FRI-017

Preclinical Pharmacokinetics of a Novel Nicorandil Prodrug

Atul Khare[1], PhD; Pramod Gupta[1], PhD; Guru Reddy[1], PhD; Shalabh Gupta[1], MD

[1]Unicycive Therapeutics, Inc.

BACKGROUND

- Mitochondrial dysfunction in renal cells play a critical role in the pathophysiology of acute kidney injury (AKI) and chronic kidney disease (CKD)[1]
- Nicorandil, a selective mitochondrial ATP-sensitive potassium channel activator,[2] may be a promising AKI treatment,[3] but its clinical use is limited by serious gastrointestinal side effects and rapid absorption and elimination[4,5]
- UNI-494, a novel nicorandil prodrug designed to improve its pharmacologic properties, may increase the short half-life and improve the safety profile of nicorandil

OBJECTIVE

We present pharmacokinetic data in dogs for UNI-494

METHODS

- Groups of 3 beagle dogs were administered a single oral dose of 3, 10, or 30 mg/kg UNI-494 at a volume of 5 mL/kg
- Clinical observations were recorded at approximately 1, 1.5, 2, 3, and 24h post-dose
- Whole blood samples were collected pre-dose and 0.083, 0.25, 0.50, 1, 1.5, 2, 4, 8, and 24h post-dose to analyze systemic exposure to UNI-494 and nicorandil
- Dose and concentration parameters (C_{max} and AUC) were used to generate linearity plots and calculate the coefficients of determination (R^2) and slopes for UNI-494 and nicorandil

RESULTS

- The mean T_{max} of nicorandil was 0.7h (3 mg/kg dose), 1.5h (10 mg/kg dose), and 1.3h (30 mg/kg dose), respectively **(Table 1)**
- The mean C_{max} and AUC of nicorandil increased linearly with UNI-494 dose amounts **(Figure 1 & 2)**

Table 1. C_{max}, T_{max} and AUC by Dose Group and Analytes in Male Beagle Dogs Following a Single Oral UNI-494 Administration (n=3 per Dose Group)

	Dose Group (mg/kg)					
	3		10		30	
	UNI-494	NIC[1]	UNI-494	NIC[1]	UNI-494	NIC[1]
C_{max} (ng/mL)	43	1,300	178	3,070	1,500	7,530
T_{max} (Hr)	0.3	0.7	0.3	1.5	0.3	1.3
AUC (Hr*ng/mL)	34	3,400	162	11,400	1,510	38,000

1 NIC=Nicorandil

Figure 1. Mean C_{max} of Nicorandil and UNI-494 by UNI-494 Dose After Single Dosing in Dogs

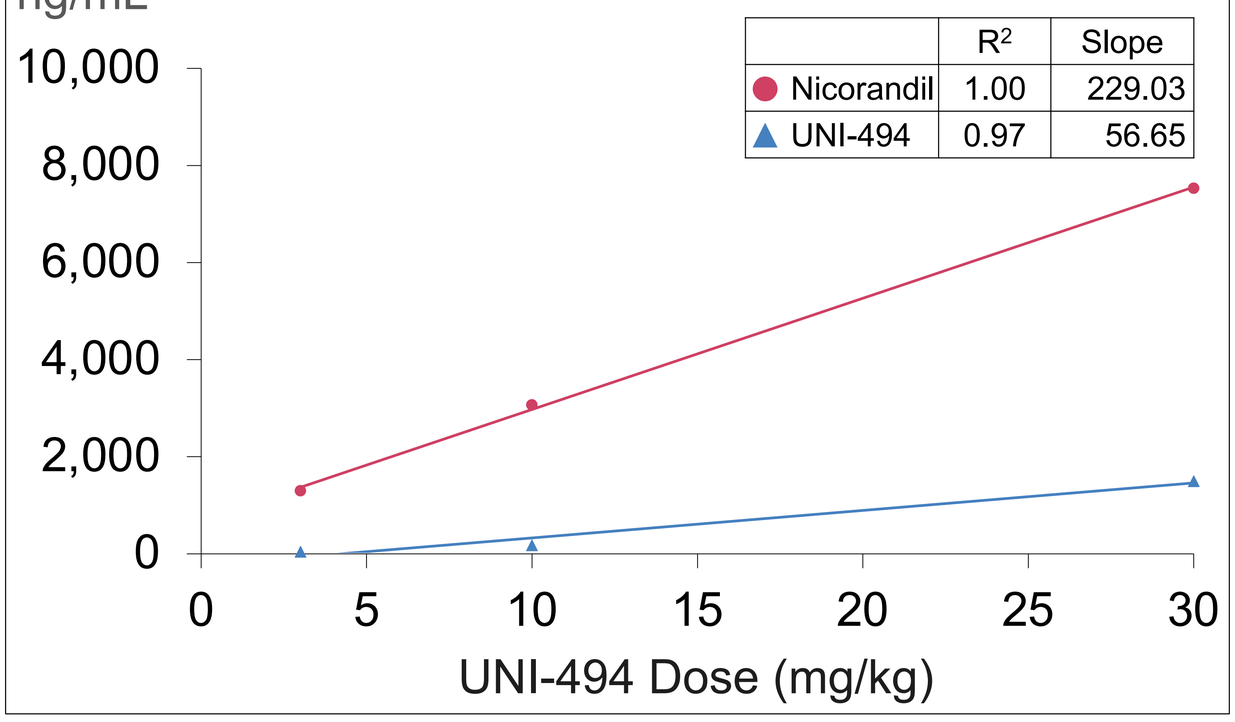
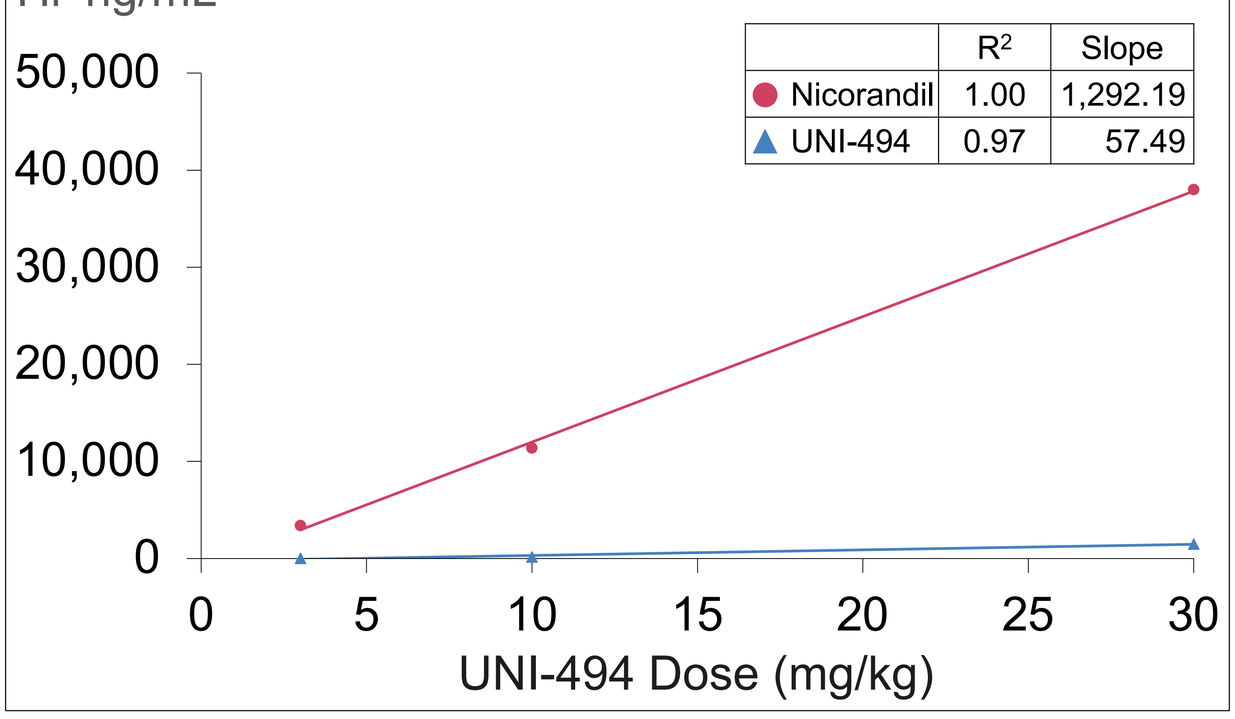


Figure 2. Mean AUC of Nicorandil and UNI-494 by UNI-494 Dose After Single Dosing in Dogs



CONCLUSIONS

- Nicorandil was rapidly formed from the prodrug UNI-494
- Mean C_{max} for nicorandil was >5-fold greater than that of UNI-494, demonstrating the efficient conversion of the prodrug to the active drug
- The conversion was consistent across dose groups

IMPLICATIONS

- These results indicate that UNI-494 is a rationally designed drug
- Future studies should evaluate this promising treatment in the target population of patients with acute kidney injury

References:

1. Zhang X, et al. *Int J Mol Sci*. 2021.
2. Kuno A, et al. *Basic Res Cardiol*. 2007.
3. Rabea M, et al. *QJM*. 2021.
4. Frydman AM, et al. *Am J Cardiol*. 1989.
5. SANOFI. IKOREL 10mg and 20mg Tablets (nicorandil) Package Leaflet. 2021.

Acknowledgments:
Writing support was provided by Xelay Acumen Group, Inc., and funded by Unicycive Therapeutics, Inc.

Presented at the International Society of Nephrology (ISN) World Congress of Nephrology, March 30 - April 02, 2023, Bangkok, Thailand