Sa4121

Lorundrostat for Treatment of Obesity-Related, Aldosterone-Dependent Hypertension – an Endotype-Specific, Targeted Approach to the Treatment of Uncontrolled Hypertension

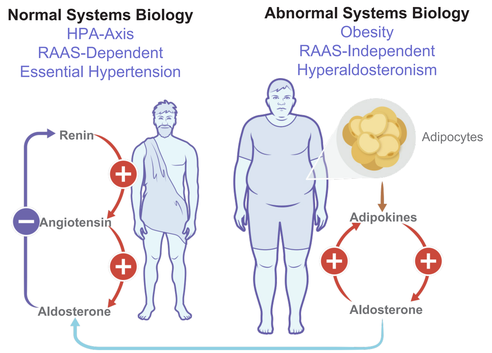
David M Rodman, MD, Borut Cizman, MD

Mineralys Therapeutics, Radnor, PA

INTRODUCTION

- Inadequate blood pressure (BP) control remains a leading cause of morbidity and mortality, and novel antihypertensive agents with transformational potential have been lacking
- Escape from upstream, RAAS pathway inhibition is a major challenge that reduces the efficacy of strategies targeting renin and angiotensin, including renin inhibitors, RNAi and antisense reduction of the renin substrate angiotensinogen, angiotensin-converting enzyme, and angiotensin receptor blockers
- Downstream inhibitors of the RAAS pathway, targeting the mineralocorticoid receptor, are effective in treatment but limited by on- and off-target effects, including unacceptable hormonal effects and, less common but clinically significant, increases in serum potassium
- The prevalence of obesity is increasing and known to be associated with increased aldosterone production, increased prevalence of hypertension (HTN) and, more recently, mechanistically linked to a positive feedback loop with an afferent limb characterized by an abnormal visceral adipocyte secretome driving increased adrenal aldosterone production and an efferent limb characterized by increased circulating aldosterone stabilizing the adipocyte secretory phenotype
- We propose that this pathological obesity-leptin-aldosterone positive feedback loop supersedes the normal renin-angiotensin negative feedback loop and can be targeted by lorundrostat, a novel aldosterone-synthase inhibitor

Figure 1. Obesity-leptin-aldosterone hypertension endotype



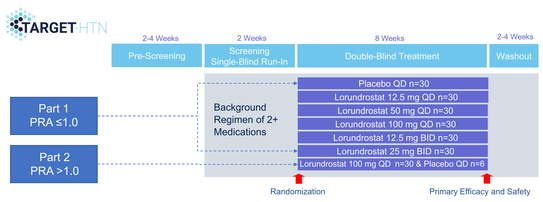
Obesity leads to a stable, pathological positive feedback loop that drives and maintains elevated aldosterone production, superseding the normal renin-angiotensin negative feedback loop. HPA, hypothalamic-pituitary-adrenal; RAAS, renin-angiotensin-aldosterone system.

OBJECTIVES

- To provide proof-of-concept that aldosterone synthase inhibition by lorundrostat reduces aldosterone production and ameliorates uncontrolled and/or resistant HTN in a dose-dependent fashion
- To provide an initial characterization of the tolerability, safety, and therapeutic index of lorundrostat in individuals with poorly controlled HTN despite treatment with 2 or more antihypertensive agents

METHODS

Figure 2. TARGET-HTN study design



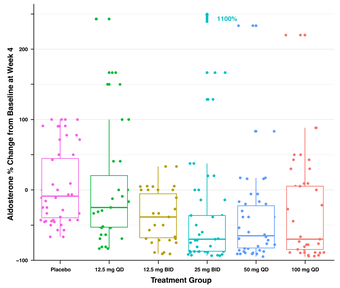
Actual randomized: Part 1 N=163; Part 2 N=37. BID, twice daily; PRA, plasma renin activity (ng/mL/h); QD, once daily.

Table 1. Baseline demographics and clinical characteristics

	Part 1 (N=163)	Part 2 (N=37)
Age, years	65.6±0.8	66.0±1.8
Male	41.7	32.4
Black or African American	39.3	21.6
Hispanic or Latino	46.6	51.4
BMI, kg/m^2	31.2±0.4	30.7±0.7
AOBP systolic BP, mmHg	142.2±1.0	139.1±1.4
AOBP diastolic BP, mmHg	81.5±0.8	79.1±1.6
eGFR, mL/min/1.73m^2	78.9±1.3	79.6±2.4
Diabetes	37.4	48.6
Heart failure	3.1	0
Previous myocardial infarction	5.5	5.4
2 background HTN medications	52.8	64.9
≥3 background HTN medications	47.2	35.1
Use of thiazide or thiazide-like diuretic	56.4	64.9
Use of ACEi or ARB	77.9	94.6

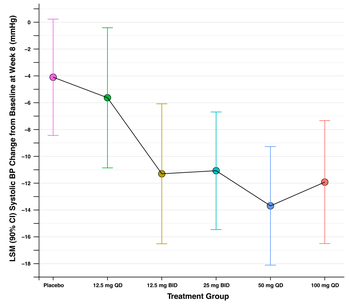
Mean±SD or %. ACEi, angiotensin-converting enzyme inhibitor; AOBP, automated office blood pressure; ARB, angiotensin receptor blocker; BMI, body mass index; BP, blood pressure; HTN, hypertension; SD, standard deviation.

Figure 3. Percent change in serum aldosterone at week 4



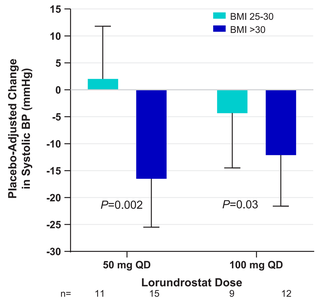
Daily dose (mg/24 h) in Part 1 cohort. BID, twice daily; QD, once daily.

Figure 4. Change in systolic BP at week 8



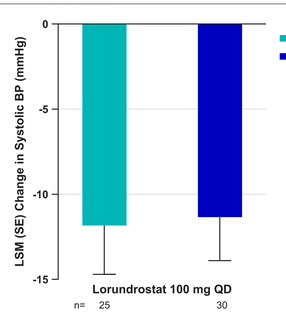
Mixed model repeated measures and automated office blood pressure in Part 1 cohort. BID, twice daily; BP, blood pressure; LSM, least squares mean; QD, once daily.

Figure 5. Increased baseline BMI predicted enhanced systolic BP response to lorundrostat



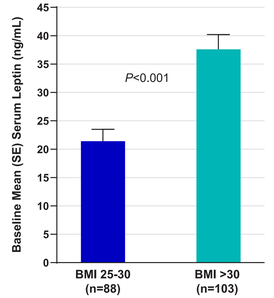
Mean (90% CI) placebo-adjusted change from baseline at 8 weeks in AOBP systolic BP in Part 1 cohort. AOBP, automated office blood pressure; BMI, body mass index (kg/m^2); BP, blood pressure; QD, once daily.

Figure 6. Baseline low PRA versus normal to high PRA had similar systolic BP response to lorundrostat



LSM (SE) change in AOBP systolic BP from baseline at 8 weeks. Subjects with baseline PRA ≤1.0 from Part 1 cohort. Subjects with baseline PRA >1.0 from Part 2 cohort. AOBP, automated office blood pressure; BP, blood pressure; LSM, least squares mean; PRA, plasma renin activity (ng/mL/h); QD, once daily; SE, standard error.

Figure 7. Higher baseline BMI was associated with higher baseline serum leptin



Part 1 and Part 2 cohorts combined. BMI, body mass index (kg/m^2); SE, standard error.

CONCLUSIONS

- **Lorundrostat was effective and well tolerated**
- **Adults with obesity and uncontrolled and/or resistant HTN had enhanced BP reduction in response to lorundrostat**
- **The enhanced BP lowering effect in obese individuals was unrelated to baseline PRA or baseline aldosterone to renin ratio (not shown), consistent with uncoupling of the normal renin-aldosterone negative feedback loop**
- **Circulating leptin, which is a major driver of adrenal aldosterone production, was increased in proportion to the baseline BMI**
- **Aldosterone-targeted precision therapy may allow early identification, intervention, and improved clinical outcome in the obesity-leptin-aldosterone hypertension endotype**

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DISCLOSURES

DMR and BC: Employees of Mineralys Therapeutics, LLC.

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