FIRST-IN-HUMAN STUDY OF LORUNDROSTAT, A POTENT AND HIGHLY SELECTIVE ALDOSTERONE SYNTHASE INHIBITOR

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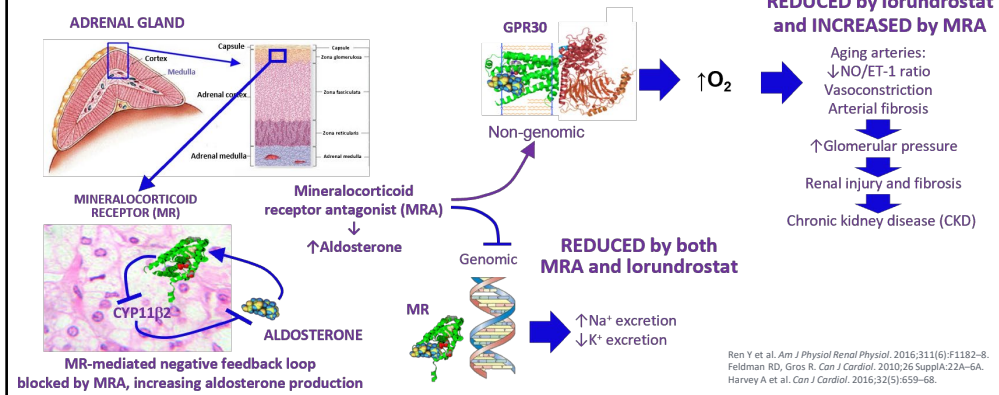
RATIONALE FOR DEVELOPING AN ALDOSTERONE SYNTHASE INHIBITOR (ASI)

Current standard-of-care for treatment of hypertension and cardiorenal diseases includes use of a mineralocorticoid receptor antagonist (MRA) to inhibit aldosterone signaling. Despite the use of MRAs, a high unmet medical need remains. One potential reason for this is the large increase in circulating aldosterone that results from MRA treatment, leading to increased non-genomic signaling through GPR30 (GPER), which, in aging individuals, may increase renal and vascular dysfunction and remodeling.



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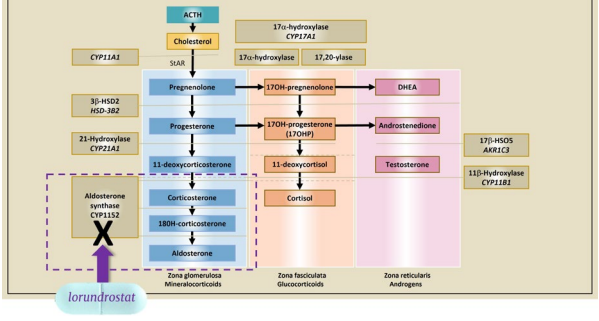
ET-1, endothelin-1; GPER, G protein–coupled estrogen receptor 1; GPR30, G protein–coupled receptor 30; NO, nitric oxide.

STEROIDOGENESIS—PATHWAY

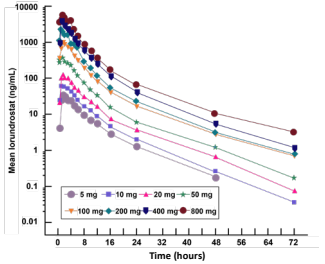


ACTH, adrenocorticotropic hormone; AKR, aldo-keto reductase; CYP, cytochrome P450; DHEA, dehydroepiandrosterone; HSD, hydroxy-delta-5-steroid dehydrogenase; StAR, steroidogenic acute regulatory protein.

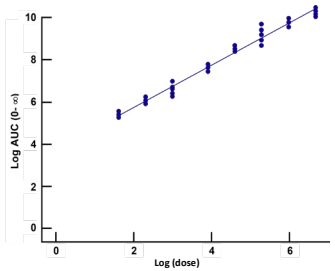
KEY OBJECTIVES OF THE PHASE 1 TRIAL

- Primary: Safety and tolerability
- Secondary: Pharmacokinetics

SINGLE-ASCENDING DOSE EXPOSURE (SAD)



DOSE PROPORTIONALITY



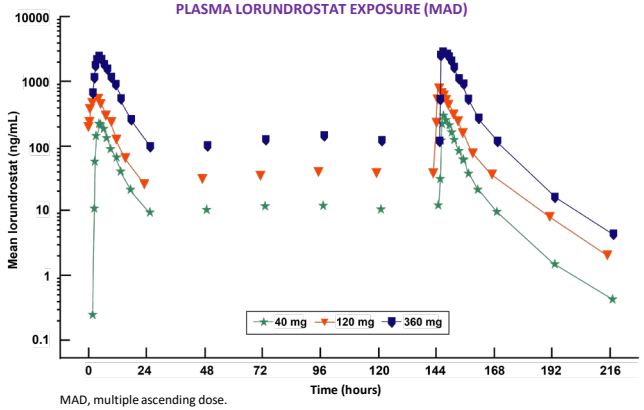
AUC, area under the curve.

SUMMARY OF LORUNDROSTAT PLASMA PK PARAMETERS (SAD)

Parameter	Statistic	5 mg (N=6)	10 mg (N=6)	20 mg (N=6)	50 mg (N=6)	100 mg (N=6)	200 mg (N=6)	400 mg (N=6)	800 mg (N=6)
$AUC_{0\text{-}24}$ (h*ng/mL)	Mean	212	420	709	2053	5093	10288	16617	28290
	SD	24	44	185	245	458	3446	2724	3546
$AUC_{0\text{-}last}$ (h*ng/mL)	Mean	229	450	764	2153	5366	10645	17257	29331
	SD	25	47	183	260	493	3486	2907	3623
$AUC_{0\text{-}\infty}$ (h*ng/mL)	Mean	232	452	770	2157	5376	10660	17275	29385
	SD	25	46	183	259	495	3483	2906	3623
C_{max} (ng/mL)	Mean	36.69	76.26	140.60	572.78	1211.00	2847.50	4454.83	7708.50
	SD	6.71	20.38	76.14	205.74	248.34	1015.24	862.39	1617.12
t_{max} (h)	Median	1.50	1.25	1.50	1.00	1.51	1.25	1.25	1.50
	Min, Max	1.00, 3.00	0.98, 1.50	1.00, 3.02	0.50, 3.00	0.52, 3.00	1.00, 3.02	0.50, 3.00	0.52, 4.02
$t_{½}$ (h)	Mean	8.29	7.92	10.03	9.13	9.95	9.92	9.70	10.54
	SD	0.74	0.92	1.87	1.87	0.90	3.61	2.28	2.09

$AUC_{0\text{-}24}$, area under the curve from dosing to 24 hours post-dose; $AUC_{0\text{-}last}$, area under the curve from dosing to last measured concentration; $AUC_{0\text{-}\infty}$, area under the curve from dosing to time infinity; C_{max}, highest concentration; Max, maximum; Min, minimum; $t_{1/2}$, half-life; t_{max}, time that drug is at maximum concentration; PK, pharmacokinetic; SAD, single ascending dose; SD, standard deviation.

PLASMA LORUNDROSTAT EXPOSURE (MAD)



MAD, multiple ascending dose.

SUMMARY OF LORUNDROSTAT PLASMA PK PARAMETERS (MAD)

Parameter	Statistics	40 mg od		120 mg od		360 mg od	
		Day 1 (n=9)	Day 7 (n=9)	Day 1 (n=9)	Day 7 (n=9)	Day 1 (n=9)	Day 7 (n=8)
$AUC_{0\text{-}24}$ (h*ng/mL)	Mean	1574	1795	4876	5816	19335	21825
	SD	282	312	1024	1315	3111	3955
$AUC_{0\text{-}\infty}$ (h*ng/mL)	Mean	1644	1954	5035	6468	19912	23668
	SD	298	366	1043	1481	3359	4457
C_{max} (ng/mL)	Mean	252.26	365.14	886.67	1038.74	3220.00	3812.13
	SD	64.36	46.48	291.12	342.81	1170.98	1282.32
t_{max} (h)	Median	3.00	2.00	3.00	1.52	3.00	2.50
	Min, Max	2.00, 5.00	1.00, 3.00	0.50, 5.00	0.52, 5.00	0.50, 8.00	1.00, 4.00
$t_{½}$ (h)	Mean	5.33	9.10	4.41	11.94	4.36	9.24
	SD	0.88	1.79	0.79	2.46	0.53	2.45

$AUC_{0\text{-}24}$: area under the curve from dosing to 24 hours post-dose; $AUC_{0\text{-}\infty}$, area under the curve from dosing to time infinity; C_{max}, highest concentration; MAD, multiple ascending dose; Max, maximum; Min, minimum; $t_{1/2}$, half-life; od, once daily; PK, pharmacokinetic; t_{max}, time that drug is at maximum concentration.

SAFETY – INCIDENCE OF ADVERSE EVENTS IN THE MAD SAFETY ANALYSIS SET

System Organ Class Preferred term	Placebo (n=9) n (%) e	40 mg (n=9) n (%) e	120 mg (n=9) n (%) e	360 mg (n=9) n (%) e	Overall (N=36) n (%) e
Nervous system disorders	2 (22.2) 2	2 (22.2) 3	3 (33.3) 3	2 (22.2) 2	9 (25.0) 10
Headache	2 (22.2) 2	1 (11.1) 1	1 (11.1) 1	0 (0.0) 0	4 (11.1) 4
Dizziness postural	0 (0.0) 0	1 (11.1) 1	1 (11.1) 1	1 (11.1) 1	3 (8.3) 3
Somnolence	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	1 (11.1) 1	1 (2.8) 1
Dizziness	0 (0.0) 0	0 (0.0) 0	1 (11.1) 1	0 (0.0) 0	1 (2.8) 1
Dysgeusia	0 (0.0) 0	1 (11.1) 1	0 (0.0) 0	0 (0.0) 0	1 (2.8) 1
Cardiac disorders	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	1 (11.1) 1	1 (2.8) 1
Sinus tachycardia	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	1 (11.1) 1	1 (2.8) 1
Respiratory, thoracic, and mediastinal disorders	1 (11.1) 1	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	1 (2.8) 1
Dyspnea	1 (11.1) 1	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	1 (2.8) 1
Gastrointestinal disorders	0 (0.0) 0	1 (11.1) 1	0 (0.0) 0	0 (0.0) 0	1 (2.8) 1
Nausea	0 (0.0) 0	1 (11.1) 1	0 (0.0) 0	0 (0.0) 0	1 (2.8) 1

n, number of subjects with relevant adverse events; e, number of relevant adverse events.

CONCLUSIONS

- Single-ascending doses of 5–800 mg and 7-days of multiple-ascending doses of 40–360 mg of lorundrostat were well tolerated with a low incidence of adverse events
- Mean t_{max} was 1–1.5 hours and mean $t_{1/2}$ was 7.9–10.5 hours in the SAD component and $t_{1/2}$ was 9.1–11.9 hours in the MAD component
- There was a low incidence of adverse events that was not dose-dependent
- Based on these findings, development of lorundrostat has progressed; a Phase 2 safety and dose-ranging trial in subjects with hypertension has been completed and a pivotal registration program is anticipated to begin in 2023

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