Brincidofovir [BCV (CMX001)] inhibits viral replication and is active against all 5 families of dsDNA viruses causing human disease. Chimerix is developing BCV for multiple indications leading with prevention of CMV in transplant patients. Jointly, BCV is being developed for treatment of smallpox under the “Animal Rule”. This randomized, blinded, placebo-controlled study determined the efficacy of BCV for prevention of mortality caused by intradermal infection with a lethal inoculum of RPXV strain Utrecht. Infected rabbits were randomized to treatment at the first observation of secondary lesions. Treatment regimens consisted of 3 oral 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 to placebo, a statistically significant, dose dependent increase in survival was observed at the 20/5/5 and 20/20/20 mg/kg doses; demonstrating that BCV is effective for treatment of lethal poxvirus infection when administered after appearance of clinical signs of disease, specifically appearance of secondary lesions remote from the inoculation site.

An independent cohort of rabbits was added to study the PK of the 20/5/5 mg/kg regimen of BCV, when dose was initiated Day 4 post-infection. The concentration of cidofovir-diphosphate (CDV-PP), the active antiviral, was assessed in peripheral blood mononuclear cells (PBMCs) to support scaling to a human dose for treatment of smallpox. Rabbit PBMC CDV-PP exposure was less than or equal to that in humans given doses currently under evaluation in clinical studies for other dsDNA viruses. These data support the feasibility of scaling doses of BCV that are effective in a lethal animal model of smallpox to a human dose that is under evaluation in a Phase 3 clinical study for prevention of CMV. This work was supported by the Biomedical Advanced Research and Development Authority (BARDA) under contract HHSO100201100013C.