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In-vitro activity of APX001A and comparators against clinical isolates of rare moulds

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Background: APX001A is a novel antifungal that inhibits Gwt1, a protein that plays an important role in fungal cell wall integrity. Previous studies have shown APX001A has broad activity against yeasts, *Aspergillus* and rare moulds, including, *Fusarium* and *Scedosporium*. The aim of this study was to further evaluate the activity of APX001A and other antifungal agents against rare moulds

Material/methods: 200 strains were tested for antifungal susceptibility following EUCAST and CLSI methodologies. All strains were obtained from clinical samples and identified to species level by sequencing the Internal Transcribed Spacer (ITS) and part of the beta tubulin in *Aspergillus* spp. and *Scedosporium* spp. or elongation factor alpha in *Fusarium* spp.. Ten strains of each of the following species were tested: *Rhizopus arrhizus, Lichtheimia ramosa, Mucor circinelloides, Lichtheimia corymbifera, Rhizopus microsporus, Rhizomucor pusillus, Cunninghamella bertholletiae, Scedosporium apiospermum, Lomentospora prolificans, Scedosporium boydii, Scedosporium aurantiacum, Fusarium oxysporum, Fusarium verticillioides, Aspergillus lentulus, Aspergillus alliaceus, Aspergillus calidoustus, Aspergillus fumigatiaffinis, Aspergillus pseudofischeri, Aspergillus udagawae* and *Alternaria alternata.* The antifungals used were: amphotericin B (range 0.03-16 mg/L), posaconazole (0.015-8 mg/L), micafungin (0.004-2 mg/L) and APX001A (0.015-8 mg/L). *Aspergillus flavus* ATCC204304 and *Aspergillus fumigatus* ATCC204305 were used as quality control strains. Minimal Inhibitory Concentrations (MIC) for amphotericin B and posaconazole and Minimum Effective Concentrations (MEC) for micafungin and APX001A were read after 24 and 48 hours of incubation.

Results: APX001A was the most active drug against all isolates of *Scedosporium* and *Lomentospora* species and was the only compound with MEC_{90} ≤2 mg/L (EUCAST). Cryptic species of *Aspergillus* were inhibited by APX001A and micafungin with MEC_{90} values of ≤ 0.5 mg/L and ≤ 2 mg/L, respectively, except for *A. calidoustus* with a micafungin MEC_{90} of 4 mg/L. APX001A showed variable activity against *Fusarium*, with some strains showing MEC ≤0.06 mg/L and others showing MEC >8 mg/L (EUCAST). APX001A had moderate activity against *A. alternata* (MEC_{50} ≤0.5 mg/L and MEC_{90} >2 mg/L), with micafungin being the most active drug for this species (MEC_{90} <2mg/L). Amphotericin B was the most active compound for Mucorales with MIC_{90} values (inhibition of 90% of the isolates) <2 mg/L for all species except for *C. bertholletiae* with MIC_{90} >4 mg/L. APX001A was not active against any species of Mucorales with MEC_{50} values for EUCAST at 24h of > 2mg/L for all species

Conclusions: APX001A was active against *Scedosporium, Lomentospora,* all cryptic species of *Aspergillus* and some strains of *Fusarium* spp. It was inactive against the Mucorales species evaluated. Amphotericin B was the most active compound for Mucorales and *Fusarium* spp. APX001A showed good activity against species with intrinsic resistance to amphotericin B and/or azoles. APX001A was the only drug active against the multiresistant species *L. prolificans* and *A. calidoustus*.