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.

1. Painter GR & Hostetler KY. Trends Biotechnol. 2004;22:423-7.
2. Lanier R, et al. Viruses. 2010;2:2740-62.
3. Xiong X, et al. Antimicrob Agents Chemother. 1997;41:594-9.
4. Prasad VK, et al. Biol Blood Marrow Transplant. 2017;23:S57-S8 [abstract].
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

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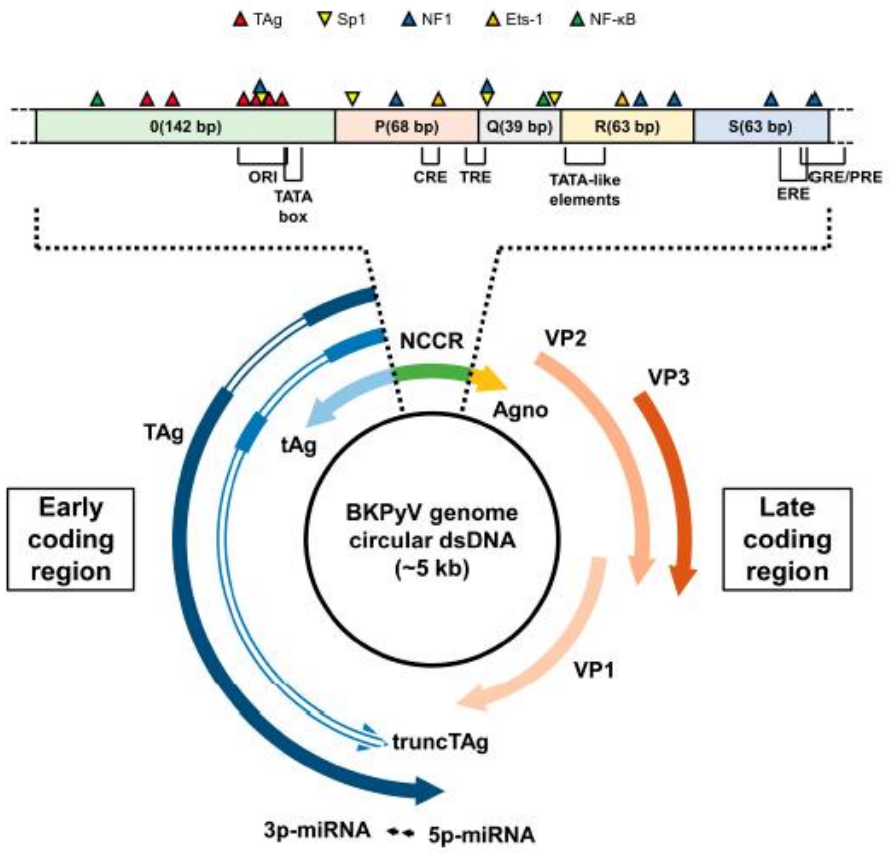
Genetic Organization of Polyomavirus

- 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

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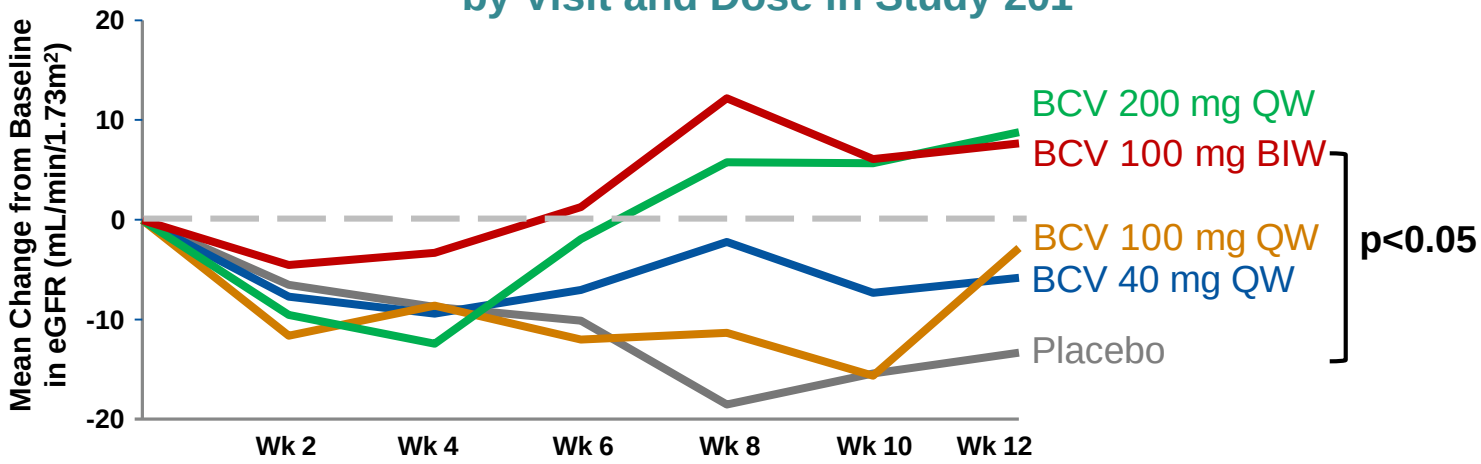
Improved Renal Function in HCT Recipients on BCV: Evidence of Potential Effect on BKV

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



Time of Dosing (from randomization into Study 201**)**

Baseline GFR	Week 2	Week 4	Week 6	Week 8	Week 10	Post-Week 1
Placebo	-7 (56)	-9 (46)	-10 (35)	-19 (36)	-15 (21)	-13 (57)
Brincidofovir 100 mg BIW	-5 (49)	-3 (44)	1 (33)	12 (31)	6 (21)	8 (49)
				p=0.0013	**p=0.0103**	**p=0.0025**

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

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PROPHYLAXIS ANIMAL MODEL

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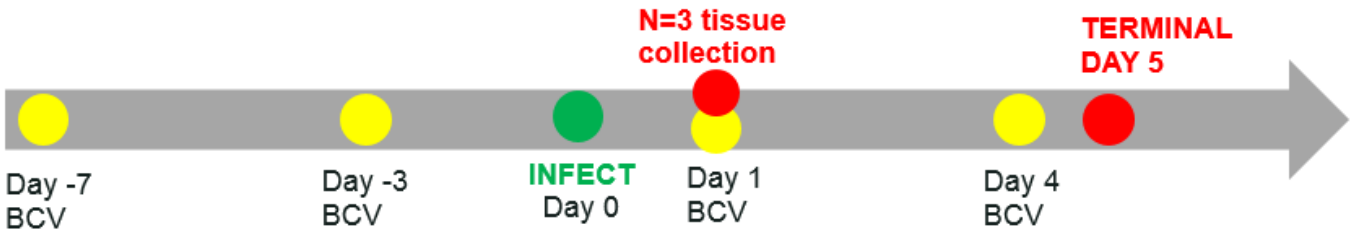
BCV Prophylaxis in an Acute MuPyV Infection Model

BCV Dose (mg/kg BiW)	Viral Inoculum	Female B6 Mice (n=)	Day 1 interim tissue collection[a]
0	10^4	5	
	10^5	5	
	10^6	5	
20	0 [b]	6	3
	10^4	5	
	10^5	5	
	10^6	5	
40	0 [b]	6	3
	10^4	5	
	10^5	5	
	10^6	5	

[a] Day 1 (n=3/dose group) tissue collection (pre-3rd 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)

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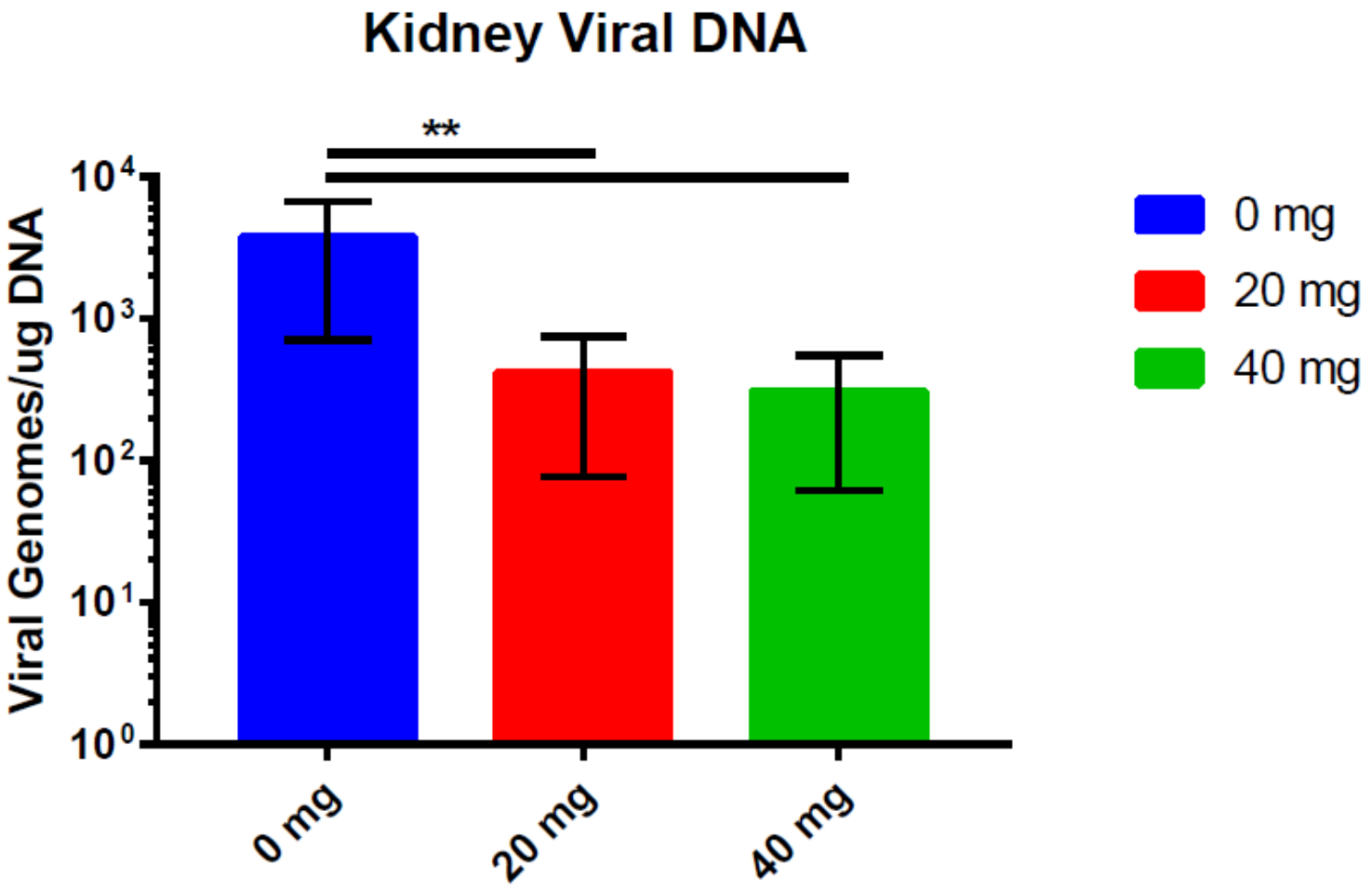
Viral Genome qPCR- Kidney *(10^6 initial viral inoculum)*

≥ 20 mg/kg i.p BCV decreased viral load in the kidney by ~1 log
** 10^4 and 10^5 inoculum undetectable in kidney at Day 5



*n=5; Bars represent mean ± SD; Mann-Whitney test- ** p<0.01*

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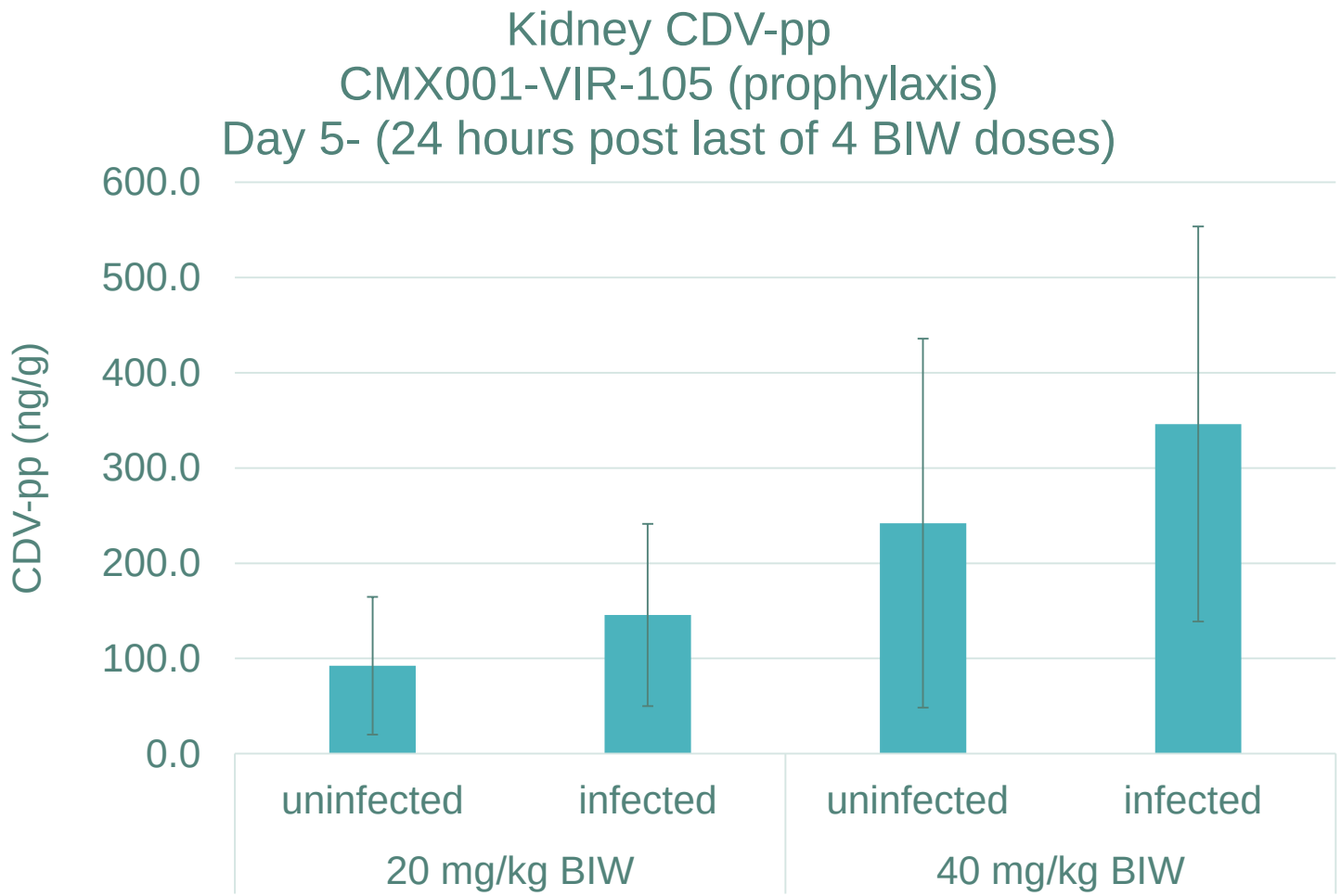
Kidney CDV-pp in infected and uninfected animals



- 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.

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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

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TREATMENT ANIMAL MODEL

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

			Infection (10^6)	i.p. BCV (mg/kg)						
		n=	Day 0	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Group 1	Uninfected Placebo	3	0	0	0	0	0	0	0	Terminal
Group 2	Infected Single Dose Placebo	3	10^6	0	--	--	--	--	--	
Group 3	Infected Daily Placebo	3	10^6	0	0	0	0	0	0	
Group 4	Infected BIW Placebo	3	10^6	0	--	--	0	--	--	
Group 5	Infected Single Dose	6	10^6	80	--	--	--	--	--	
Group 6	Infected Daily	6	10^6	13	13	13	13	13	13	
Group 7	Infected BIW	6	10^6	40	--	--	40	--	--	

Endpoints

- Kidney viral load at Day 7 by qPCR
- Kidney CDV-pp concentrations at Day 7
- Plasma BCV concentrations at Day 7

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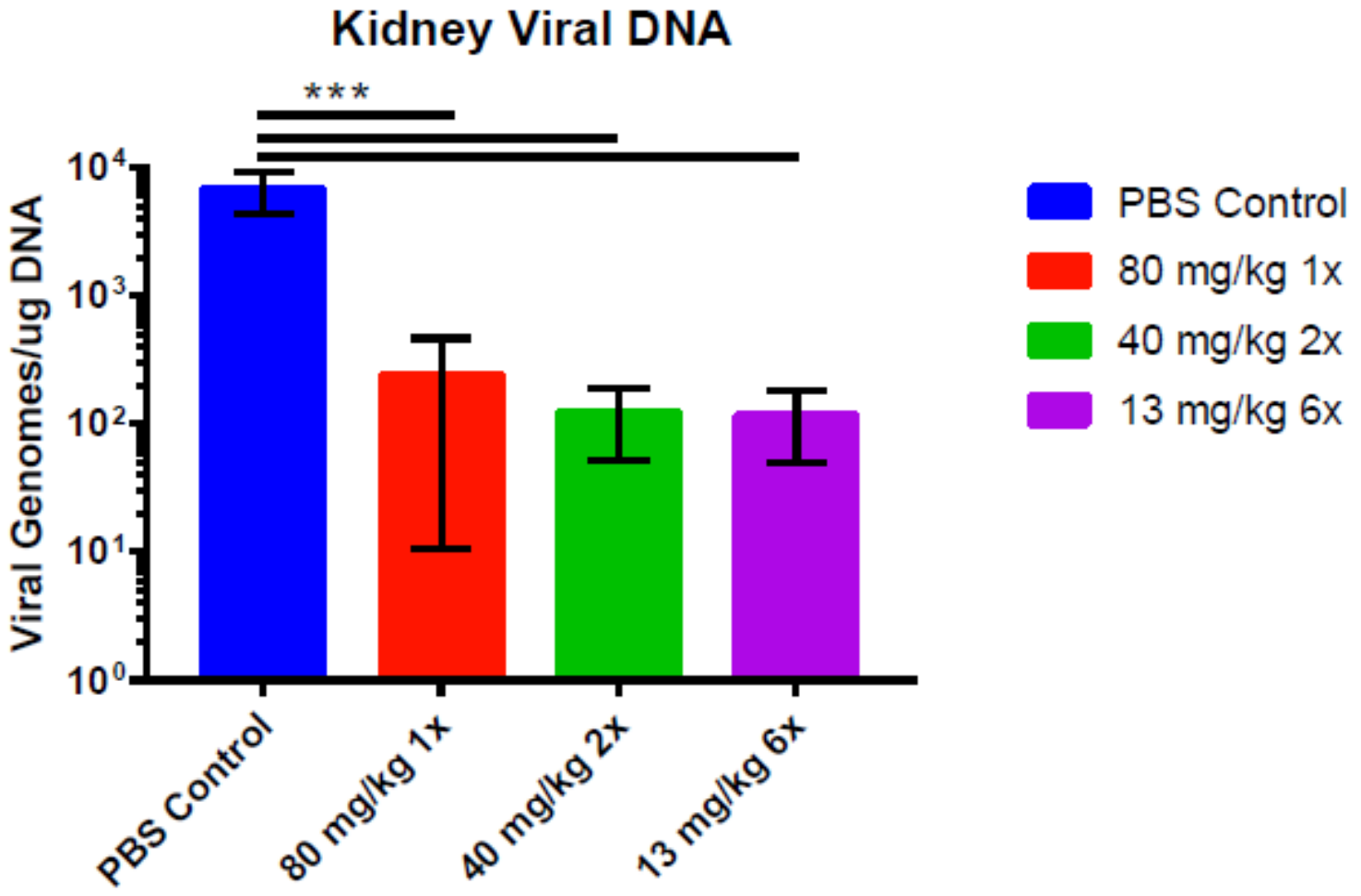
BCV demonstrates antiviral activity in the kidneys of mice infected with MuPyV



*Bars represent mean ± SD; Mann-Whitney test- *** p<0.001*

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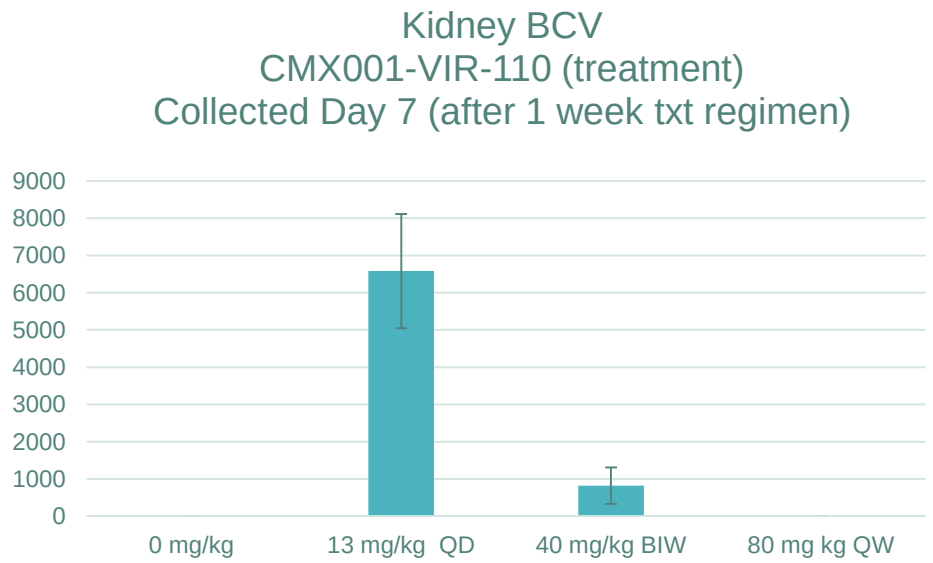
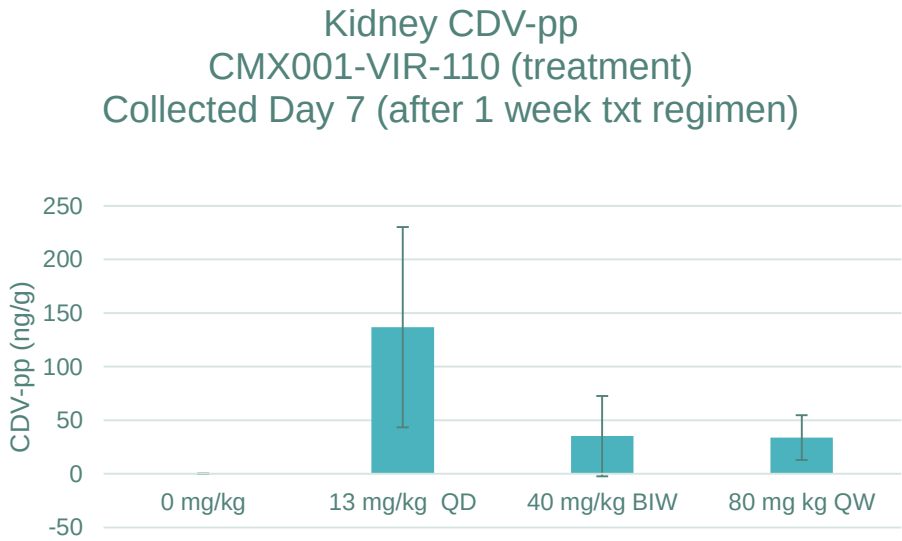
Mouse Kidney CDV-pp seen at all doses





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Treatment Model Conclusions

- BCV reduced MuPyV viral load in the kidney ≥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.

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