Orally Administered UNI-494 Is Well-Tolerated in Dogs

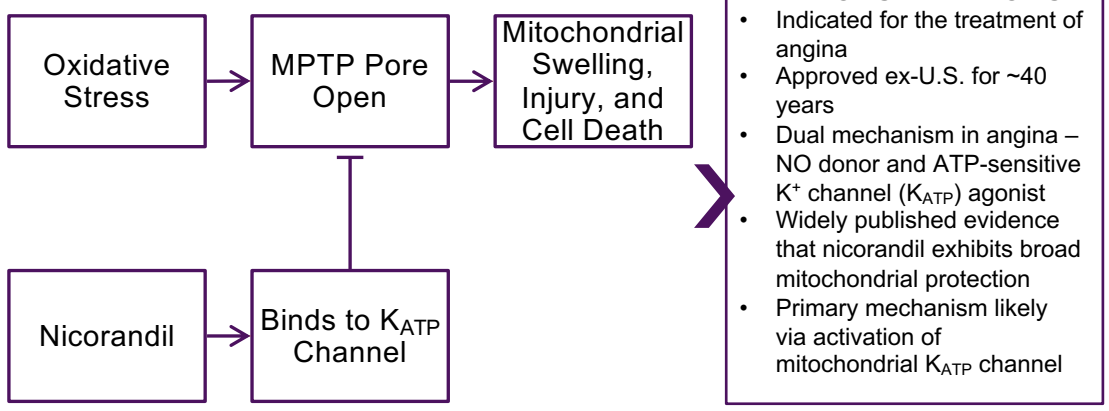
Guru Reddy[1], Pramod Gupta[1], Atul Khare[1], Shalabh Gupta[1]

[1]Unicycive Therapeutics, Inc.

Background

- Nicorandil is a selective mitochondrial ATP-sensitive potassium channel activator[1] that may be beneficial for several disease states, including acute kidney injury[2] **(Figure 1)**
- However, its clinical use is limited by serious gastrointestinal (GI) side effects and rapid absorption and elimination[3,4]
- UNI-494, a novel nicorandil prodrug, may increase the short half-life and improve the safety profile of nicorandil

Figure 1. Nicorandil Blocks MPTP Pores by Binding to K_{ATP} Channel



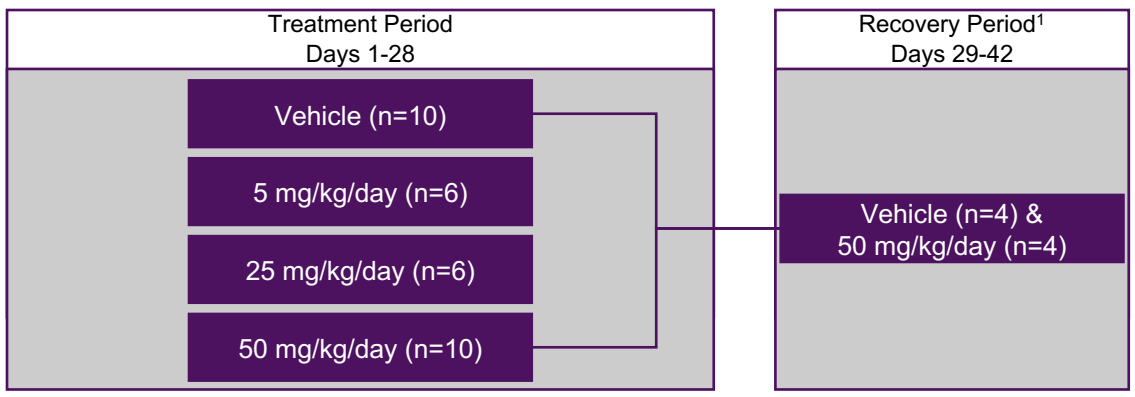
Objective

We present safety data from a study of UNI-494 in a dog model

Methods and Materials

- UNI-494 was administered orally to 32 Beagle dogs over 28 days with a 14-day recovery period **(Figure 2)**
- Dogs were assigned to 4 groups: 0 (control), UNI-494 5, 25, and 50 mg/kg/day **(Figure 2)**
- Each group contained 3 male and 3 female dogs, with 2 additional animals of each sex in the control and highest UNI-494 dose groups to assess recovery **(Figure 2)**
- Safety parameters included in-life observations and measurements (e.g., morbidity/mortality checks, clinical signs, body weight, food consumption, ophthalmological examinations), post-treatment and post-recovery ECG and respiratory parameters, clinical chemistry, urinalysis, coagulation and hematology, toxicokinetic analysis and post-treatment and post-recovery organ weights, macroscopic findings, and histopathology

Figure 2. UNI-494 Dog Toxicity Study Design

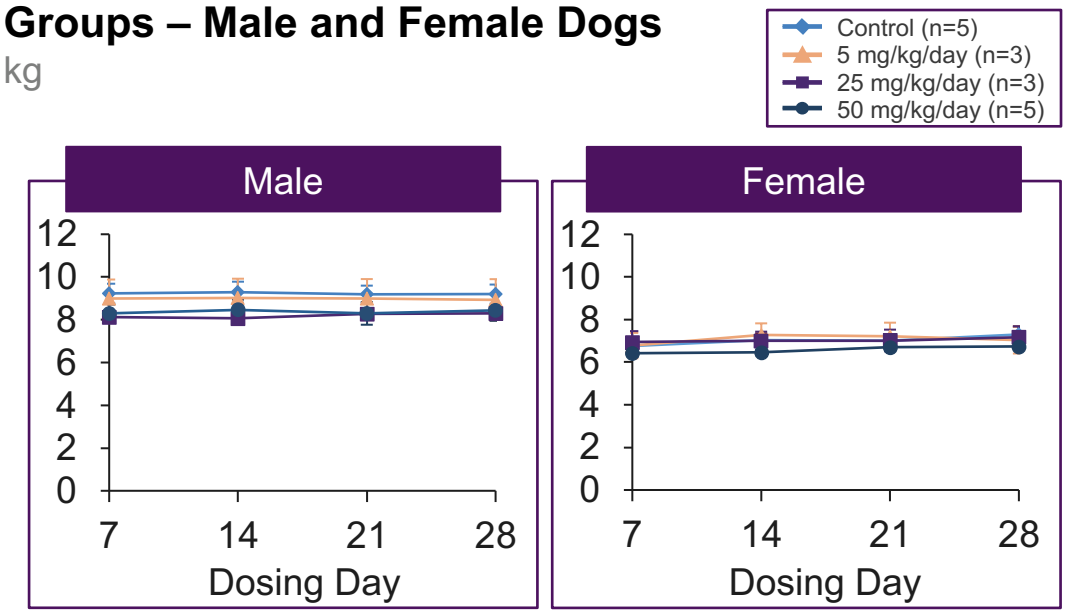


1 The study included additional animals in the control and highest dosage groups, in order to study the reversibility, persistence or delayed occurrence of toxic effects for 14 days post treatment

Results

- No adverse UNI-494-related clinical signs, changes in body weight, food consumption, ophthalmological examinations, hematology, clinical chemistry, urinalysis, organ weight, or macroscopic observations were observed in the UNI-494 5, 25, or 50 mg/kg/day dose groups **(Figure 3)**
- Microscopic changes consisting of vascular wall thickening/perivascular fibroplasia in the heart, acinar cell apoptosis/necrosis in the pancreas, and tubular degeneration in the kidney were observed in the UNI-494 25 and 50 mg/kg/day groups
- There were no unscheduled deaths
- Exposure to UNI-494 (AUC_{0-t} and C_{max}) increased in a dose dependent manner over the dose range of 5 to 50 mg/kg following both single and multiple doses for both sexes
- Following both single and multiple administrations, the mean T_{max} for all doses of UNI-494 was <1 hour (mean T_{max} = 0.235 – 0.826 h). The time to peak concentration of nicorandil was observed earlier for the 5 mg/kg dose (mean T_{max} = 0.487-0.997 h) when compared to the 25 and 50 mg/kg doses (mean T_{max} = 1.35-2.99 h) **(Figure 4)**

Figure 3. Mean (±SE) Body Weight by Dose Groups – Male and Female Dogs



Conclusions

- UNI-494 was rapidly converted to nicorandil
- UNI-494 exposure increased in a dose-dependent manner
- UNI-494 5 mg/kg/day was well tolerated and was assessed as the No Observed Adverse Effect Level (NOAEL)

Implications

- Based on the NOAEL in dogs, the maximum recommended starting dose in humans with a 10x safety margin is 16 mg
- This information should be used to design further efficacy and safety studies of UNI-494

References:
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2. Rabea M, et al. *QJM.* 2021.
3. Frydman AM, et al. *Am J Cardiol.* 1989.
4. SANOFI. IKOREL 10mg and 20mg Tablets (nicorandil) Package Leaflet. 2021.

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