Efficacy and Pharmacokinetics of Brincidofovir for Treatment of Lethal Rabbitpox Virus (RPXV) Infection in NZW Rabbits: A Model of Human Smallpox

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Abstract

Brincidofovir [BCV (CMX001)] inhibits viral replication and is active against all 5 families of dsDNA 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 inoculum of rabbitpox virus strain Utrecht. 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, 19, and 19 animals, 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 in humans given doses currently under evaluation for prevention of CMV. These data demonstrate the feasibility of scaling doses of BCV that are effective in a lethal animal model of smallpox to a human dose.

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.

Experimental Design

Group	Number Randomized [a]	BCV Dose (mg/kg)	Timing of Dose Administration		
			First Dose	Second Dose	Third Dose
1	16 (7M/9F)	5 +5+5	At or within 4 hours of 1st observation of 2° lesions (RD0)	At 1st observation of 2° lesions plus 48 (± 4) hours (RD2)	At 1st observation of 2° lesions plus 96 (± 4) hours (RD4)
2	15 (10M/5F)	20+5+5			
3	15 (8M/7F)	20+20+20			
4	16 (6M/10F)	0+0+0			
5 (PK)	9 males	20+5+5	Day 4 post infection (ID4)	48 (± 4) hours after first dose (ID6)	96 (± 4) hours after first dose (ID8)
		PBMC PK Samples (Hrs):	12, 24, 48	N/A	Predose, 24, 48, 72, 120 and 168

[a] The target minimum randomization was 6/sex/group.
RD = Randomization Day (unique for each animal based on first observation of lesions in that animal).

Results

Figure 1. Normalized Timelines for Key Disease Milestones from Day 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, q48 hour regimen for RPXV is proposed to scale to a 2 week treatment course in humans.

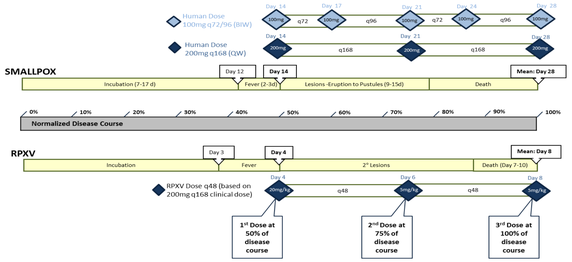
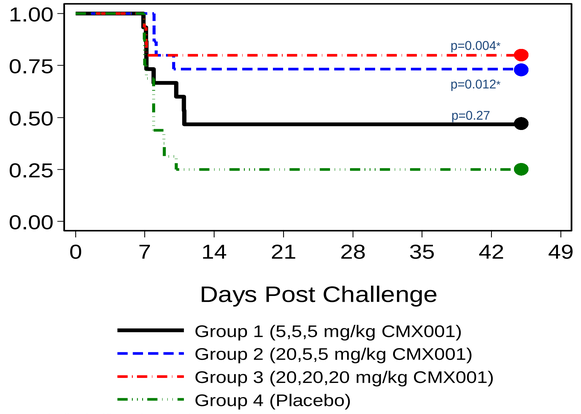


Figure 2. Kaplan-Meier Curves Representing Time to Death. Both the 20/5/5 and 20/20/20 mg/kg dose groups (Groups 2 and 3) exhibited statistically significantly higher survival relative to placebo (Group 4). Improved survival, albeit not significant, was also observed at 5/5/5 mg/kg.



*Statistically significant ($p \leq 0.05$)

Figure 3. 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 PI) 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.

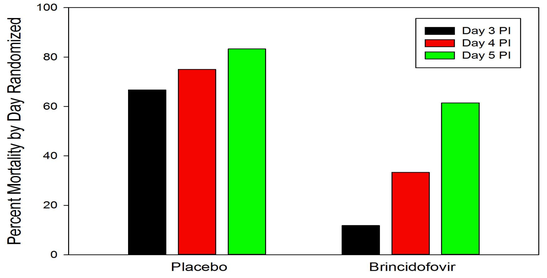


Figure 4. Mean Change from Baseline in Rabbitpox Viremia. There was a dose-related decrease in viral load in rabbits administered BCV as compared with those administered placebo. The difference was apparent by Day 6 post-infection. Data are presented as the change from baseline, with the last observation carried forward for any animals that died prior to the scheduled termination.

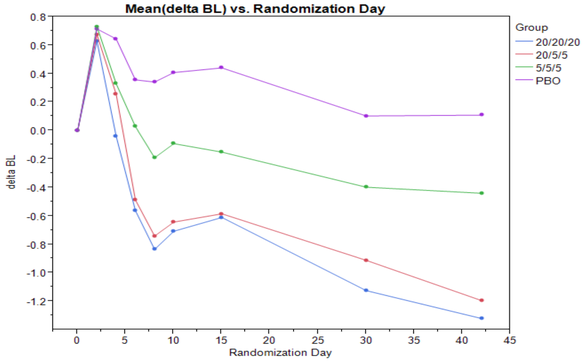
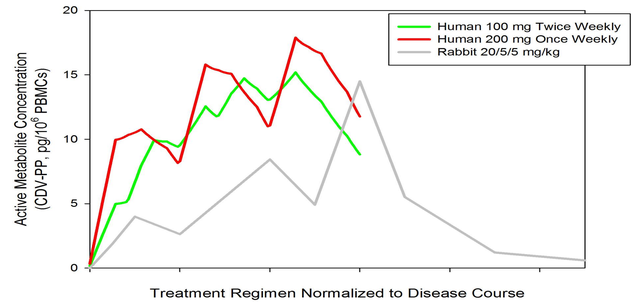


Figure 5. Exposure to the Active Metabolite at an Efficacious Dose in the RPXV Model Compared with Exposures in Humans Given Two Regimens of BCV Proposed for Treatment of Smallpox. Concentrations of CDV-PP, the active antiviral metabolite of BCV, in humans given either a 100 mg twice weekly or a 200 mg once weekly regimen of BCV exceed those in rabbits. PBMCs were used to compare relative tissue levels in rabbits and humans. Both treatment regimens are under evaluation for treatment of other serious viral diseases; Brincidofovir has been administered to more than 1000 human subjects.



Conclusions

- Intradermal inoculation with a lethal dose (300 PFU) of rabbitpox virus (Utrecht) resulted in qPCR quantifiable blood viremia by Day 3 post-inoculation with lesions appearing between Days 3 and 5 post-inoculation in all main study animals.
- Both the 20/20/20 (p=0.004) and 20/5/5 mg/kg (p=0.012) 3-dose, q48 hour regimens of BCV demonstrated a statistically significant survival benefit compared with placebo when initiated at the first observation of secondary lesions.
- A trend suggestive of increased survival relative to the placebo was also observed in the 5/5/5/ mg/kg cohort, however, this difference was not statistically significant (p=0.27).
- Exposure to the active metabolite of BCV, CDV-PP, in humans at doses currently being evaluated for other viral diseases are equal to or higher than those produced in rabbits by an efficacious regimen in the RPXV model.
- Therefore, a 3 dose regimen of 20/5/5 mg/kg given q48 hours, when initiated at the first observation of secondary lesions, is an efficacious dose in the intradermal rabbitpox model of smallpox and can be scaled to a human dose regimen of either 100 mg twice weekly or 200 mg once weekly.

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