

## A Phase 3 Randomized Double-Blind Multicenter Study to Compare the Efficacy and Safety of Micafungin versus Amphotericin B Deoxycholate for the Treatment of Neonatal Candidiasis

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### Synopsis:

To evaluate the efficacy and safety of micafungin in comparison to Amphotericin B Deoxycholate (CAB) in the treatment of proven neonatal candidiasis and to further evaluate the pharmacokinetics of micafungin, as well as CAB, in this patient population.

- The primary endpoint for the study is fungal free survival at one week following the last dose of study drug.
- The secondary objectives are to:
  1. Time to mycological clearance of invasive candidiasis.
  2. Time to positive clinical response (complete or partial).
  3. Fungal free survival in patients with end-organ dissemination at End of Study Drug
  4. Therapy and one week after last dose of study drug.
  5. Clinical response (complete, partial, stabilization, progression) at the End of Study Drug
  6. Therapy and one week after last dose of study drug.
  7. Eradication, persistence at End of Study Drug Therapy and one week after last dose of study drug
  8. Overall incidence of emergent and recurrent fungal infections through the End of Study.

The incidence of candidiasis is rising steadily. *Candida* species are now the fourth most common organism recovered from the bloodstream of hospitalized patients. [Jarvis WR, Clin Inf Dis, 1995] *Candida* species are a leading cause of infectious mortality in the neonatal intensive care unit (NICU). The incidence of candidemia in extremely low birth weight (ELBW) infants varies from 4-18% [Benjamin DK et al, J Pediat 2003; Kaufman D et al, 2001; Stoll BJ et al, 2002; Benjamin DK et al, J Pediat 2003]. Neonatal candidemia has an attributable mortality of 20-30% [Stoll BJ et al, Pediat 2002]. In addition to significant mortality, candidiasis frequently results in severe morbidity. *Candida* species invade virtually all tissues, including the neonatal retina, brain, heart, lung, liver, spleen, and joints; invasive *Candida* infections cause blindness, developmental delay, and the need for invasive corrective procedures [Benjamin DK et al, J Pediat 2003]. The most common species causing neonatal candidiasis are *C. albicans* and *C. parapsilosis*.

Micafungin is a cyclic lipopeptide antifungal of the echinocandin class. Echinocandins are noncompetitive inhibitors of (1, 3)- $\beta$ -D-glucan synthase, a fungus specific enzyme crucial to the biosynthesis of cell wall component glucan. Thus, echinocandins compromise fungal cell wall integrity and cause fungal cell death. The activity of micafungin against *Candida* species has been well documented both in vitro as well as in vivo. Micafungin has been shown to be more active in vitro and to have more potent fungicidal activity than CAB, fluconazole and itraconazole against clinical isolates of *C. albicans* (including fluconazole resistant strains), *C. tropicalis*, *C. glabrata*, and *C. krusei*. Micafungin is approved by the U.S. Food and Drug Administration for the treatment of esophageal candidiasis and the prophylaxis of *Candida* infections in hematopoietic stem cell transplant recipients.