

# Tissue Distribution of Radioactivity after Intravenous and Oral Administration of [<sup>14</sup>C]Brincidofovir to Rats

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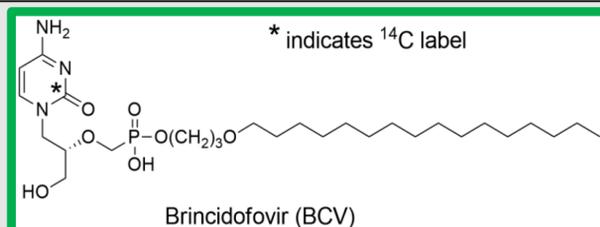


## PURPOSE

To determine the tissue distribution of radioactivity after single intravenous (IV) or oral (PO) administration of [<sup>14</sup>C]brincidofovir (BCV) to rats.

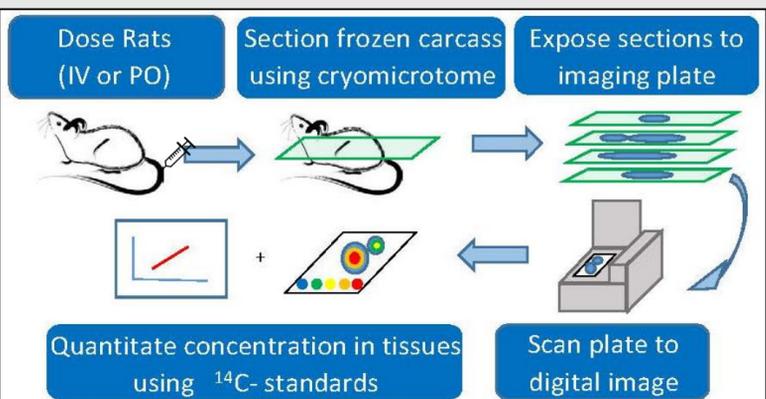
## BACKGROUND

- BCV is in development as an orally-administered lipid conjugate nucleotide for treatment of adenovirus in hematopoietic cell transplant (HCT) recipients and other immunocompromised patients.
- Oral administration has resulted in dose-limiting GI events in hematopoietic stem cell transplant (HCT) patients.
- Development of an IV formulation has been initiated, with minimal GI toxicity observed in rats after repeat IV administration for up to 1 month.



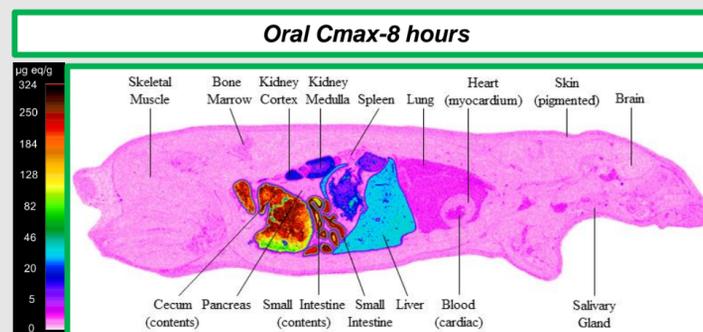
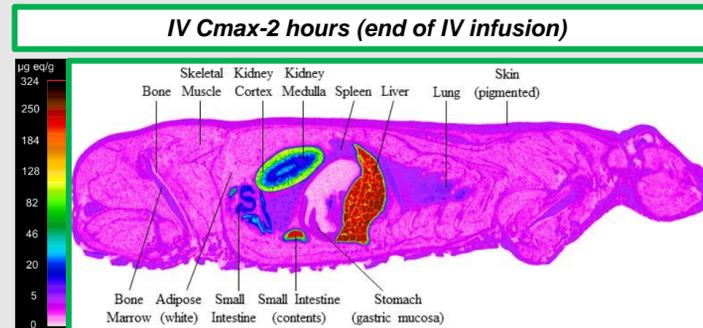
## METHODS

- [<sup>14</sup>C]BCV was administered to pigmented and non-pigmented rats by 2-hour IV infusion or by oral gavage at a dose of 15 mg/kg.
- Tissue distribution was determined by quantitative whole body autoradiography at 1, 2, 4, 8, 24, 72, 96 hours, 7 and 35 days post-dose (n=1/time point).



## RESULTS

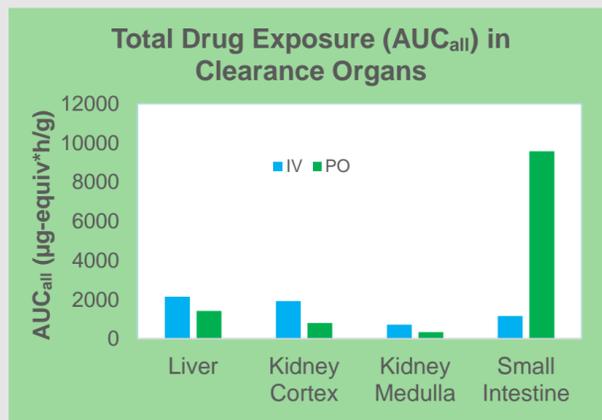
### IV versus PO General Distribution



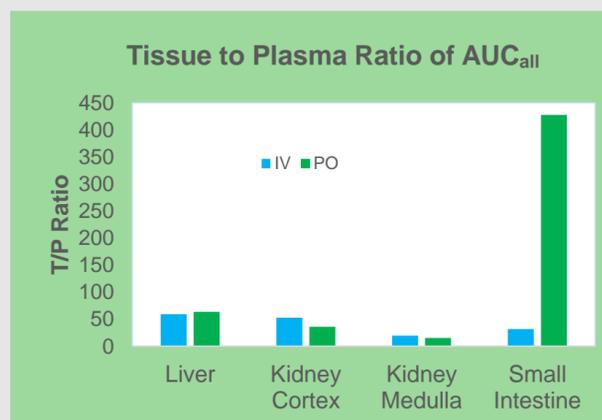
- Radioactivity was well distributed with similar qualitative distribution patterns of the radioactivity after IV and oral administration.
- Peak concentrations of radioactivity in most tissues occurred at 4 to 8 h after oral administration, or at the end of the 2h IV infusion.
- Tissue radioactive exposure was generally higher after IV than after oral gavage administration.
- Tissues with lowest concentrations of radioactivity were brain, spinal cord, skeletal muscle, white adipose tissue and bone.
- Brain and spinal cord radioactivity was higher after IV than after oral administration (~20% of plasma concentration compared to ~5% after oral administration).

### Drug Exposure in Small Intestine and Organs of Elimination

Tissue radioactive concentrations in small intestinal tissue after IV administration were approximately 1/10 the concentrations in small intestinal tissue after oral administration.

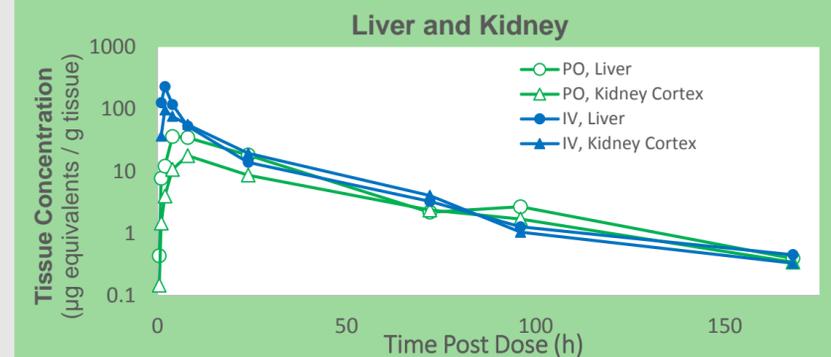
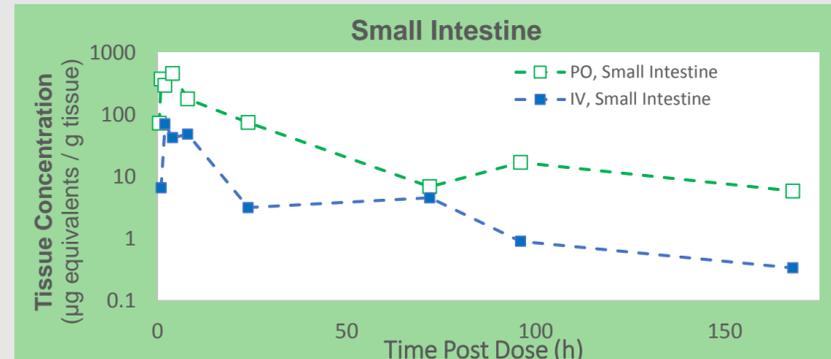


Regardless of route of administration, tissues with highest concentrations of radioactivity were associated with organs of clearance or elimination (liver, kidney and small intestine).



The tissue-to-plasma ratios (T/P, Tissue AUC<sub>all</sub>/Plasma AUC<sub>all</sub>) in these organs were high (>30) and for kidney and liver were similar between the IV and oral routes of administration.

### Elimination from Tissues



- At 168 h post-dose, tissue concentrations in most tissues were less than 1 µg-equivalent/g tissue.
- At 35 days post-dose, radioactivity was below the limit of quantification in all tissues except for bone marrow, lymph node, spleen and adrenal gland after IV administration, and small intestine, liver and kidney cortex after PO administration.
- No evidence of specific association with melanin containing tissues was detected for either administration route.

## CONCLUSIONS

- Compared to the oral route, IV administration of [<sup>14</sup>C]BCV in rats resulted in lower small intestinal concentrations of BCV-related radioactivity, and similar concentrations in liver and kidney.
- These reduced intestinal tissue concentration data suggest that the IV route may result in improved tolerability in patients susceptible to GI toxicity.

## ACKNOWLEDGEMENTS

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