 (APX50), and 100 (APX100) mg/kg Q12h PO, or AmB deoxycholate (DAmB) at 1 mg/kg IV. Treatment started 24h after intravenous inoculation and continued for up to 6 days. Blood samples for serum (1→3)-β-D-glucan (BG) levels were obtained every other day. Plasma pharmacokinetic blood samples were drawn from each rabbit receiving APX001 on day 6 at the following time points: pre-dose, 1h, 2h, 4h, 6h, 8h, and 12h.

Results: Rabbits treated with APX25, APX50, APX100 Q12h, and DAmB demonstrated significant decreases in fungal burden (log CFU/g) in vitreous, choroid, cerebrum, and cerebellum, in comparison to those of untreated control (UC) (p<0.01). In addition, there was full clearance of C. albicans achieved in CSF, meninges, and spinal cord in all treatment groups. These data directly correlated with a significant decline of BG levels during therapy in comparison to those of UC (p<0.01). The plasma Cmax of APX001A ranged from 3.95±0.4 to 11.47±1.1 µg/mL and AUC(0-12) ranged from 15.78±3.1 to 95.91±14.6 µg·hr/mL in the dosages administered (25 mg/kg to 100 mg/kg).

Conclusions: Rabbits treated with APX25, APX50, and APX100 demonstrated significant efficacy in treatment of experimental Candida endophthalmitis and hematogenous Candida meningoencephalitis which was compatible in activity to that of DAmB.