Background: Isavuconazole demonstrated efficient brain penetration in rats. Comparative brain penetration of isavuconazole and voriconazole was assessed.

Methods: 25 mg/kg isavuconazole equivalent was dosed orally (10:1 mix of isavuconazonium sulfate to isavuconazole) to 20 rats (60–130 g) for brain penetration and 30 rats (297–352 g) for excretion studies. Following a single oral dose, rats were sacrificed at various time points (pre-dose, 0.25, 0.5, 1, 2, 3, 6, 8, and 24 h post-administration). Brain and plasma concentrations were determined with validated liquid chromatography–mass spectrometry/mass spectrometry method. Results: Isavuconazole concentrations in brain were similar to those in plasma. The maximum concentration in brain was approximately double that observed in plasma (average individual concentration ratio, 1.8; coefficient of variation [CV], 16%). Total exposure over the dosing period was almost double for isavuconazole in brain and plasma compared with voriconazole. Similar to isavuconazole, brain concentrations of voriconazole were approximately double that observed in plasma (average individual plasma concentration ratio, 1.8; coefficient of variation [CV], 16%).

Conclusions: Isavuconazole concentrations in brain reached peak concentrations approximately 3 h after oral administration (as isavuconazonium sulfate) to determine plasma and brain levels and overall exposure in brain were almost 2-fold higher than plasma. Isavuconazonium sulfate is the prodrug of the active triazole isavuconazole. Isavuconazole concentrations in the rat were similar in brain and plasma and declined in parallel to those in plasma. AUC was approximately double that observed in plasma (average individual concentration ratio, 1.8; coefficient of variation [CV], 16%).