61ST ERA CONGRESS STOCKHOLM & VIRTUAL MAY 23-26, 2024

UNI-494 Phase I Safety, Tolerability and Pharmacokinetics: Trial in Progress

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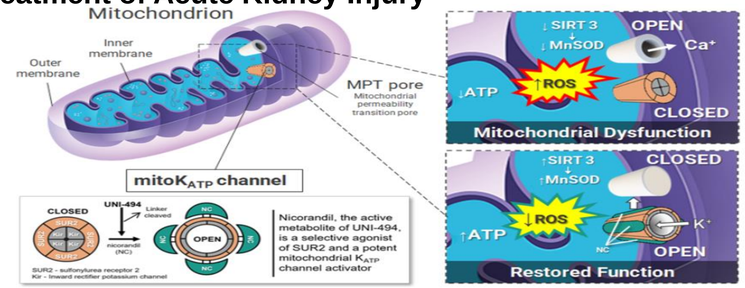
BACKGROUND

- Acute kidney injury (AKI) is a clinical syndrome defined by the sudden loss of kidney function[1], resulting in an inability to maintain electrolyte, acid-base and water balance[2,3]
- Currently, there are no effective treatments for AKI approved by the US Food and Drug Administration or the European Medicines Agency (EMA); management of the condition is primarily supportive[2,4]
- The most common cause of AKI was thought to be ischemia[3]
- However, more recently the focus has shifted from clinical causes to the underlying cellular processes inherent in these situations, in particular the dysfunction of mitochondria in AKI[4]
- Inflammation and reactive oxygen species (ROS) driven mPTP opening causes mitochondrial dysfunction/swelling and eventual cell death over time
- This is implicated in a wide range of acute diseases including acute kidney disease (AKI) originating from ischemia reperfusion injury (IRI) or delayed graft function (DGF)
- Furthermore, unresolved inflammation exacerbates sustained mPTP opening, evident in chronic kidney diseases (CKD)
- Nicotinamide adenine dinucleotide (NAD+) can suppress the frequency and duration of mPTP opening
- UNI-494 is a novel nicotinamide ester derivative and selective mitochondrial ATP-sensitive potassium channel activator that binds to the ATP-sensitive potassium (KATP) channels, which reverses the mitochondrial dysfunction by closing mPTP pore **(Figure 1)**

Figure 1. The Primary Mode of Action of UNI-494 in the Treatment of Acute Kidney Injury



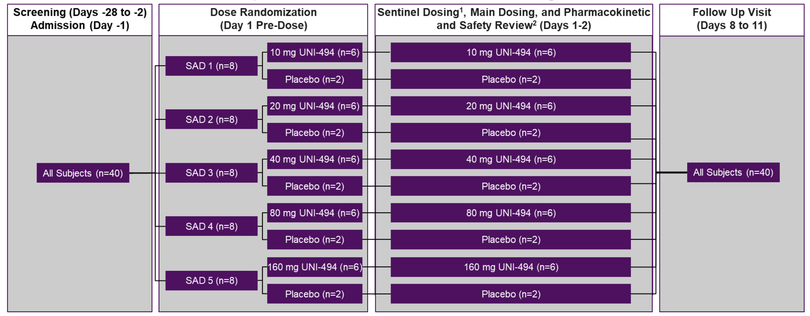
OBJECTIVE

This study aims to evaluate the safety, tolerability, and pharmacokinetics (PK) of UNI-494

METHODS

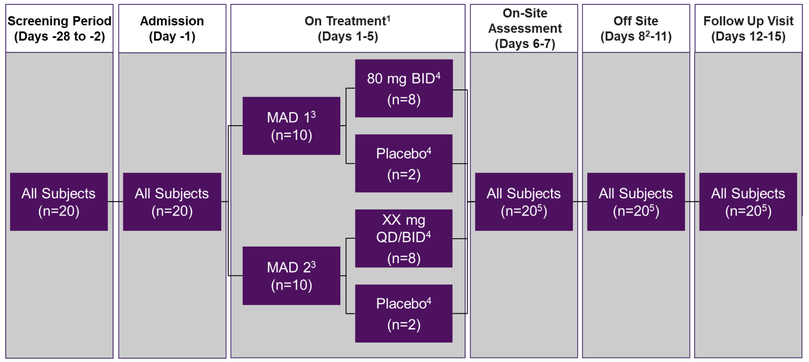
- This is a single-center, double-blind, placebo-controlled, randomized single ascending dose (SAD) (Part 1) **(Figure 2)** and multiple ascending dose (MAD) (Part 2) **(Figure 3)** study in healthy male subjects and female subjects of non-childbearing potential
- Part 1 will enroll up to approximately 40 subjects in 5 cohorts of 8 subjects each (randomized to a ratio of 6 active and 2 placebo per cohort) **(Figure 2)**
- Main inclusion criteria were healthy males and WONCBP, aged 18 to 55 inclusive at the time of signing informed consent
- Body mass index (BMI) of 18.0 to 32.0 kg/m2 as measured at screening
- There will be an interim decision meeting after each cohort/period, to review the safety, tolerability, and pharmacokinetics (PK) data up to 48 hours post-dose in order to decide the dose level for the subsequent cohort
- Part 2 will enroll approximately 20 subjects in 2 cohorts of 10 subjects each, randomized to a ratio of 8 active treatment to 2 placebo who will be dosed for 5 days **(Figure 3)**
- The dose level for the Part 2 Cohort 1 (80 mg BID) was selected based on the safety, tolerability, and PK data from Part 1
- Pharmacokinetic assessments included collecting blood samples for PK analysis at regular time intervals, and analysis of the plasma concentration-time data for UNI-494, nicorandil and 1-cyclohexylethylamine
- The safety assessments included adverse events monitoring, ECG, vital signs, clinical laboratory tests (clinical chemistry, hematology, and urinalysis), and physical examinations

Figure 2. UNI-494 Phase 1 Trial in Progress Study Design Part 1 – SAD Study with Sentinel Dosing[1]



1 The first two subjects of each cohort (i.e one receiving active and one subject receiving placebo; (sentinel group) will be dosed prior to the remaining subjects (main group)
2 After review of safety data up to the 24 hours post-dose period, the decision of whether to dose the remaining subjects in the cohort (5 for UNI-494 and 1 for Placebo) will be made

Figure 3. UNI-494 Phase 1 Trial in Progress Study Design Part 2 – MAD Study



1 Sentinel dosing in Part 2 is dependent on the safety, tolerability and PK data from 48 hours post-dose from the preceding cohorts in Part 1 of the study
2 Discharge from clinical unit 48 h post-final dose (Day 8)
3 It's planned that subjects will be dosed in the fasted state and once daily, however this may change to dosing in the fed state and/or twice daily based on emerging PK data from Part 1 Single Ascending Dose study
4 Dose level, prandial status and dosing frequency will be determined during interim data reviews based on safety, tolerability and PK data up to 48 hours post-dose from preceding cohorts from Part 1 and from previous cohorts in Part 2, where applicable
5 N number may not be 20 when early withdrawal of patients occurs

RESULTS

We intend to present results elucidating safety, tolerability, and pharmacokinetics of UNI-494 in healthy subjects by 2H 2024

CONCLUSIONS

The safety, tolerability, and pharmacokinetics of UNI-494 in healthy subjects will be evaluated in this study

References:
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2. Mercado MG. et al., *Am Fam Physician*. 2019. Dec.
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Acknowledgments:
Writing support was provided by Xelay Acumen Group, Inc., and funded by Unicycive Therapeutics, Inc.