UNI-494 Phase I Safety, Tolerability, and Pharmacokinetics

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BACKGROUND

- Currently, there are no effective treatments approved for acute kidney injury (AKI)[1,2]
- Inflammation and reactive oxygen species driven mitochondrial permeability transition pore (mPTP) opening causes mitochondrial dysfunction/swelling and cell death[3-7]
- This is implicated in acute diseases originating from ischemia reperfusion injury or delayed graft function (DGF)[3-7]
- Furthermore, unresolved inflammation exacerbates sustained mPTP opening, evident in chronic kidney diseases[8,9]
- UNI-494 is a selective mitochondrial ATP-sensitive potassium channel (KATP) activator which reverses the mitochondrial dysfunction by closing mPTP

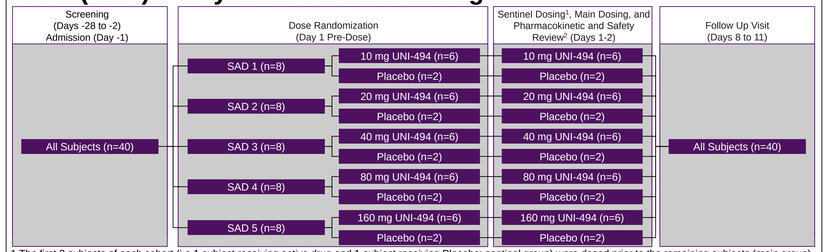
OBJECTIVE

We present results from a phase 1 study evaluating safety, tolerability, and pharmacokinetics (PK) of UNI-494 capsules administered to healthy subjects

METHODS

- This was a single-center, double-blind, placebo-controlled, randomized single ascending dose (SAD) study in healthy males and females of non-childbearing potential
- Study enrolled up to 40 subjects in 5 cohorts of 8 subjects each (6 active/2 placebo per cohort) **(Figure 1)**
- There was an interim decision meeting after each dose cohort to review the safety, tolerability, and PK data up to 48 h post-dose to decide the dose level for the subsequent cohort
- Safety assessments and systemic exposure to UNI-494 and its metabolites (nicorandil and CHEA) were conducted

Figure 1. UNI-494 Phase 1 Study Design Part 1 – Single Ascending Dose (SAD) Study with Sentinel Dosing[1]



1 The first 2 subjects of each cohort (i.e 1 subject receiving active drug and 1 subject receiving Placebo; sentinel group) were 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) was made

RESULTS

- Following single oral administration of 10, 20, 40, 80, and 160 mg UNI-494 capsules, most treatment-emergent adverse events (TEAEs) were mild severity (93%), there were no severe TEAEs, and no subjects were withdrawn for adverse events **(Table 1)**
- In the SAD cohorts, overall exposures to UNI-494 were low due to rapid conversion to nicorandil; mean nicorandil C_{max} was 14.9, 52.8, and 80.3 ng/mL and mean $AUC_{(0\text{-}last)}$ was 44.6, 154, and 308 hour*ng/mL for the 40, 80, and 160 mg UNI-494 dose groups, respectively **(Table 2)**

Table 1. Overall Summary of Treatment-Emergent Adverse Events (TEAEs) by Treatment Groups

Number (Percent) of Patients

Systems Organ Class Preferred Term	Placebo (n=10)	UNI-494 Dose					All Active (n=30)
		10 mg (n=6)	20 mg (n=6)	40 mg (n=6)	80 mg (n=6)	160 mg (n=6)	
Any TEAE	2 (20)	2 (33)	3 (50)	2 (33)	3 (50)	4 (67)	14 (47)
Headache	0	1 (17)	0	1 (17)	0	3 (50)	5 (17)
Dizziness	1 (10)	0	0	0	0	2 (33)	2 (7)
Fatigue	0	0	0	1 (17)	0	1 (17)	2 (7)
Lipase Increased	0	1 (17)	1 (17)	0	0	0	2 (7)
Nausea	0	0	0	0	1 (17)	1 (17)	2 (7)
Vomiting	0	0	0	0	1 (17)	1 (17)	2 (7)

Table 2. Median (Range) of T_{max}, and Mean (SD, CV%) of C_{max} and $AUC_{0\text{-}last}$[1], by Cohort, Following a Single Oral UNI-494 Administration (n=6 per Cohort)

	T_{max} (Hour)			C_{max} (ng/mL)			$AUC_{0\text{-}last}$[1] (Hour*ng/mL)		
	UNI-494	NIC[2]	CHEA[3]	UNI-494	NIC[2]	CHEA[3]	UNI-494	NIC[2]	CHEA[3]
Cohort 1 10 mg UNI-494	1.0 (0.5-24.2) [n=4[4]]	NC[5]	NC[5]	1.0 (0.6, 67.2) [n=4[4]]	NC[5]	NC[5]	1.6 (1.3, 80.5) [n=3[4]]	NC[5]	NC[5]
Cohort 2 20 mg UNI-494	1.0 (0.4, 1.5) [n=6[4]]	4.0 (3.1, 4.0) [n=6[4]]	NC[5]	0.7 (0.3, 48.7) [n=6[4]]	8.8 (5.9, 66.4) [n=6[4]]	NC[5]	1.4 (0.5, 35.1) [n=4[4]]	NC[5]	NC[5]
Cohort 3 40 mg UNI-494	0.5 (0.5, 1.5) [n=4[4]]	4.0 (3.0, 6.1) [n=6[4]]	NC[5]	0.7 (0.1, 22.2) [n=4[4]]	14.9 (8.1, 54.3) [n=6[4]]	NC[5]	0.9 (0.2, 18.6) [n=4[4]]	44.6 (11.0, 24.7) [n=3[4]]	NC[5]
Cohort 4 80 mg UNI-494	1.0 (0.5, 1.0) [n=6[4]]	4.0 (3.0, 4.2) [n=5[4]]	12.0 (10.0, 16.0) [n=4[4]]	2.0 (1.1, 55.1) [n=6[4]]	52.8 (29.3, 55.5) [n=5[4]]	14.0 (2.2, 15.8) [n=4[4]]	4.5 (2.0, 45.0) [n=5[4]]	154 (104, 67.7) [n=5[4]]	NC[5]
Cohort 5 160 mg UNI-494	1.5 (1.0, 1.5) [n=5[4]]	4.0 (3.0, 6.2) [n=5[4]]	12.1 (10.0, 16.0) [n=5[4]]	1.8 (1.0, 53.7) [n=5[4]]	80.3 (18.3, 22.8) [n=5[4]]	32.1 (9.7, 30.1) [n=5[4]]	4.6 (2.9, 64.0) [n=5[4]]	308 (187, 60.5) [n=5[4]]	755 (325, 43.1) [n=5[4]]

1 Area under the concentration-time curve from time zero until the last observed concentration
2 NIC=Nicorandil
3 CHEA=1-Cyclohexylethylamine
4 T_{max}, C_{max} and $AUC_{0\text{-}last}$ were observed for subjects that had quantifiable plasma concentrations from 0.5 hours post dose
5 NC=Not calculable

CONCLUSIONS

- Single dose of 10-160 mg of UNI-494 capsules were safe and well-tolerated in healthy volunteers
- UNI-494 was rapidly converted to nicorandil
- Exposure to nicorandil increased in a dose-proportional manner
- Therapeutic levels (AUC >200 hour*ng/mL) of nicorandil achieved at 160 mg UNI-494

DISCUSSION

- The rapid conversion of UNI-494 to nicorandil and 1-cyclohexylethylamine indicates a potential for a fast-acting therapy for the prevention of DGF and other AKI clinical conditions
- Future studies should evaluate this promising treatment in the target population of patients with AKI

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