ACTIVITY OF BRINCIDOFOVIR (BCV) AGAINST MURINE POLYOMAVIRUS (MUPYV) IN A MOUSE INFECTION MODEL

Kidney Week 2018 Poster # SA-PO642

BRINCIDOFOVIR(BCV) DEMONSTRATES ANTIVIRAL ACTIVITY AGAINST MURINE POLYOMAVIRUS (MUPYV) IN A MOUSE MODEL OF ACUTE INFECTION

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BCV Background

- BCV is a lipid conjugate of the nucleotide analog cidofovir (CDV, CMX021).
- The lipid conjugate facilitates entry of BCV into the cell via endogenous lipid uptake pathways.¹,²
- Intracellularly, BCV is converted to active cidofovir diphosphate (CDV-PP).
- CDV-PP exerts an antiviral effect by acting as a potent alternate substrate inhibitor of viral DNA synthesis.³
- Gastrointestinal events (e.g., diarrhea) have been dose limiting with longer-term oral BCV dosing.⁴,⁵
- The development of an IV formulation of BCV has demonstrated improved tolerability allowing administration of higher doses or longer durations of BCV.⁶
- IV BCV facilitates delivery of consistent concentrations of BCV and CDV-pp to tissues, including the kidney, allowing for improved efficacy against viruses with kidney tropism such as BK virus.

⁵ Grossi IM, et al. The Toxicologist: Supplement to Toxicological Sciences, Society of Toxicology. 2017:[abstract 1687]
⁶ Poster # 1421 presented at ID Week Congress, San Francisco, CA, USA, October 3-7, 2018
Genetic Organization of Polyomavirus

- Polyomaviruses are a family of small DNA viruses that persistently infect their hosts for life.
- Human polyomavirus, BKV, is responsible for kidney transplant rejections.
- Since polyomaviruses are species-specific, the MuPyV-mouse model enables study of polyomavirus pathogenesis in a natural host.

Closed circular dsDNA molecule
Transcription is bidirectional from ORI in the NCCR
Early coding region encodes large T (TAg) and small T (tAg)
Late coding region encodes structural proteins VP1, VP2 and VP3

Large T antigen is a multi-function protein
- TAg stimulates cell cycle progression and counteracts apoptosis
- ATPase/helicase
- Binds to host DNA polymerase; role in DNA replication
Improved Renal Function in HCT Recipients on BCV: Evidence of Potential Effect on BKV

Mean (N) Change from Baseline in eGFR (mL/min/1.73 m²) by Visit and Dose in Study 201

<table>
<thead>
<tr>
<th>Baseline GFR</th>
<th>Week 2</th>
<th>Week 4</th>
<th>Week 6</th>
<th>Week 8</th>
<th>Week 10</th>
<th>Post-Week 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>-7 (56)</td>
<td>-9 (46)</td>
<td>-10 (35)</td>
<td>-19 (36)</td>
<td>-15 (21)</td>
<td>-13 (57)</td>
</tr>
<tr>
<td>Brincidofovir 100 mg BIW</td>
<td>-5 (49)</td>
<td>-3 (44)</td>
<td>1 (33)</td>
<td>12 (31)</td>
<td>6 (21)</td>
<td>8 (49)</td>
</tr>
</tbody>
</table>

p = 0.0013  p = 0.0103  p = 0.0025

eGFR: estimated glomerular filtration rate
Data from Study 201 presented at BMT Tandem, February 2013
PROPHYLAXIS ANIMAL MODEL

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# BCV Prophylaxis in an Acute MuPyV Infection Model

<table>
<thead>
<tr>
<th>BCV Dose (mg/kg BiW)</th>
<th>Viral Inoculum</th>
<th>Female B6 Mice (n=)</th>
<th>Day 1 interim tissue collection(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>(10^4)</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(10^5)</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(10^6)</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>(0^b)</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>(10^4)</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(10^5)</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(10^6)</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>40</td>
<td>(0^b)</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>(10^4)</td>
<td>5</td>
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</tr>
<tr>
<td></td>
<td>(10^5)</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(10^6)</td>
<td>5</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\) Day 1 (n=3/dose group) tissue collection (pre-3\(^{rd}\) BCV dose)

\(^b\) Day 5 (n=3 / BCV dose group) to provide comparison of BCV/CDV-pp exposures in infected vs non-infected mice

### Endpoints
- Viral load in kidney at day 5 by qPCR
- Kidney BCV and CDV-pp concentrations
- Plasma BCV concentrations (in progress)
Viral Genome qPCR - Kidney \((10^6 \text{ initial viral inoculum})\)

\geq 20 \text{ mg/kg i.p} \ BCV \text{ decreased viral load in the kidney by } \sim 1 \log

** \(10^4\) and \(10^5\) inoculum undetectable in kidney at Day 5

** p<0.01
Kidney CDV-pp in infected and uninfected animals

- CDV-pp concentrations in kidney on Day 1 were below limit of detection (*data not shown*).
- Day 1 collection (prior to infection) was 3 days after most recent BCV dose.
- Kidneys collected on Day 5 (24 hours after most-recent BCV dose) demonstrated dose responsive levels of tissue CDV-pp.
- Inter-animal variability led to inconclusive findings regarding infected vs. uninfected CDV-pp concentrations.
Conclusions

- BCV reduced MuPyV viral load when administered ≥ 20 mg/kg via IP administration to mice given 2 BIW doses of BCV pre- and post-infection.
- While this experiment evaluated the prophylactic administration of BCV, undetectable levels of CDV-pp in the kidney on the day of infection (Day 1) suggests that BCV could be effective in a treatment scenario.
- Additional data are being generated to characterize the pharmacokinetics (PK) of BCV and CDV-pp in the plasma and kidney of mice given BCV via IP administration to facilitate comparison to human plasma exposure.
TREATMENT ANIMAL MODEL

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## CMX001-VIR-110: Post Infection BCV I.P. Via 3 Dosing Regimens

<table>
<thead>
<tr>
<th>Group</th>
<th>Infection (10^6)</th>
<th>i.p. BCV (mg/kg)</th>
<th>Terminal</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n= Day 0 Day 1 Day 2 Day 3 Day 4 Day 5 Day 6 Day 7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group 1</td>
<td>Uninfected Placebo</td>
<td>3 0 0 0 0 0 0 0</td>
<td></td>
</tr>
<tr>
<td>Group 2</td>
<td>Infected Single Dose Placebo</td>
<td>3 10^6 0 -- -- -- -- --</td>
<td></td>
</tr>
<tr>
<td>Group 3</td>
<td>Infected Daily Placebo</td>
<td>3 10^6 0 0 0 0 0 0</td>
<td></td>
</tr>
<tr>
<td>Group 4</td>
<td>Infected BiW Placebo</td>
<td>3 10^6 0 -- -- 0 -- --</td>
<td></td>
</tr>
<tr>
<td>Group 5</td>
<td>Infected Single Dose</td>
<td>6 10^6 80 -- -- -- -- --</td>
<td></td>
</tr>
<tr>
<td>Group 6</td>
<td>Infected Daily</td>
<td>6 10^6 13 13 13 13 13 13 13</td>
<td></td>
</tr>
<tr>
<td>Group 7</td>
<td>Infected BiW</td>
<td>6 10^6 40 -- -- 40 -- --</td>
<td></td>
</tr>
</tbody>
</table>

### Endpoints
- Kidney viral load at Day 7 by qPCR
- Kidney CDV-pp concentrations at Day 7
- Plasma BCV concentrations at Day 7
BCV demonstrates antiviral activity in the kidneys of mice infected with MuPyV

Bars represent mean ± SD; Mann-Whitney test- *** p<0.001
Mouse Kidney CDV-pp seen at all doses

Kidney BCV
CMX001-VIR-110 (treatment)
Collected Day 7 (after 1 week txt regimen)

Kidney CDV-pp
CMX001-VIR-110 (treatment)
Collected Day 7 (after 1 week txt regimen)
Treatment Model Conclusions

- BCV reduced MuPyV viral load in the kidney $\geq 2 \log_{10}$ when administered to MuPyV infected mice once weekly at 80 mg/kg, twice weekly at 40 mg/kg, or daily for 6 days at 13 mg/kg via IP administration.
- Six days after a single 80 mg/kg dose, viral load was reduced in the presence of no detectable kidney BCV and ~30 ng/g CDV-pp. These data suggest the potential to employ a once weekly dosing regimen.
- Additional data are being generated to characterize the pharmacokinetics (PK) of BCV and CDV-pp in the plasma and kidney of mice given BCV via IP administration to facilitate comparison to human plasma exposure.