Supratherapeutic Doses of Pozdeutinurad: Pharmacokinetic and Pharmacodynamic Assessment in Healthy Subject Volunteers

Zancong Shen[1], Andrea Clouser Roche[1], Janina Rivera[1], Jia Hu[1], Rongzi Yan[1], Shunqi Yan[1], and Robert T. Keenan[1]

[1]Arthrosi Therapeutics, Inc., a Sobi Company, San Diego, CA, USA

713

CONCLUSIONS

- Pozdeutinurad (AR882, POZD) exposure increases approximately dose proportionally across doses up to 400 mg.
- In this lead-in phase, no abnormal trends in laboratory or ECG findings were observed.
- The 400 mg dose was therefore selected as the supratherapeutic dose for evaluation in the next phase of the QT-concentration study.

INTRODUCTION

- POZD is a highly selective and potent uric acid transporter-1 (URAT1) inhibitor, which blocks uric acid reabsorption in the kidney proximal tubule, resulting in normalized uric acid excretion and reduced serum urate (SU) levels.
- Phase 2 trials demonstrated robust SU lowering at both doses of POZD 50 and 75 mg QD and was generally well tolerated. [1,2]
- A supratherapeutic dose of POZD, at least 3- to 4-fold higher than the clinical dose, is needed to evaluate the effect on cardiac repolarization.

OBJECTIVE

- Here we present the results of the Dose – PK/PD relationships during this lead-in phase of the concentration-QT study.

METHODS

- In the lead-in phase, 40 healthy male subject volunteers were enrolled in a randomized, double-blind, placebo-controlled design.
- Sentinel doses were administered at doses >100 mg. Escalating doses started at 100 and advanced to 200, 300, 350 and 400 mg.
- Each cohort consisted of 2 placebo and 6 active subjects.
- Serial blood samples were collected for measurement of concentrations of POZD and its active metabolite AR896, as well as SU.
- Adverse events (AE), laboratory safety tests, vital signs, and electrocardiograms (ECG) were collected throughout the study.

RESULTS

- Exposures from the 400 mg dose adequately cover high exposure clinical scenarios simulated from the program for both POZD and AR896, the active metabolite (**Figure 1**).
- POZD C_{max} and AUC, as well as AR896 AUC, increased approximately dose proportionally, whereas AR896 C_{max} increased less than dose proportionally **(Table 1).**
- SU lowering profile **(Figure 2)** shows the effect increased by dose and plateaued at 350 mg and doses above. The maximum percent change in SU levels (E_{max}) occurred at 24 hours post-dose at each dose. Maximum reduction was greater than 50% for all doses and appeared to achieve saturation stage at 350 and 400 mg.
- No abnormal trends in ECG or laboratory findings were observed.

Table 1: Key Pharmacokinetic Parameters of Pozdeutinurad following Escalating Single Doses (Mean ± SD)

Analyte	Dose (mg)/N	*T_{max} (hr)	C_{max} (µg/mL)	AUC_{last} (µg·hr/mL)	AUC_{inf} (µg·hr/mL)	$t_{1/2}$ (hr)
POZD	100/6	2.0 (1.0-3.0)	7.75 (1.31)	112 (26.8)	113 (26.8)	11.2 (3.16)
	200/6	2.5 (1.0-4.0)	13.0 (2.04)	194 (27.0)	194 (27.2)	11.4 (4.00)
	300/6	2.3 (1.5-3.0)	18.0 (3.29)	392 (267)	394 (271)	15.0 (9.44)
	350/6	2.5 (1.5-4.0)	23.0 (3.48)	366 (44.5)	367 (44.5)	10.3 (1.58)
	400/6	3.5 (2.5-4.1)	27.5 (5.19)	549 (193)	549 (193)	12.7 (3.06)
AR896	100/6	7.0 (6.0-10.0)	0.536 (0.232)	16.7 (6.85)	16.9 (6.99)	27.9 (18.5)
	200/6	6.0 (4.0-8.0)	0.806 (0.263)	22.8 (4.58)	22.9 (4.59)	17.4 (8.62)
	300/6	9.0 (6.0-12.0)	0.982 (0.360)	36.0 (6.21)	36.2 (6.07)	19.5 (10.9)
	350/6	6.0 (4.0-8.0)	1.13 (0.423)	36.5 (13.0)	36.5 (13.0)	14.2 (2.52)
	400/6	10.0 (6.0-12.0)	1.54 (0.715)	65.2 (36.6)	65.6 (36.9)	22.1 (11.5)
POZD Proportionality	100-400	Power model exponent	0.887 CI90% (0.780-0.995)		1.08 CI90% (0.878-1.28)	
AR896 Proportionality	100-400	Power model exponent	0.658 CI90% (0.385-0.931)		0.813 CI90% (0.567-1.06)	

*T_{max} is presented as median (range)

Figure 1. Pozdeutinurad (A) or AR896 (B) Exposures Adequately Cover High Clinical Scenarios

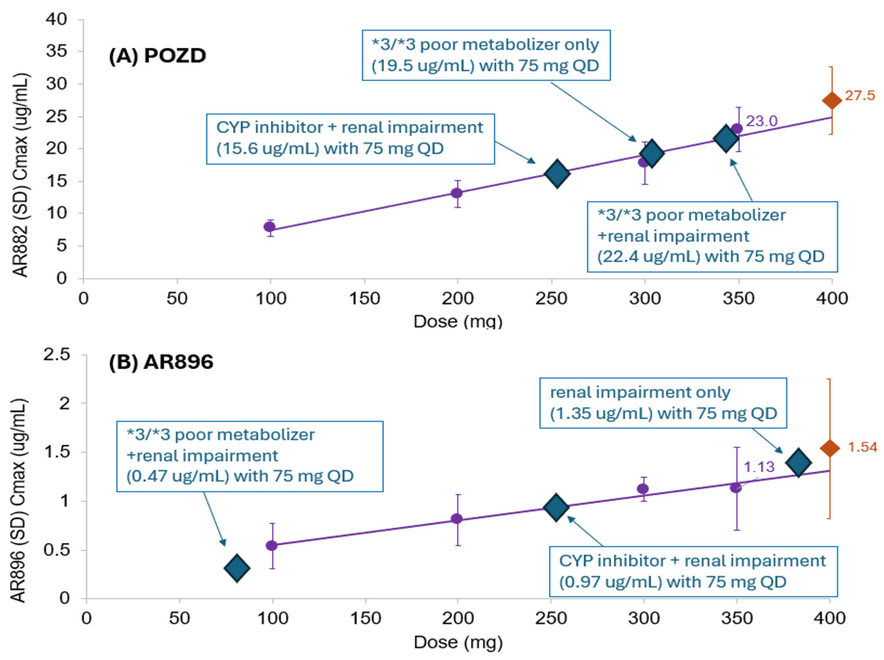
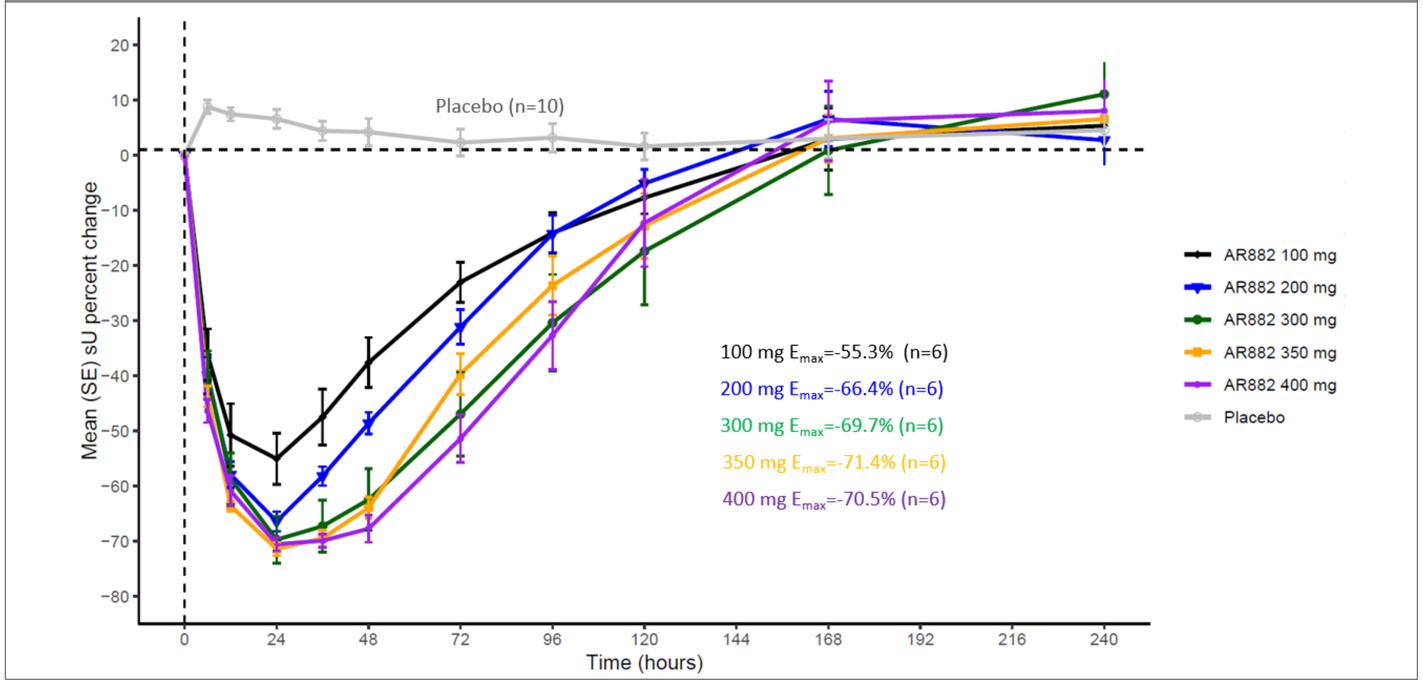


Figure 2. Mean (± SE) SU Lowering Effect following a Single Oral Dose of Pozdeutinurad 100 to 400 mg in Healthy Subject Volunteers



REFERENCES

1. Wei JCC, et al. A 12-Week, Randomized, Double-blinded, placebo-controlled Phase 2B study of Safety, Tolerability and Efficacy of AR882 in Gout Patients [abstract]. *Ann Rheum Dis.* 2023; 82 (suppl 1).
2. Keenan R, et al. Efficacy of Pozdeutinurad (AR882) in Treatment Naïve and Suboptimally Treated Gouty Arthritis with Tophi [abstract]. *Arthritis Rheumatol.* 2025; 77 (suppl 9).

ACKNOWLEDGEMENTS

The authors thank the volunteers, the investigators and their team at Dr Vince Clinical Research who took part in the study, as well as Racheal Kendrick, Certara Inc, for consulting advice on dose selection. Sobi reviewed and provided feedback on the poster. The authors had full editorial control of the poster and provided their final approval of all content.

DISCLOSURES

The study was funded by Arthrosi Therapeutics Inc, a Sobi Company. All authors are employees of Arthrosi Therapeutics Inc, a Sobi Company.

Copies of this poster obtained through QR Code are for personal use only