Brincidofovir (BCV) inhibits viral replication and is active against all 3 families of DNA viruses that cause human disease. Chimerix is developing BCV for multiple indications leading with prevention of CMV in transplant patients. Simultaneously, Chimerix is developing BCV for treatment of smallpox under the “Animal Rule”. This randomized, blinded, placebo-controlled study determined the effectiveness of BCV for prevention of mortality caused by infection with a lethal strain of rabbitpox virus strain (RPXV). Infected rabbits were randomized to treatment at the first observation of secondary lesions confirmed by 2 independent technicians. Lesions triggering randomization were observed on Days 3, 4 and 5 post infection in 24, 18, and 3 rabbits, respectively. Each treatment regimen consisted of 3 doses spaced at 48 hours beginning at randomization. Doses of 5/5/5, 20/5/5 and 20/20/20 mg/kg BCV were evaluated. Compared with placebo, a dose dependent increase in survival was observed in all BCV treatment groups with statistical significance achieved at the 20/5/5 and 20/20/20 mg/kg doses. These data demonstrate that BCV is effective for treatment of lethal poxvirus infection even when administered after appearance of clinical signs of disease, late in the course of infection. In the PK arm, administration of BCV was initiated on Day 4 post infection. The concentration of cidofovir diphosphate (CDV-PP), the active antiviral, was determined in peripheral blood mononuclear cells (PBMCs) to scale to a human dose for treatment of smallpox. CDV-PP exposure in PBMCs from rabbits given the 20/5/5 mg/kg regimen was less than or equal to that of Infection to Death or Resolution of Disease in the Intradermal Rabbitpox (RPXV) Model Compared with Human Smallpox. Clinical signs appear at approximately the mid point of disease in both rabbits and humans. A 3 dose, 48 hour regimen for RPXV is proposed to scale to a 2 week treatment course in humans.

**Objectives**

- To compare the effectiveness of each of 3 different regimens of BCV with placebo, in a blinded study, when treatment is initiated at the first observation of secondary lesions.
- To determine concentrations of the active antiviral, CDV-PP, following the first and third dose of a three dose regimen for use in scaling to a human dose.

**Results**

1. **Normalized Timelines for Key Disease Milestones from Day 0 (inoculation) to Death or Resolution of Disease in the Intradermal Rabbitpox (RPXV) Model Compared with Human Smallpox.**
2. **Percent Mortality by Day Randomized for Brincidofovir Compared with Placebo Treated Animals.** Rabbits were randomized at the first observation of lesions. All rabbits met randomization criteria on either Day 3, 4 or 5 following inoculation, as shown in black, red, and green, respectively. As expected, mortality was independent of the Day of Randomization for placebo treated animals. By contrast, early randomization to Brincidofovir (Day 3) resulted in improved survival compared with animals randomized late in the disease course (Day 5 PI). The median time to death in placebo treated animals was Day 8.
3. **Figure 3. Percent Mortality by Day Randomized for Brincidofovir Compared with Placebo Treated Animals.**

**Conclusions**

- By contrast, early randomization to Brincidofovir (Day 3) exhibited statistically significantly higher survival relative to placebo (Group 4). Improved survival, albeit not significant, was also observed at 5/5/5 mg/kg.

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