# *In vivo* efficacy of olorofim against systemic infection caused by *Scedosporium apiospermum*, *Pseudallescheria boydii*, and *Lomentospora prolificans* in neutropenic CD-1 mice

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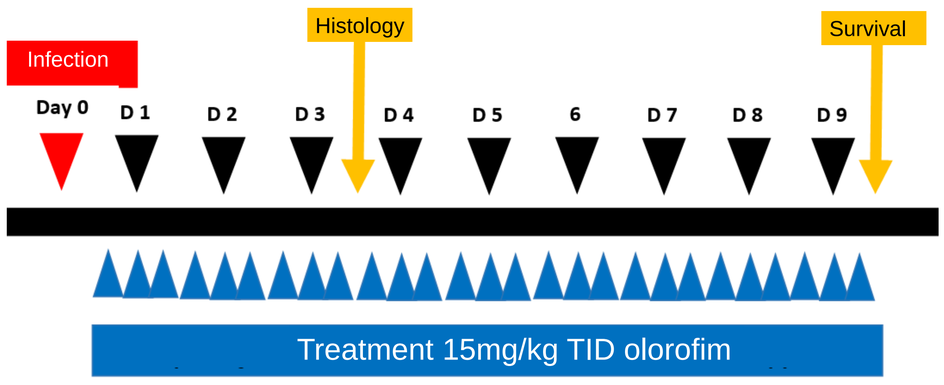
## Introduction

Clinically relevant members of the *Scedosporium/ Pseudallescheria* species complex and *Lomentospora prolificans* are generally resistant to currently available systemic antifungal agents and infections due to these species are difficult to treat. Alternative treatments with new classes of antifungals may improve therapeutic outcomes of the disease caused by these difficult to treat molds.

## Methods

We studied the *in vivo* efficacy of olorofim (formerly F901318), a new fungicidal agent that prevents growth of many ascomycetous mold species via inhibition of de novo pyrimidine biosynthesis, against scedosporiosis caused by three species in neutropenic CD-1 mice. Cyclophosphamide immunosuppressed mice infected with *Scedosporium apiospermum*, *Pseudallescheria boydii* and *Lomentospora prolificans* (5 x10^4 CFU/mice, tail vein infection) were treated by intraperitoneal administration of olorofim (15 mg/kg every 8 h for 9 days). The efficacy of olorofim treatment was assessed by survival rate at day 10 (end of treatment) and at day 14 post infection, and tissue histopathology 3 days post infection.

**Figure 1.** Schematic of experimental design.




## Results

In the neutropenic CD-1 mice, olorofim therapy significantly improved survival compared to the untreated controls; 80%, 100% and 100% of treated mice survived infection by *Scedosporium apiospermum*, *Pseudallescheria boydii*, and *Lomentospora prolificans,* respectively, while less than 20% of the control mice (PBS-treated) survived at 14 days post infection. Furthermore, histopathological slides of kidneys revealed only small numbers of fungal elements in the olorofim-treated mice, whilst numerous fungal hyphae were present in control mice.

**Figure 2.** *In vitro* antifungal susceptibility profile (µg/ml) of *Scedosporium-Pseudallescheria* species-complex used in animal studies, using CLSI guidelines.

| | Amphotericin B | Voriconazole | Olorofim |
|---|---|---|---|
| ***Scedosporium apiospermum*** | **8** | **1** | **0.016** |
| ***Pseudallescheria boydii*** | **8** | **0.25** | **0.016** |
| ***Lomentospora prolificans*** | **8** | **8** | **0.031** |

**Figure 3.** Efficacy of olorofim against *Scedosporium apiospermum*, *Pseudallescheria boydii* and *Lomentospora prolificans*. Olorofim treatment significantly improved survival compared to the non-treated controls in CD-1 mice. Control groups received PBS. For all groups, *n*=10.

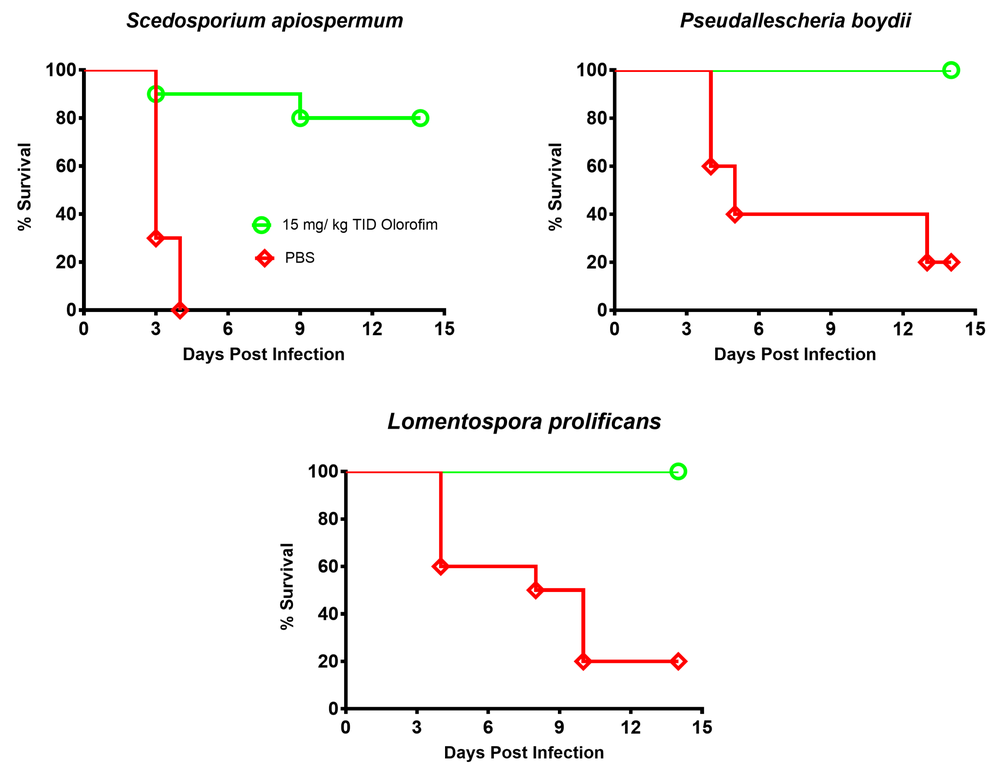
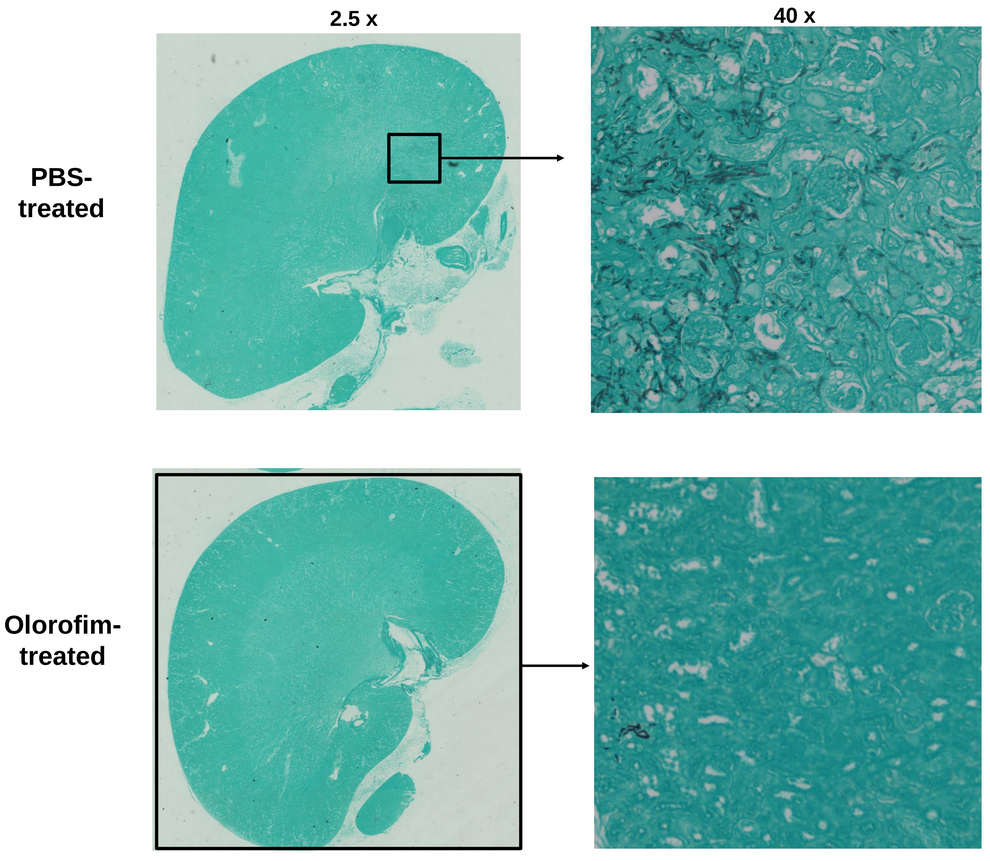



**Figure 4.** In histopathology sections taken 3 days post infection in CD-1 mice, fungal elements were visible throughout the kidney in control animals infected with all three species. However, only few lesions with hyphal elements were observed in the animals which received olorofim therapy. The figure represents GMS stained sections of kidneys in CD-1 mice infected with *Lomentospora prolificans.*




## Conclusion

- Overall, treatment with olorofim improved the survival of the mice infected with all three species causing scedosporiosis and showed rapid clearance of fungi from the kidney by histological staining.
- These results show olorofim to be a promising therapeutic agent for systemic scedosporiosis, a difficult disease to treat with currently available antifungals.

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