

METHODS OF TREATING HYPERTENSION IN OBESE SUBJECTS

[0001] This application claims priority of U.S. Provisional Application No. 63/400,305, filed August 23, 2022, the contents of which is hereby incorporated by reference.

[0002] Throughout this application, various publications are referenced, including referenced in parenthesis. The disclosures of all publications mentioned in this application in their entireties are hereby incorporated by reference into this application in order to provide additional description of the art to which this invention pertains and of the features in the art which can be employed with this invention.

FIELD OF THE INVENTION

[0003] This invention relates to methods of treating hypertension by inhibiting aldosterone synthase (CYP 11 β 2 beta hydroxylase).

BACKGROUND OF THE INVENTION

[0004] Aldosterone is the principal mineralocorticoid in humans, produced in the zona glomerulosa of the adrenal cortex by aldosterone synthase (CYP 11 β 2 beta hydroxylase). Aldosterone is a key component of the renin-angiotensin-aldosterone system (RAAS), acting primarily as a regulator of electrolyte and fluid homeostasis.

[0005] Mineralocorticoid receptor-blocking agents (mineralocorticoid receptor antagonists, MRA), such as spironolactone and eplerenone, prevent aldosterone from binding with the mineralocorticoid receptor. Several clinical studies have demonstrated their benefit in treating hypertension. Given the role aldosterone plays in RAAS, inhibition of aldosterone synthase represents a possible alternative to mineralocorticoid receptor-blocking agents for the treatment of hypertension. However, previous studies suggest that some of the effects of aldosterone may occur independently of stimulation of the mineralocorticoid receptor/classic steroid-receptor complex modulation (Grossmann, C., & Gekle, M., 2009; Good, D. W., 2007; Mihailidou, A. S., & Funder, J. W., 2005). In addition, mineralocorticoid receptors are not selective for aldosterone, instead having similar affinity for the glucocorticoids cortisol and corticosterone.

[0006] Given the complexities of the renin-angiotensin-aldosterone system, use of aldosterone synthase inhibitors to treat hypertension carries many uncertainties. It is unknown whether

inhibition of aldosterone synthase can be used to effectively treat hypertension while maintaining an acceptable safety and side-effect profile. Further, because of the complex and often idiosyncratic etiology of hypertension, not all hypertensive subjects will respond in the same way to a given anti-hypertensive medication. Thus, identification of specific patient populations who benefit most from inhibition of aldosterone synthase remains an important goal in the field of cardiovascular health.

SUMMARY OF THE INVENTION

[0007] This invention provides a method of treating hypertension in a hypertensive subject having a body mass index of at least 30, the method comprising administering to the subject a CYP 11 β 2 beta hydroxylase inhibitor once or twice per day in an amount sufficient to treat hypertension in the hypertensive subject.

[0008] This invention also provides a method of treating hypertension in a male hypertensive subject having a waist-hip ratio above 0.90, or in a female hypertensive subject having a waist-hip ratio above 0.85, the method comprising administering to the subject a CYP 11 β 2 beta hydroxylase inhibitor once or twice per day in an amount sufficient to treat hypertension in the hypertensive subject.

[0009] This invention also provides a method of treating hypertension in a hypertensive subject in need thereof, the method comprising

- (a) measuring
 - (i) a systolic blood pressure of greater than 130 mmHg in said subject;
 - (ii) a diastolic BP of greater than 80 mmHg in said subject; and
 - (iii) a body mass index (BMI) of at least 30, preferably 30-50, more preferably 30-40, in said subject, or a waist-hip ratio above 0.90 in said subject if the hypertensive subject is male, or a waist-hip ratio above 0.85 in said subject if the hypertensive subject is female; andadministering to said subject an effective amount of a CYP 11 β 2 beta hydroxylase inhibitor.

[0010] This invention also provides a method of identifying a subject for hypertension treatment with a CYP 11 β 2 beta hydroxylase inhibitor, the method comprising:

- (a) measuring a systolic blood pressure of greater than 130 mmHg in said subject;
- (b) measuring a diastolic BP of greater than 80 mmHg in said subject; and
- (c) measuring a body mass index (BMI) of at least 30, preferably 30-50, more preferably 30-40, in said subject, or measuring a waist-hip ratio above 0.90 in said subject if the subject is male, or measuring a waist-hip ratio above 0.85 in said subject if the subject is female;

thereby identifying said subject for hypertension treatment with a CYP 11 β 2 beta hydroxylase inhibitor.

BRIEF DESCRIPTION OF THE DRAWINGS

[0011] Figure 1: Compound A HBr Study Schema. ABPM = ambulatory blood pressure monitoring; BP = blood pressure; BID = twice daily; EOT = end of treatment; FU = follow up; PRA = plasma renin activity; QD = once daily. ^a = If Screening results were available, inclusion/exclusion evaluation was performed. If subject was not eligible based on Screening results, they did not continue to Visit 4. If Screening results were not available, subject proceeded to Visit 4. If Screening results were not available at Visit 4, subject should attend Visit 5 to determine final eligibility. If eligible based on Screening results, ABPM assessment begins at Visit 5. ^b = The ABPM procedure initiated at home approximately 24 hours before Randomization (Study Day 1). Alternatively, sites were permitted choose to schedule an office visit on Study Day 0 (Visit 5) to initiate the ABPM procedure. Training for the ABPM procedure was done either at an office visit or via phone.

[0012] Figure 2: Waterfall plots showing the AOBP change in systolic blood pressure at week 8. The figure shows waterfall plots of the full analysis and safety set (FAS) analysis of placebo, 50mg QD and 100mg QD groups and the per-protocol (PP) analysis of the 100 mg group. A modeled mean and per-protocol observed mean values are also shown for each group.

[0013] Figure 3: Waterfall plots showing the AOBP change in systolic blood pressure at week 8. The figure shows waterfall plots of the FAS analysis of 12.5mg QD, 12.5 mg BID, and 25 mg BID using all subjects with week 8 measurement. Modeled mean and per-protocol observed mean values are also shown for each group.

[0014] Figure 4: A bar graph showing the mean change in systolic blood pressure from baseline. The figure provides a final analysis including both full analysis set (FAS, all evaluable subjects receiving at least one dose of Compound A HBr) and per-protocol (PP, only those receiving $\geq 75\%$ of study drug with week 8 visit). Part 2 data shows the interim average of last visit week 5-6.

[0015] Figure 5: Graph of mean observed automated office blood-pressure change from baseline at week 8 for QD dosing regimens, showing a dose-response to Compound A HBr. BID per-protocol cohorts are shown on the far right of the graph.

[0016] **Figure 6:** Graph showing the systolic blood pressure change from baseline at week 8 for a 50 mg QD, 100 mg QD, 12.5 mg BID, and 25 mg BID pooled cohort, the lowest response quartile of the pooled cohorts, the highest response quartile of the pooled cohort, and placebo.

[0017] **Figure 7:** A waterfall plot showing change in systolic blood pressure from placebo and 100 mg QD groups pooled from both Parts 1 and 2. Part 2 data from interim snapshot with all subjects randomized and average last visit week 5-6, minimum week 2.

[0018] **Figure 8:** A graph showing the change in estimated glomerular filtration rate (eGFR) in different dosing cohorts.

[0019] **Figure 9:** A graph showing an example of ambulatory 24-hour blood pressure monitoring. The graph shows the 24-hour ambulatory blood pressure (systolic) of a subject receiving Compound A HBr 100mg QD versus baseline, showing an average 24-hour blood pressure reduction and restoration of normal nocturnal dipping pattern.

[0020] **Figure 10:** A graph showing the change in systolic blood pressure at week 8 relative to baseline as measured using the ABPM full analysis set.

[0021] **Figure 11:** Waterfall plots showing the 24-hour average and overnight average ABPM change at 8 weeks relative to baseline. 100 mg QD dose levels provide excellent 24-hour blood pressure reduction. Overnight blood pressure reduction from the 100 mg QD dose level appears to be superior to 25 mg BID.

[0022] **Figure 12:** Modelled (MMRM) Least Square Mean (SEM) Change from Baseline at Week 8 in Seated Automated Office-Measured Systolic Blood Pressure (mmHg), Part 1 (Full Analysis Set). Error bars represent SEM. Numbers inside the bars represent the number of subjects with non-missing data. P-values represent statistically significant difference compared with placebo. *p=0.0114. **p=0.042. Abbreviations: BID, twice daily; mg, milligrams; mmHg, millimeters of mercury; QD, once daily; SBP, systolic blood pressure; SEM, standard error of the mean.

[0023] **Figure 13:** Modelled (MMRM) Least Square Mean (SEM) Change from Baseline at Week 8 in Seated Automated Office-Measured Systolic Blood Pressure (mmHg), Parts 1 & 2 (Full Analysis Set). Error bars represent SEM. Numbers inside the bars represent the number of subjects with non-missing data. Abbreviations: mg, milligrams; mmHg, millimeters of mercury; MMRM,

mixed model repeated measures; QD, once daily; SBP, systolic blood pressure; SEM, standard error of the mean.

[0024] Figure 14: Boxplot of Measured Change from Baseline at Week 8 in Seated Automated Office-Measured Systolic Blood Pressure (mmHg), Part 1 (Full Analysis Set). $\diamond$, mean; —, median; outlier. Upper and lower boundaries of each box represent 1st and 3rd quartiles. Abbreviations: BID, twice daily; mg, milligrams; mmHg, millimeters of mercury; QD, once daily; SBP, systolic blood pressure.

[0025] Figure 15: Boxplot of Measured Change from Baseline at Week 8 in Seated Automated Office-measured Systolic Blood Pressure (mmHg) in Subjects Randomized to 100 mg QD, Parts 1 & 2 (Full Analysis Set). $\diamond$, mean; —, median; 1, outlier. Upper and lower boundaries of each box represent 1st and 3rd quartiles. Abbreviations: mg, milligrams; mmHg, millimeters of mercury; QD, once daily; SBP, systolic blood pressure.

[0026] Figure 16: Proportion of Subjects with Seated Automated Office-Measured SBP/DBP $\leq 130/80$ mmHg at Week 8, Part 1 (Full Analysis Set). Subjects missing an assessment at Week 8 or who had received rescue medications prior to Week 8 were considered as failures. Numbers inside bars represent the number of subjects achieving AOBP $\leq 130/80$ mmHg.

[0027] Figure 17: Proportion of Subjects with Seated Automated Office-Measured SBP/DBP $\leq 130/80$ mmHg at Study Week 8 in Subjects Randomized to 100 mg QD, Parts 1 & 2 (Full Analysis Set). Subjects missing an assessment at Week 8 or who had received rescue medications prior to Week 8 were considered as failures. Numbers inside bars represent the number of subjects achieving AOBP $\leq 130/80$ mmHg.

[0028] Figure 18: Time (Weeks) to First Occurrence of Seated Automated Office-Measured SBP/DBP $\leq 130/80$ mmHg, Part 1 (Full Analysis Set). Subjects who failed to achieve a BP of $\leq 130/80$ mmHg prior to Week 8/EoT were censored at the Week 8/EoT date. Subjects who were lost to follow-up prior to Week 8/EoT were censored at the date of the last known BP assessment. Subjects who took rescue medications were censored on the date of rescue medication initiation. Missing events correspond to subjects who didn't have post-baseline assessments for BP. For subject 146-040, the study duration (>27 weeks) and treatment duration (>18 weeks) were longer than planned due to AEs leading to temporary discontinuation.

[0029] Figure 19: Time (Weeks) to First Occurrence of Seated Automated Office-Measured SBP/DBP $\leq 130/80$ mmHg in Subjects Randomized to 100 mg QD, Parts 1 & 2 (Full Analysis Set). Subjects who failed to achieve a BP of $\leq 130/80$ mmHg prior to Week 8/EoT were censored at the Week 8/EoT date. Subjects who were lost to follow-up prior to Week 8/EoT were censored at the date of the last known BP assessment. Subjects who took rescue medications were censored on the date of rescue medication initiation. Missing events correspond to subjects who didn't have post-baseline assessments for BP.

[0030] Figure 20: Mean (SEM) Change in Serum Potassium from Baseline over Time in QD Dose Cohorts, Part 1 (Safety Analysis Set).

[0031] Figure 21: Mean (SEM) Change in Serum Potassium from Baseline over Time in BID Dose Cohorts, Part 1 (Safety Analysis Set).

[0032] Figure 22: Mean (SEM) Change in Serum Potassium from Baseline over Time, Part 2 (Safety Analysis Set).

[0033] Figure 23: Mean (SEM) Change in Serum Sodium from Baseline over Time in QD Dose Cohorts, Part 1 (Safety Analysis Set)

[0034] Figure 24: Mean (SEM) Change in Serum Sodium from Baseline over Time in BID Dose Cohorts, Part 1 (Safety Analysis Set)

[0035] Figure 25: Mean (SEM) Change in Serum Sodium from Baseline over Time, Part 2 (Safety Analysis Set)

[0036] Figure 26: Relationship between median baseline body mass index (BMI, kg/m²) and serum leptin (ng/dl). Data was derived from pooled data from low renin subjects (Part-1) from the lorundrostat 25mg BID, 50mg QD and 100mg QD cohorts. Each of these cohorts demonstrated significant reduction in median serum aldosterone at week 4 compared to baseline (9.6%, 65.2%, 70.0%, respectively).

[0037] Figure 27: Relationship between BMI at baseline and mean change in systolic BP (mmHg), measured by AOBP, at week 8 compared to baseline. Data was derived from pooled data from low renin subjects (Part-1) from the lorundrostat 25mg BID, 50mg QD and 100mg QD cohorts.

DETAILED DESCRIPTION OF THE INVENTION

Methods of treating hypertension

[0038] This invention provides a method of treating hypertension in a hypertensive subject having a body mass index of at least 30, the method comprising administering to the subject a CYP 11 β 2 beta hydroxylase inhibitor once or twice per day in an amount sufficient to treat hypertension in the hypertensive subject.

[0039] This invention also provides a method of treating hypertension in a male hypertensive subject having a waist-hip ratio above 0.90, or in a female hypertensive subject having a waist-hip ratio above 0.85, the method comprising administering to the subject a CYP 11 β 2 beta hydroxylase inhibitor once or twice per day in an amount sufficient to treat hypertension in the hypertensive subject.

[0040] This invention also provides a method of treating hypertension in a hypertensive subject having a body mass index of more than 30, preferably 30-50, more preferably 30-40, the method comprising administering to the subject a CYP 11 β 2 beta hydroxylase inhibitor once or twice per day in an amount sufficient to treat hypertension in the hypertensive subject.

[0041] This invention also provides a method of treating hypertension in a hypertensive subject having a serum leptin concentration of at least 30 ng/dL, preferably at least 35 ng/dL, more preferably at least 40 ng/dL, or more preferably 30-50 ng/dL, 30-45 ng/dL, or 35-50 ng/dL, the method comprising administering to the subject a CYP 11 β 2 beta hydroxylase inhibitor once or twice per day in an amount sufficient to treat hypertension in the hypertensive subject.

[0042] In some embodiments, the hypertensive subject has:

- (a) a plasma aldosterone concentration of greater than or equal to 6 ng/dL by immunoassay in said subject; and/or
- (b) a plasma aldosterone concentration of greater than or equal to 1 ng/dL by LC-MS in said subject.

[0043] Plasma aldosterone concentration can be measured by standard, commercially available tests known in the art. Such measurements can be conducted by FDA-approved laboratories. See, e.g., Stowasser et al, Clin Biochem Rev, 31(2):39-56 (2010), citing Schirpenbach, et al. Clinical chemistry 52, no. 9 (2006): 1749-1755. Notably, the assays for

measuring aldosterone reported in Schirpenbach, et al. are immunoassays. As reported in Guo et al. The Journal of Clinical Endocrinology & Metabolism 103, no. 11 (2018): 3965-3973, LC-MS assays have been shown to have a higher specificity. In an embodiment, a plasma aldosterone concentration of greater than or equal to 6 ng/dL as measured by an immunoassay such as ELISA corresponds to a plasma aldosterone concentration of greater than or equal to about 1 ng/dL as measured by LC-MS.

[0044] This invention also provides a method of treating hypertension in a hypertensive subject in need thereof, the method comprising

- (a) measuring
 - (i) a systolic blood pressure of greater than 130 mmHg in said subject;
 - (ii) a diastolic BP of greater than 80 mmHg in said subject; and
 - (iii) a body mass index (BMI) of at least 30, preferably 30-50, more preferably 30-40, in said subject, or a waist-hip ratio above 0.90 in said subject if the hypertensive subject is male, or a waist-hip ratio above 0.85 in said subject if the hypertensive subject is female; and
- (b) administering to said subject an effective amount of a CYP 11 β 2 beta hydroxylase inhibitor.

[0045] This invention also provides a method of treating hypertension in a hypertensive subject in need thereof, the method comprising

- (a) measuring in said hypertensive subject
 - (i) a systolic blood pressure of greater than 130 mmHg;
 - (ii) a diastolic BP of greater than 80 mmHg; and
 - (iii) one or more or all of the following:
 - (1) a body mass index (BMI) of at least 30, preferably more than 30, preferably 30-50, more preferably 30-40;
 - (2) a waist-hip ratio above 0.90 if the hypertensive subject is male or a waist-hip ratio above 0.85 if the hypertensive subject is female; and
 - (3) a serum leptin of at least 30 ng/dL, preferably at least 35 ng/dL, more preferably at least 40 ng/dL, or more preferably 30-50 ng/dL, 30-45 ng/dL, or 35-50 ng/dL; and

- (b) administering to said subject an effective amount of a CYP 11 β 2 beta hydroxylase inhibitor.

[0046] This invention also provides a method of treating hypertension in a hypertensive subject in need thereof, the method comprising

- (a) receiving an identification of the hypertensive subject as having
 - (i) a systolic blood pressure of greater than 130 mmHg;
 - (ii) a diastolic BP of greater than 80 mmHg; and
 - (iii) one or more or all of the following:
 - (1) a body mass index (BMI) of at least 30, preferably more than 30, preferably 30-50, more preferably 30-40;
 - (2) a waist-hip ratio above 0.90 if the hypertensive subject is male or a waist-hip ratio above 0.85 if the hypertensive subject is female; and
 - (3) a serum leptin of at least 30 ng/dL, preferably at least 35 ng/dL, more preferably at least 40 ng/dL, or more preferably 30-50 ng/dL, 30-45 ng/dL, or 35-50 ng/dL; and
- (b) administering to said subject an effective amount of a CYP 11 β 2 beta hydroxylase inhibitor.

[0047] In embodiments of this invention, step (a) further comprises:

- (a) measuring a plasma aldosterone concentration of greater than or equal to 6 ng/dL in said subject by immunoassay; or
- (b) measuring a plasma aldosterone concentration of greater than or equal to 1 ng/dL in said subject by LC-MS.

[0048] In embodiments of this invention, step (a) further comprises receiving an identification of the hypertensive subject as having:

- (a) a plasma aldosterone concentration of greater than or equal to 6 ng/dL as measured by immunoassay; or
- (b) a plasma aldosterone concentration of greater than or equal to 1 ng/dL as measured by LC-MS.

[0049] In embodiments of the invention, the hypertensive subject is taking or has taken a hypertension medication selected from a diuretic, an ACE inhibitor, an angiotensin receptor

blocker, a calcium channel blocker, or a combination of two or more thereof. In embodiments of the invention, the hypertensive subject is taking or has taken at least two of said hypertension medications.

[0050] In embodiments of the invention, 50% or more of CYP 11 β 2 beta hydroxylase's activity is inhibited for 40-60% of a 24-hour period.

[0051] In embodiments of the invention, 50% or more of CYP 11 β 2 beta hydroxylase's activity is inhibited for between 10 to 14 hours of a 24-hour period.

[0052] In embodiments of the invention, the CYP 11 β 2 beta hydroxylase inhibitor reduces the serum aldosterone level of the subject by 50-90% relative to the subject's pre-drug level of serum aldosterone for a period not less than eight hours and not greater than 16 hours.

[0053] In embodiments of the invention, the CYP 11 β 2 beta hydroxylase inhibitor reduces the serum aldosterone level of the subject by 60-80% relative to the subject's pre-drug level of serum aldosterone for a period not less than eight hours and not greater than 16 hours.

[0054] In embodiments of the invention, the CYP 11 β 2 beta hydroxylase inhibitor allows serum aldosterone of the subject to return to the subject's pre-drug level of serum aldosterone or greater during the period between 16 and 24 hours after the dose is administered.

[0055] In embodiments of the invention, 50% or more of CYP 11 β 2 beta hydroxylase's activity is inhibited for between 1 and 16 hours, or preferably for between 3 and 8 hours, of a 24-hour period.

[0056] In embodiments, the CYP 11 β 2 beta hydroxylase inhibitor is administered once per day in an amount sufficient to:

- (a) inhibit 50% or more of CYP 11 β 2 beta hydroxylase's activity for between 1 and 16 hours, preferably for between 3 and 8 hours;
- (b) inhibit 60% or more of CYP 11 β 2 beta hydroxylase's activity for between 1 and 13 hours, preferably for between 2 and 6 hours;
- (c) inhibit 70% or more of CYP 11 β 2 beta hydroxylase's activity for between 1 and 9 hours, preferably for between 2 and 5 hours;
- (d) inhibit 80% or more of CYP 11 β 2 beta hydroxylase's activity for between 1 and 6 hours, preferably for between 1 and 3 hours; and/or

- (e) inhibit 90% or more of CYP 11 β 2 beta hydroxylase's activity for between 0 and 3 hours, preferably for between 0 and 1 hour;
to thereby treat hypertension in the hypertensive subject.

[0057] In embodiments, the CYP 11 β 2 beta hydroxylase inhibitor is administered once per day in an amount sufficient to:

- (a) inhibit 50% or more of CYP 11 β 2 beta hydroxylase's activity for between 1 and 20 hours, preferably for between 4 and 11 hours;
- (b) inhibit 60% or more of CYP 11 β 2 beta hydroxylase's activity for between 1 and 17 hours, preferably for between 3 and 9 hours;
- (c) inhibit 70% or more of CYP 11 β 2 beta hydroxylase's activity for between 1 and 15 hours, preferably for between 2.5 and 7 hours;
- (d) inhibit 80% or more of CYP 11 β 2 beta hydroxylase's activity for between 1 and 10 hours, preferably for between 2 and 5 hours; and/or
- (e) inhibit 90% or more of CYP 11 β 2 beta hydroxylase's activity for between 1 and 5 hours, preferably for between 0.5 and 2.5 hours;
to thereby treat hypertension in the hypertensive subject.

[0058] In embodiments of the invention, the CYP 11 β 2 beta hydroxylase inhibitor is administered to the subject once per day. In embodiments of the invention, the CYP 11 β 2 beta hydroxylase inhibitor is administered in the morning. In embodiments of the invention, the CYP 11 β 2 beta hydroxylase inhibitor is administered to the subject twice per day. In a preferred embodiment of the invention, the CYP 11 β 2 beta hydroxylase inhibitor is administered to the subject once per day in the morning.

[0059] In embodiments of the invention, the CYP 11 β 2 beta hydroxylase inhibitor:

- (a) is administered daily for at least one week;
- (b) is administered daily for at least two weeks;
- (c) is administered daily for at least four weeks; or
- (d) is administered daily for at least eight weeks.

[0060] In embodiments of the invention, the hypertensive subject's ambulatory systolic blood pressure is reduced by at least 10 mmHg, by 10-55 mmHg, by 10-50 mmHg, by 10-45 mmHg, by 10-40 mmHg, by 10-35 mmHg, by 10-30 mmHg, by 10-25 mmHg, by 10-20 mmHg, or by 10-15

mmHg, relative to the hypertensive subject's ambulatory systolic blood pressure prior to administration of the CYP 11 β 2 beta hydroxylase inhibitor, preferably relative to the hypertensive subject's ambulatory systolic blood pressure prior to administration of the CYP 11 β 2 beta hydroxylase inhibitor for a period of at least eight weeks.

[0061] In embodiments of the invention, the hypertensive subject's ambulatory diastolic blood pressure is reduced by at least 5 mmHg, by 5-25 mmHg, by 5-20 mmHg, or by 5-15 mmHg relative to the hypertensive subject's ambulatory diastolic blood pressure prior to administration of the CYP 11 β 2 beta hydroxylase inhibitor, preferably relative to the hypertensive subject's ambulatory diastolic blood pressure prior to administration of the CYP 11 β 2 beta hydroxylase inhibitor for a period of at least eight weeks.

[0062] In embodiments of the invention:

- (a) the subject's office-measured systolic blood pressure is lowered relative to the subject's office-measured systolic blood pressure prior to administration of the CYP 11 β 2 beta hydroxylase inhibitor; and/or
- (b) the subject's 24-hour ambulatory systolic blood pressure is lowered relative to the subject's ambulatory systolic blood pressure prior to administration of the CYP 11 β 2 beta hydroxylase inhibitor.

[0063] In embodiments of the invention:

- (a) the subject's office-measured systolic blood pressure is lowered by at least 10 mmHg relative to the subject's office-measured systolic blood pressure prior to administration of the CYP 11 β 2 beta hydroxylase inhibitor; and/or
- (b) the subject's ambulatory systolic blood pressure is lowered by at least 10 mmHg relative to the subject's ambulatory systolic blood pressure prior to administration of the CYP 11 β 2 beta hydroxylase inhibitor.

[0064] In embodiments of the invention:

- (a) the subject's office-measured diastolic blood pressure is lowered relative to the subject's office-measured diastolic blood pressure prior to administration of the CYP 11 β 2 beta hydroxylase inhibitor;

- (b) the subject's office-measured systolic and diastolic blood pressure is lowered relative to the subject's office-measured systolic and diastolic blood pressure prior to administration of the CYP 11 β 2 beta hydroxylase inhibitor;
- (c) the subject's ambulatory systolic and diastolic blood pressure is lowered relative to the subject's ambulatory systolic and diastolic blood pressure prior to administration of the CYP 11 β 2 beta hydroxylase inhibitor; and/or
- (d) the subject's systolic blood pressure is reduced to less than 130 mmHg and/or the subject's diastolic blood pressure is reduced to less than 80 mmHg.

[0065] In embodiments of the invention:

- (a) the subject's ambulatory systolic blood pressure is lowered by at least 10 mmHg, and the subject's ambulatory diastolic blood pressure is lowered by at least 5 mmHg each relative to the subject's ambulatory systolic and diastolic blood pressure, respectively, prior to administration of the CYP 11 β 2 beta hydroxylase inhibitor;
- (b) the subject's office-measured systolic blood pressure is lowered by at least 10 mmHg and the subject's office-measured diastolic blood pressure is lowered by at least 5 mmHg, each relative to the subject's office-measured systolic and diastolic blood pressure, respectively, prior to administration of the CYP 11 β 2 beta hydroxylase inhibitor; and/or
- (c) the subject's systolic blood pressure is reduced to less than 130 mmHg and/or the subject's diastolic blood pressure is reduced to less than 80 mmHg.

[0066] In embodiments of the invention, the duration of inhibition of CYP 11 β 2 beta hydroxylase activity is sufficient to maintain a state of sodium and volume depletion in the hypertensive subject.

[0067] In embodiments of the invention, the method does not produce a persistent state of hyperkalemia or mild non-anion gap metabolic acidosis in the hypertensive subject.

[0068] In embodiments of the invention, the CYP 11 β 2 beta hydroxylase inhibitor does not substantially accumulate in the hypertensive subject, preferably wherein the lack of substantial accumulation of the CYP 11 β 2 beta hydroxylase inhibitor in the hypertensive subject allows for the hypertensive subject's aldosterone levels to return to pre-drug baseline within 24-48 hours of

the CYP 11 β 2 beta hydroxylase inhibitor being administered, more preferably within 16-24 hours of the CYP 11 β 2 beta hydroxylase inhibitor being administered.

[0069] In embodiments of the invention, the hypertensive subject's potassium levels are generally maintained in a clinically normal range, preferably wherein the hypertensive subject's potassium levels are mildly elevated relative to the hypertensive subject's potassium levels prior to administration of the CYP 11 β 2 beta hydroxylase inhibitor, more preferably wherein the hypertensive subject's potassium levels are elevated by 0.35 mmol/L or less, more preferably wherein the hypertensive subject's potassium levels are maintained below a level of 5.5 mmol/L, more preferably wherein the hypertensive subject's potassium levels are maintained between 3.5 mEq/l to 5.1 mEq/l.

[0070] In embodiments of the invention, the CYP 11 β 2 beta hydroxylase inhibitor is administered to the hypertensive subject in an amount which:

- (a) suppresses aldosterone production in the subject;
- (b) increases serum and/or plasma potassium levels in the subject; and/or
- (c) increases plasma renin activity (PRA) in the subject.

[0071] In embodiments of the invention:

- (a) serum and/or plasma aldosterone AUC-24 is reduced in the subject by at least 25% relative to the aldosterone levels in the subject prior to administration of the CYP 11 β 2 beta hydroxylase inhibitor;
- (b) serum and/or plasma potassium levels in the subject are increased by at least 0.2 mMol/L relative to the serum and/or plasma potassium levels in the subject prior to administration of the CYP 11 β 2 beta hydroxylase inhibitor; and/or
- (c) PRA in the subject is increased by at least 5 ng/ml/hr relative to the PRA in the subject prior to administration of the CYP 11 β 2 beta hydroxylase inhibitor.

[0072] In embodiments of the invention, the hypertensive subject's aldosterone level follows a substantially normal circadian rhythm.

[0073] In embodiments of the invention, the hypertensive subject's average systolic blood pressure during sleep is reduced (a) relative to the hypertensive subject's average systolic blood pressure during sleep prior to receiving the CYP 11 β 2 beta hydroxylase inhibitor, and/or (b)

relative to the hypertensive subject's average daytime systolic blood pressure. In embodiments, the hypertensive subject's average systolic blood pressure during sleep is reduced:

- (a) by at least 10%, by between 10% and 40%, by between 10% and 30%, or by between 10% and 20% relative to the hypertensive subject's average daytime systolic blood pressure; and/or
- (b) by at least 8 mmHg, by at least 10mmHg, by between 8 and 55 mmHg, by between 10 and 45 mmHg, or by between 10 and 25 mmHg, relative to the hypertensive subject's average systolic blood pressure during sleep prior to receiving the CYP 11 β 2 beta hydroxylase inhibitor.

[0074] In embodiments of the invention, said CYP 11 β 2 beta hydroxylase inhibitor is selective for inhibition of CYP 11 β 2 beta hydroxylase activity relative to inhibition of CYP 11 β 1 beta hydroxylase activity, preferably wherein the inhibition constant (K_i) for CYP 11 β 1 beta hydroxylase divided by the K_i for CYP 11 β 2 beta hydroxylase is greater than 100.

[0075] In embodiments of the invention, the CYP 11 β 2 beta hydroxylase inhibitor is administered to the hypertensive subject in an amount below the amount which causes the subject's serum and/or plasma 11-deoxycortisterone (11-DOC) levels to exceed 600 pmol/L, preferably below the amount which causes the subject's serum and/or plasma 11-DOC levels to exceed 400 pmol/L.

[0076] In embodiments of the invention, the CYP 11 β 2 beta hydroxylase inhibitor is administered to the hypertensive subject in an amount below the amount which causes an accumulation of 11-DOC above 0.1 ng/ml in the subject.

[0077] In embodiments of the invention, the CYP 11 β 2 beta hydroxylase inhibitor is administered to the hypertensive subject in an amount which does not cause a clinically meaningful upregulation of the subject's adrenocortical hormone synthesis.

[0078] In embodiments of the invention, the CYP 11 β 2 beta hydroxylase inhibitor is administered to the hypertensive subject in an amount which:

- (a) does not cause a clinically meaningful reduction of the subject's serum and/or plasma cortisol levels, relative to the subject's serum and/or plasma cortisol levels prior to administration of the CYP 11 β 2 beta hydroxylase inhibitor;

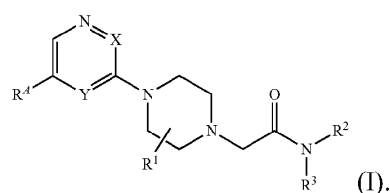
- (b) does not cause a clinically meaningful increase in the subject's serum and/or plasma 11-DOC levels relative to the subject's serum and/or plasma 11-DOC levels prior to administration of the CYP 11 β 2 beta hydroxylase inhibitor; and/or
- (c) does not cause a clinically meaningful increase in the subject's serum and/or plasma 11-deoxycortisol levels relative to the subject's serum and/or plasma 11-deoxycortisol levels prior to administration of the CYP 11 β 2 beta hydroxylase inhibitor.

[0079] In embodiments of the invention, the CYP 11 β 2 beta hydroxylase inhibitor is administered to the hypertensive subject in an amount:

- (a) which does not cause a reduction of more than 20% in the subject's serum and/or plasma cortisol levels, relative to the subject's serum and/or plasma cortisol levels prior to administration of the CYP 11 β 2 beta hydroxylase inhibitor, preferably which does not cause a reduction of more than 10% in the subject's serum and/or plasma cortisol levels, relative to the subject's serum and/or plasma cortisol levels prior to administration of the CYP 11 β 2 beta hydroxylase inhibitor;
- (b) which does not cause an increase of more than 20% in the subject's serum and/or plasma 11-DOC levels relative to the subject's serum and/or plasma 11-DOC levels prior to administration of the CYP 11 β 2 beta hydroxylase inhibitor, preferably which does not cause an increase of more than 10% in the subject's serum and/or plasma 11-DOC levels relative to the subject's serum and/or plasma 11-DOC levels prior to administration of the CYP 11 β 2 beta hydroxylase inhibitor; and/or
- (c) which does not cause an increase of more than 20% in the subject's serum and/or plasma 11-deoxycortisol levels relative to the subject's serum and/or plasma 11-deoxycortisol levels prior to administration of the CYP 11 β 2 beta hydroxylase inhibitor, preferably which does not cause an increase of more than 10% in the subject's serum and/or plasma 11-deoxycortisol levels relative to the subject's serum and/or plasma 11-deoxycortisol levels prior to administration of the CYP 11 β 2 beta hydroxylase inhibitor.

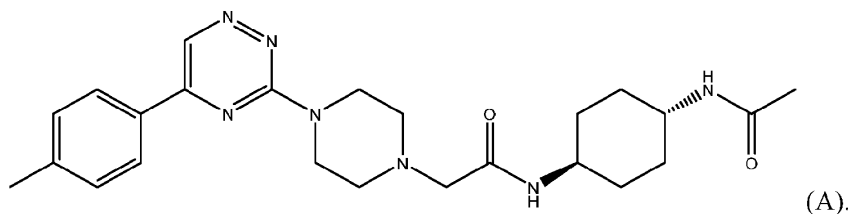
[0080] In embodiments of the invention, the CYP 11 β 2 beta hydroxylase inhibitor is a compound described in US Patent No. 10,029,993, the disclosure of which is incorporated by reference herein. In embodiments, the CYP11 β 2 beta hydroxylase inhibitor is a compound described in US Patent No. 10,329,263, the disclosure of which is incorporated by reference herein. In embodiments, the CYP11 β 2 beta hydroxylase inhibitor is a 1,2,4-triazine compound or a pharmaceutically acceptable salt thereof.

[0081] In embodiments, the CYP11 β 2 beta hydroxylase inhibitor is a compound of formula (I) or a pharmaceutically acceptable salt thereof:



- 1) wherein X and Y represent any of the following (i) to (iii):
 - (i) X is N, and Y is CH or C—R^Y,
 - (ii) X is CH, and Y is N, or
 - (iii) X is CH, and Y is CH;
- 2) R^Y represents an alkyl group;
- 3) R^A represents a cycloalkyl group which may be substituted, a cycloalkenyl group which may be substituted, an aryl group which may be substituted, or a 6- to 10-membered monocyclic or bicyclic heteroaryl group which may be partially hydrogenated and may be substituted;
- 4) R¹ represents a hydrogen atom, or an alkyl group;
- 5) R² represents an alkyl group which may be substituted, a cycloalkyl group which may be substituted, an aliphatic heterocyclic group which may be substituted, or a heteroaryl group which may be partially hydrogenated and may be substituted; and
- 6) R³ represents a hydrogen atom, or an alkyl group, or a pharmaceutically acceptable salt thereof.

[0082] In embodiments, said CYP 11 β 2 beta hydroxylase inhibitor is a compound of Formula (A) (also referred to herein as “Compound A”) or a pharmaceutically acceptable salt thereof:



[0083] In embodiments, the CYP11 β 2 beta hydroxylase inhibitor is a pharmaceutically acceptable salt of the compound of Formula (A).

[0084] In embodiments, the CYP11 β 2 beta hydroxylase inhibitor is a monohydrobromide salt of the compound of Formula (A), i.e. Compound A HBr.

[0085] In embodiments, the CYP11 β 2 beta hydroxylase inhibitor is the free base form of the compound of Formula (A).

[0086] In embodiments, preferably wherein the CYP11 β 2 beta hydroxylase inhibitor is Compound A, more preferably Compound A HBr:

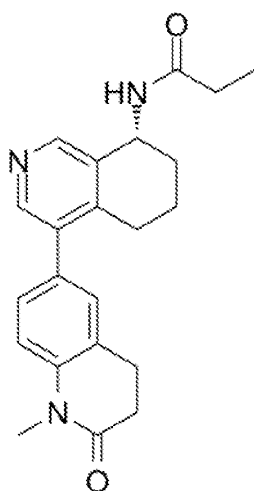
- (a) between 5 mg and 100 mg of the CYP 11 β 2 beta hydroxylase inhibitor is administered orally twice a day, 12 hours apart;
- (b) between 10 mg and 50 mg of the CYP 11 β 2 beta hydroxylase inhibitor is administered orally twice a day, 12 hours apart;
- (c) between 5 mg and 100 mg of the CYP 11 β 2 beta hydroxylase inhibitor is administered orally once a day; or
- (d) between 10 mg and 50 mg of the CYP 11 β 2 beta hydroxylase inhibitor is administered orally once a day.

[0087] In embodiments, preferably wherein the CYP11 β 2 beta hydroxylase inhibitor is Compound A, more preferably Compound A HBr:

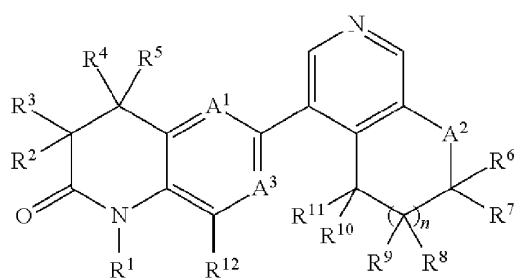
- (a) 12.5 mg of the CYP 11 β 2 beta hydroxylase inhibitor is administered orally twice a day, 12 hours apart;
- (b) 25 mg of the CYP 11 β 2 beta hydroxylase inhibitor is administered orally twice a day, 12 hours apart;

- (c) 12.5 mg of the CYP 11 β 2 beta hydroxylase inhibitor is administered orally once a day;
- (d) 50 mg of the CYP 11 β 2 beta hydroxylase inhibitor is administered orally once a day; or
- (e) 100 mg of the CYP 11 β 2 beta hydroxylase inhibitor is administered orally once a day.

[0088] In an embodiment, the CYP 11 β 2 beta hydroxylase inhibitor is a compound having the following structure, or a pharmaceutically acceptable salt thereof.



[0089] In an embodiment, the CYP 11 β 2 beta hydroxylase inhibitor is a compound having the following structure:



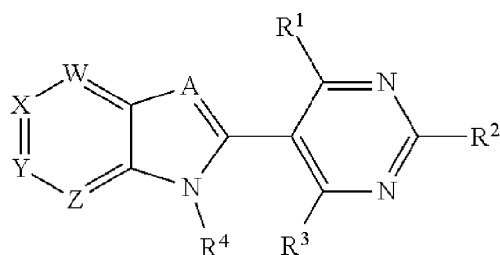
or a pharmaceutically acceptable salt thereof, wherein:

- (a) R^1 is C_1 - C_7 -alkyl;
- (b) R^2 , R^3 , R^4 , and R^5 are H;
- (c) R^6 is H, halogen or C_1 - C_7 -alkyl;

- (d) R^7 , R^8 , R^9 , R^{10} , and R^{11} are H;
- (e) R^{12} is H or halogen;
- (f) A^1 is CR^{13} ;
- (g) A^2 is NR^{14} or $CR^{15}R^{16}$;
- (h) A^3 is CR^{17} ;
- (i) R^{13} is H or halogen;
- (j) R^{14} is $-(CR^{20}R^{21})_q-(CR^{22}R^{23})_r-(CR^{24}R^{25})_p-NR^{26}R^{27}$, wherein the sum of q, r and p is at least 2;
- (k) R^{15} is $-(CR^{20}R^{21})_q-(CR^{22}R^{23})_r-(CR^{24}R^{25})_p-NR^{26}R^{27}$;
- (l) R^{16} is H;
- (m) or R^6 and R^{16} together with the carbon atoms to which they are attached form a double bond;
- (n) R^{17} , R^{20} , R^{21} , R^{22} , R^{23} , R^{24} , R^{25} , and R^{26} are H;
- (o) R^{27} is H, $-S(O)_2R^{31}$, $-C(O)R^{31}$ or $-C(O)OR^{31}$, wherein in case R^{26} is H and R^{27} is H, then the sum of q, r and p is at least 1;
- (p) R^{31} is C_1 - C_7 -alkyl, chloropyridinyl, hydroxyl- C_1 - C_7 -alkyl or C_3 - C_8 -cycloalkyl;
- (q) n is zero or 1;
- (r) p is zero or 1;
- (s) q is zero or 1; and
- (t) r is zero or 1.

[0090] Synthesis of these compounds is described in U.S. Patent No. 9,353,081 B2, the entire contents of which are hereby incorporated by reference. In an embodiment, the CYP 11 β 2 beta hydroxylase inhibitor is a compound described in U.S. Patent No. 9,353,081 B2, preferably a compound selective for inhibition of CYP 11 β 2 beta hydroxylase activity relative to inhibition of CYP 11 β 1 beta hydroxylase activity, more preferably wherein the inhibition constant (K_i) for CYP 11 β 1 beta hydroxylase divided by the K_i for CYP 11 β 2 beta hydroxylase is greater than 100.

[0091] In an embodiment, the CYP 11 β 2 beta hydroxylase inhibitor is a compound having the following structure:



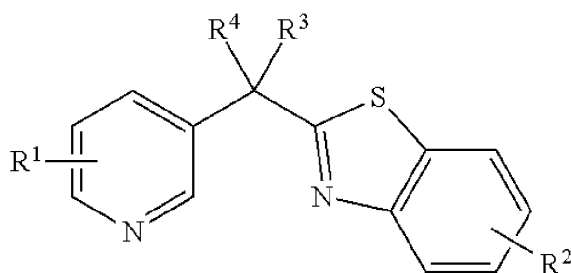
or a pharmaceutically acceptable salt thereof, wherein:

- (a) A is N;
- (b) W is CR₆;
- (c) X is CR₆;
- (d) Y is CR₆;
- (e) Z is CR₆;
- (f) R₁ is hydrogen, halogen, cyano, acyl, alkyl, alkenyl, alkynyl, haloalkyl, alkoxy, haloalkoxy, cycloalkyl, cycloalkoxy, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl, heterocycloalkylalkyl, NRaRb, NHSO₂Rc, (CH₂)_nNRaRb, (CH₂)_nNHSO₂Rd, (CH₂)_nNHCO₂Rd, CO₂Re, CORf, (CH₂)_nORf, or CReRfOH;
- (g) R₂ is hydrogen, cyano, acyl, alkyl, alkenyl, alkynyl, haloalkyl, alkoxy, haloalkoxy, cycloalkyl, cycloalkoxy, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl, heterocycloalkylalkyl, NHSO₂Rc, CH₂NRaRb, CH₂NHSO₂Rd, CO₂Re, CORf, CH₂ORf, or CReRfOH;
- (h) R₃ is hydrogen, halogen, cyano, acyl, alkyl, alkenyl, alkynyl, haloalkyl, alkoxy, haloalkoxy, cycloalkyl, cycloalkoxy, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl, heterocycloalkylalkyl, NRaRb, NHSO₂Rc, (CH₂)_nNRaRb, (CH₂)_nNHSO₂Rd, CO₂Re, CORf, (CH₂)_nORf, or CReRfOH;
- (i) each n is independently 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10;
- (j) R₄ is alkyl, cycloalkyl, haloalkyl, or heteroalkyl;
- (k) each occurrence of R₆ is, independently, hydrogen, halogen, cyano, haloalkyl, alkyl, cycloalkyl, haloalkyl, alkoxy, haloalkoxy, alkylsulfonyl, or carboxyl; and
- (l) each occurrence of Ra, Rb, Rc, Rd, Re, and Rf are, independently, hydrogen, acyl, alkyl, alkenyl, alkynyl, heteroalkyl, haloalkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, alkoxyalkyl, C(O)OC₁₋₆ alkyl, C(O)C₁₋₆

alkyl, a nitrogen protecting group when attached to a nitrogen atom, or an oxygen protecting group when attached to an oxygen atom; or Ra and Rb together with the atoms to which they are attached form a heterocycloalkyl ring; or Re and Rf together with the atoms to which they are attached form a cycloalkyl ring.

[0092] Synthesis of this compound is described in U.S. Patent No. 10,538,511 the entire contents of which are hereby incorporated by reference. In an embodiment, the CYP 11 β 2 beta hydroxylase inhibitor is a compound described in U.S. Patent No. 10,538,511, preferably a compound selective for inhibition of CYP 11 β 2 beta hydroxylase activity relative to inhibition of CYP 11 β 1 beta hydroxylase activity, more preferably wherein the inhibition constant (Ki) for CYP 11 β 1 beta hydroxylase divided by the Ki for CYP 11 β 2 beta hydroxylase is greater than 100..

[0093] In an embodiment, the CYP 11 β 2 beta hydroxylase inhibitor is a compound having the following structure:



or a salt or enantiomer thereof, wherein:

- (a) R¹ is one, two, or three independent halogen, haloalkyl, NO₂, CN, COOR⁵, SO₂R⁵, CONR⁵R⁶, SO₂NR⁵R⁶, NR⁵R⁶, OR⁵, alkyl, alkenyl, alkynyl, cycloalkyl, heteroalkyl or aryl;
- (b) R² is one or more independent halogen, haloalkyl, NO₂, CN, COOR⁵, SO₂R⁵, CONR⁵R⁶, SO₂NR⁵R⁶, NR⁵R⁶, OR⁵, alkyl, alkenyl, alkynyl, cycloalkyl, heteroalkyl, or aryl;
- (c) R³ is alkyl, alkenyl or alkynyl, any of which is further substituted by one or more R⁷;
- (d) R⁴ is NR⁵R⁶, SR⁵, or OR⁵;

- (e) R^5 and R^6 are independently hydrogen, alkyl, aryl or haloalkyl;
- (f) R^7 is H, halogen, alkyl, haloalkyl, NO_2 , CN, $COOR^8$, SO_2R^8 , $CONR^8R^9$, $SO_2NR^8R^9$, NR^8R^9 , or OR^8 ; and
- (g) R^8 and R^9 are independently hydrogen, alkyl or haloalkyl,
- (h) and wherein the compound is not benzo[d]thiazol-2-yl(pyridin-3-yl)methanol.

[0094] Synthesis of this compound is described in U.S. Patent No. 10,287,282 the entire contents of which are hereby incorporated by reference. In an embodiment, the CYP 11 β 2 beta hydroxylase inhibitor is a compound described in U.S. Patent No. 10,287,282, preferably a compound selective for inhibition of CYP 11 β 2 beta hydroxylase activity relative to inhibition of CYP 11 β 1 beta hydroxylase activity, more preferably wherein the inhibition constant (K_i) for CYP 11 β 1 beta hydroxylase divided by the K_i for CYP 11 β 2 beta hydroxylase is greater than 100.

[0095] In embodiments of the invention, the hypertensive subject has a plasma renin activity less than or equal to 1 ng/mL/hour.

[0096] In embodiments of the invention, the hypertensive subject has a plasma renin activity less than or equal to 0.6 ng/mL/hour.

[0097] In embodiments of the invention, the hypertensive subject has a plasma renin activity less than or equal to 4 ng/mL/hour.

[0098] In embodiments of the invention, the hypertensive subject has a plasma renin activity less than or equal to 3 ng/mL/hour.

[0099] In embodiments of the invention, the hypertensive subject has a plasma renin activity less than or equal to 2 ng/mL/hour.

[0100] In embodiments of the invention, the hypertensive subject has a plasma aldosterone concentration of greater than or equal to 6 ng/dL as measured by an immunoassay.

[0101] In embodiments of the invention, the hypertensive subject has a plasma aldosterone concentration of greater than or equal to 1 ng/dL as measured by LC-MS.

[0102] In a preferred embodiment of the invention, the hypertensive subject has a plasma renin activity less than or equal to 1 ng/mL/hour and a plasma aldosterone concentration of greater than or equal to 6 ng/dL as measured by an immunoassay. In a preferred embodiment of the invention,

the hypertensive subject has a plasma renin activity less than or equal to 1 ng/mL/hour and a plasma aldosterone concentration of greater than or equal to 1 ng/dL as measured by LC-MS. In a further preferred embodiment, this hypertensive subject is taking or has taken a hypertension medication selected from a diuretic, an ACE inhibitor, an angiotensin receptor blocker, a calcium channel blocker, or a combination of two or more thereof.

[0103] Alternatively, in embodiments wherein the hypertensive subject is not taking a hypertension medication selected from a diuretic, an ACE inhibitor, an angiotensin receptor blocker, a calcium channel blocker, in an embodiment the hypertensive subject has a plasma renin activity less than or equal to 0.6 ng/mL/hour and has a plasma aldosterone concentration of greater than or equal to 6 ng/dL as measured by an immunoassay or greater than or equal to 1 ng/dL as measured by LC-MS.

[0104] In embodiments of the invention, the hypertensive subject has secondary hypertension, preferably primary aldosteronism. In other embodiments of the invention, the hypertensive subject does not have primary aldosteronism, preferably wherein the hypertensive subject has primary hypertension.

[0105] This invention also provides a method of identifying a subject for hypertension treatment with a CYP 11 β 2 beta hydroxylase inhibitor, the method comprising:

- (a) measuring a systolic blood pressure of greater than 130 mmHg in said subject;
- (b) measuring a diastolic BP of greater than 80 mmHg in said subject; and
- (c) measuring a body mass index (BMI) of at least 30, preferably 30-50, more preferably 30-40, in said subject, or measuring a waist-hip ratio above 0.90 in said subject if the subject is male, or measuring a waist-hip ratio above 0.85 in said subject if the subject is female;

thereby identifying said subject for hypertension treatment with a CYP 11 β 2 beta hydroxylase inhibitor.

[0106] This invention also provides a method of identifying a subject for hypertension treatment with a CYP 11 β 2 beta hydroxylase inhibitor, the method comprising:

- (a) measuring a systolic blood pressure of greater than 130 mmHg in said subject;
- (b) measuring a diastolic BP of greater than 80 mmHg in said subject; and
- (c) measuring one or more or all of the following in said subject:

- (i) a body mass index (BMI) of at least 30, preferably 30-50, more preferably 30-40;
- (ii) a waist-hip ratio above 0.90 if the subject is male or a waist-hip ratio above 0.85 if the subject is female; and
- (iii) a serum leptin concentration of at least 30 ng/dL, preferably at least 35 ng/dL, more preferably at least 40 ng/dL, or more preferably 30-50 ng/dL, 30-45 ng/dL, or 35-50 ng/dL;

thereby identifying said subject for hypertension treatment with a CYP 11 β 2 beta hydroxylase inhibitor.

[0107] In embodiments, the method further comprises:

- (a) measuring a plasma aldosterone concentration of greater than or equal to 6 ng/dL by immunoassay in said subject; or
- (b) measuring a plasma aldosterone concentration of greater than or equal to 1 ng/dL by LC-MS in said subject.

[0108] In preferred embodiments of the invention, the subject identified for treatment with a CYP 11 β 2 beta hydroxylase inhibitor experiences an average drop of at least 10 mmHg, 10-55 mmHg, 10-50 mmHg, 10-45 mmHg, 10-40 mmHg, 10-35 mmHg, 10-30 mmHg, 10-25 mmHg, 10-20 mmHg, or 10-15 mmHg in systolic blood pressure when treated with the CYP 11 β 2 beta hydroxylase inhibitor relative to hypertensive subject's average systolic blood pressure prior to treatment with the CYP 11 β 2 beta hydroxylase inhibitor. In a particularly preferred embodiment the ambulatory systolic blood pressure of the subject identified for treatment with a CYP 11 β 2 beta hydroxylase inhibitor is reduced to less than 130 mmHg when treated with the CYP 11 β 2 beta hydroxylase inhibitor and/or the average ambulatory diastolic blood pressure of the subject identified for treatment with a CYP 11 β 2 beta hydroxylase inhibitor is reduced to less than 80 mmHg when treated with the CYP 11 β 2 beta hydroxylase inhibitor.

Compositions

[0109] This invention also provides pharmaceutical compositions for use in any one of the methods described herein.

Definitions

[0110] Unless otherwise defined, all technical and/or scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which the invention pertains. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of embodiments of the invention, exemplary methods and/or materials are described below. In case of conflict, the patent specification, including definitions, will control. In addition, the materials, methods, and examples are illustrative only and are not intended to be necessarily limiting.

[0111] In the discussion unless otherwise stated, adjectives such as “substantially” and “about” modifying a condition or relationship characteristic of a feature or features of an embodiment of the invention, are understood to mean that the condition or characteristic is defined to within tolerances that are acceptable for operation of the embodiment for an application for which it is intended. In embodiments, about means within a standard deviation using measurements generally acceptable in the art. In embodiments, about means a range extending to +/- 10% of the specified value. In embodiments, about includes the specified value. Unless otherwise indicated, the word “or” in the specification and claims is considered to be the inclusive “or” rather than the exclusive or, and indicates at least one of and any combination of items it conjoins.

[0112] It should be understood that the terms “a” and “an” as used above and elsewhere herein refer to “one or more” of the enumerated components. It will be clear to one of ordinary skill in the art that the use of the singular includes the plural unless specifically stated otherwise. Therefore, the terms “a,” “an” and “at least one” are used interchangeably in this application.

[0113] For purposes of better understanding the present teachings and in no way limiting the scope of the teachings, unless otherwise indicated, all numbers expressing quantities, percentages or proportions, and other numerical values used in the specification and claims, are to be understood as being modified in all instances by the term “about.” Accordingly, unless indicated to the contrary, the numerical parameters set forth in the following specification and attached claims are approximations that may vary depending upon the desired properties sought to be obtained. At the very least, each numerical parameter should at least be construed in light of the number of reported significant digits and by applying ordinary rounding techniques.

[0114] In the description and claims of the present application, each of the verbs, “comprise,” “include” and “have” and conjugates thereof, are used to indicate that the object or objects of the verb are not necessarily a complete listing of components, elements or parts of the subject or subjects of the verb. Other terms as used herein are meant to be defined by their well-known meanings in the art.

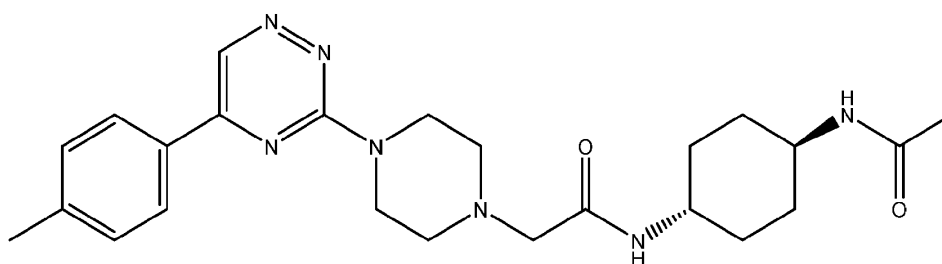
[0115] “Hypertension”, also called high blood pressure, is blood pressure that is higher than normal. In 2017, the American College of Cardiology and the American Heart Association published guidelines for hypertension management and defined hypertension as a blood pressure at or above 130 mmHg systolic blood pressure, 80 mmHg diastolic blood pressure. Stage 1 hypertension is defined as a blood pressure of 130-139 mmHg systolic blood pressure, 80-89 mmHg diastolic blood pressure, while stage 2 hypertension is defined as a blood pressure of greater than 140 mmHg systolic blood pressure, 90 mmHg diastolic blood pressure. As used herein, “hypertension” includes both stages 1 and 2 of hypertension unless indicated to the contrary. In an embodiment, the hypertensive subject has stage 1 hypertension. In another embodiment, the hypertensive subject has stage 2 hypertension. Hypertension includes high blood pressure that is multi-factorial and doesn’t have one distinct cause (primary hypertension), and high blood pressure that has a direct cause (secondary hypertension). As used herein, “hypertension” includes both primary and secondary hypertension unless indicated to the contrary. In embodiments, the hypertensive subject has primary hypertension. In other embodiments, the hypertensive subject has secondary hypertension. Primary aldosteronism (hyperaldosteronism), the most common form of secondary hypertension, is a condition that occurs when the adrenal glands produce too much aldosterone. In embodiments where the hypertensive subject has secondary hypertension, the subject has primary aldosteronism.

[0116] “CYP11 β 2”, “Cyp11B2” or “CYP11 β 2 beta hydroxylase” is a cytochrome P450 enzyme, encoded by the CYP11B2 gene in humans, which catalyzes a series of reactions leading from 11-deoxycorticosterone (i.e., an aldosterone precursor) to aldosterone. Thus, it is referred to in the art as “aldosterone synthase.” Cyp11B2 is mainly expressed in an adrenal cortex spherical layer and a level of plasma aldosterone is regulated by enzymatic activity of Cyp11B2 present in the adrenal gland. Aldosterone is expressed in other tissues, such as cardiovascular, kidney, adipose, and brain.

[0117] “CYP11 β 1”, “Cyp11B1” or “CYP11 β 1 beta hydroxylase” is a cytochrome P450 enzyme, encoded by the CYP11B1 gene in humans, which is involved in the biosynthesis of adrenal corticosteroids. It is referred to in the art as “steroid 11 β -hydroxylase.”

[0118] An “inhibitor” refers to a compound (e.g. compounds described herein) that reduces activity when compared to a control, such as absence of the compound or a compound with known inactivity. An inhibitor can be a small molecule inhibitor, an antibody inhibitor, a protein inhibitor, a biomolecule inhibitor, a natural ligand, and the like. An “inhibitor” may be in the form of a pharmaceutically acceptable salt, e.g. of the compounds described herein.

[0119] As used herein “Compound A” refers to the disubstituted 1, 2, 4-Triazine compound which is represented by Formula (A):



3-[4-[[trans-4-(acetoamino)cyclohexyl]carbamoylmethyl]piperazin-1-yl]-5-(p-tolyl)-1,2,4-triazine (A).

[0120] “Compound A HBr” refers to the hydrobromide (HBr) salt of Compound A. Weights and/or strengths of “Compound A HBr,” and “the compound” of the invention refer to the weight of the free base (i.e. Compound A) in the HBr salt and not the weight of the HBr salt.

[0121] Compound A and pharmaceutically acceptable salts thereof can be made by processes described, for example, in US Patent No. 10,029,993 and European Publication No. 3549935, the disclosures of which are incorporated by reference herein in their entirety.

[0122] “Treating” or “treatment” as used herein (and as well-understood in the art) also broadly includes any approach for obtaining beneficial or desired results in a subject’s condition, including clinical results. Beneficial or desired clinical results can include, but are not limited to, alleviation or amelioration of one or more symptoms or conditions, diminishment of the extent of a disease, stabilizing (i.e., not worsening) the state of disease, prevention of a disease’s transmission or spread, delay or slowing of disease progression, amelioration or palliation of the disease state, diminishment of the reoccurrence of disease, and remission, whether partial or total

and whether detectable or undetectable. In other words, "treatment" as used herein includes any cure, amelioration, or prevention of a disease. Treatment may prevent the disease from occurring; inhibit the disease's spread; relieve the disease's symptoms, fully or partially remove the disease's underlying cause, shorten a disease's duration, or do a combination of these things.

[0123] "Treating" and "treatment" as used herein include prophylactic treatment. Treatment methods include administering to a subject a therapeutically effective amount of an active agent. The administering step may be a single administration or may include a series of administrations. The length of the treatment period depends on a variety of factors, such as the severity of the condition, the age of the patient, the concentration of active agent, the activity of the compositions used in the treatment, or a combination thereof. It will also be appreciated that the effective dosage of an agent used for the treatment or prophylaxis may increase or decrease over the course of a particular treatment or prophylaxis regime. Changes in dosage may result and become apparent by standard diagnostic assays known in the art. In embodiments, chronic administration may be required. For example, the compositions are administered to the subject in an amount and for a duration sufficient to treat the patient. In embodiments, the treating or treatment is not prophylactic treatment.

[0124] A "diuretic" refers to a hypertension medication that increases the production of urine, thereby increasing the amount of water and salt eliminated from the body. The diuretic can be a carbonic anhydrase inhibitor, a loop diuretic, a potassium-sparing diuretic, a thiazide diuretic, or any other diuretic known in the art. Exemplary carbonic anhydrase inhibitors include acetazolamide, brinzolamide, dorzolamide, dichlorphenamide, ethoxalamide, zoniamide, indisulam, and methazolamide. Exemplary loop diuretics include bumatenide, ethacrynic acid, torsemide, and furosemide. Exemplary potassium-sparing diuretics include eplerenone, triamterene, spironolactone, and amiloride. Exemplary thiazide diuretics include indapamide, hydrochlorothiazide, chlorthalidone, metolazone, methyclothiazide, chlorothiazide, methylclothiazide, metolazone, bendroflumethiazide, polythiazide, and hydroflumethiazide. Other diuretics include pamabrom and mannitol.

[0125] An "angiotensin-converting enzyme inhibitor" or "ACE inhibitor" refers to a hypertension medication that block angiotensin I from being converted to angiotensin II, thereby

dilating blood vessels and lowering blood pressure. Exemplary ACE inhibitors include benazepril, zofenopril, perindopril, trandolapril, captopril, enalapril, lisinopril, and ramipril.

[0126] An “angiotensin receptor blocker” or “angiotensin II inhibitor” refers to a hypertension medication that blocks the receptor binding of angiotensin II, thereby dilating blood vessels and lowering blood pressure. Exemplary angiotensin receptor blockers include eprosartan, olmesartan, valsartan, candesartan, losartan, telmisartan, irbesartan, valsartan, and azilsartan medoxomil.

[0127] A “calcium channel blocker” refers to hypertension medication that can block calcium from entering the cells of the heart and arteries via a calcium channel, thereby lowering blood pressure. A calcium channel blocker can be a dihydropyridine calcium channel blocker, a phenylalkylamine calcium channel blocker, a benzothiazepine calcium channel blocker, a nonselective calcium channel blocker, or any other calcium channel blocker known in the art. Dihydropyridine calcium channel blockers include amlodipine, aranidipine, azelnidipine, barnidipine, benidipine, cilnidine, clevidipine, efonidipine, felodipine, isradipine, lacidipine, lercanidipine, manidipine, nicardipine, nifedipine, nilvadipine, nimodipine, nisoldipine, nitrendipine, and pranidipine. Phenylalkylamine calcium channel blockers include fendiline, gallipamil, and verapamil. Benzothiazepine calcium channel blockers include diltiazem. Nonselective calcium channel blockers include mibefradil, bepridil, flunarizine, fluspirilene, and fendiline. Other calcium channel blockers include gabapentin, pregabalin, and ziconotide.

[0128] A “normal circadian rhythm” for aldosterone level follows a diurnal pattern wherein the nadir is in the late evening and the peak is in the early morning, pre-arousal. In an embodiment, the hypertensive subject’s aldosterone level follows a substantially normal circadian rhythm. In one example of such an embodiment, the CYP 11 β 2 beta hydroxylase inhibitor of the invention, when dosed once daily in the morning after waking, suppresses the abnormally elevated production of Aldosterone during waking hours. In the early evening suppression of Aldosterone production starts to wane and the normal increase in serum Aldosterone returns towards normal by dawn, as it would under normal circumstances. The circadian rhythm of aldosterone in normal subjects and subjects with primary aldosteronism is described in Kem, David C., et al. “Circadian rhythm of plasma aldosterone concentration in patients with primary aldosteronism.” *The Journal of clinical investigation* 52.9 (1973): 2272-2277, the contents of which are specifically incorporated by reference herein.

[0129] This invention provides methods that reduce a hypertensive subject's systolic blood pressure "during sleep". In this context, "during sleep" refers to the period of sleep in the hypertensive subject's normal sleep/wake cycle. In other words, "during sleep" refers to the hypertensive subject's approximately seven to nine hours of sleep (typically at night) that occurs daily in between their approximately 15 to 17 hours of wakefulness and not to any short period of sleep that may occur outside of the sleep phase of the subject's normal sleep/wake cycle (i.e. naps). The blood pressure of non-hypertensive individuals typically dips during sleep, with approximately 10% to 15% lower blood pressure values during sleep relative to during wakefulness. In contrast, hypertensive subjects may experience a smaller dip in blood pressure during sleep or may not experience any dip in blood pressure at all. Thus, methods of the invention help hypertensive subjects restore the dip in blood pressure that normal, non-hypertensive subjects experience during sleep.

[0130] A subject's "pre-drug level" of serum aldosterone refers to the subject's level of serum aldosterone, at the same time of day, in the absence of being treated with the CYP 11 β 2 beta hydroxylase inhibitor. As discussed above, aldosterone level follows a diurnal pattern where the nadir is in the late evening and the peak is in the early morning, pre-arousal. Therefore, in embodiments where the dose of CYP 11 β 2 beta hydroxylase inhibitor reduces the serum aldosterone level of the subject by a certain percentage relative to their "pre-drug level", the reduction in serum aldosterone is measured relative to the same subject's serum aldosterone level in the absence of administration of the CYP 11 β 2 beta hydroxylase inhibitor at the same time of day. For example, the subject's serum aldosterone level at 11 AM when administered a CYP 11 β 2 beta hydroxylase inhibitor would be measured relative to that same subject's serum aldosterone level at 11 AM prior to any administration of the CYP 11 β 2 beta hydroxylase inhibitor.

General

[0131] For the foregoing embodiments, each embodiment disclosed herein is contemplated as being applicable to each of the other disclosed embodiment.

[0132] As used herein, all headings are simply for organization and are not intended to limit the disclosure in any manner. The content of any individual section may be equally applicable to all sections. All combinations of the various elements disclosed herein are within the scope of the invention.

[0133] Additional objects, advantages, and novel features of the present invention will become apparent to one ordinarily skilled in the art upon examination of the following examples, which are not intended to be limiting. Additionally, each of the various embodiments and aspects of the present invention as delineated hereinabove and as claimed in the claims section below finds experimental support in the following examples.

[0134] It is appreciated that certain features of the invention, which are, for clarity, described in the context of separate embodiments, may also be provided in combination in a single embodiment. Conversely, various features of the invention, which are, for brevity, described in the context of a single embodiment, may also be provided separately or in any suitable sub-combination or as suitable in any other described embodiment of the invention. Certain features described in the context of various embodiments are not to be considered essential features of those embodiments, unless the embodiment is inoperative without those elements.

[0135] Examples are provided below to facilitate a more complete understanding of the invention. The following examples illustrate the exemplary modes of making and practicing the invention. However, the scope of the invention is not limited to specific embodiments disclosed in these Examples, which are for purposes of illustration only.

EXAMPLES

Example 1

[0136] A randomized, double-blinded, placebo-controlled, dose-ranging, multicenter study was conducted to evaluate the effect of orally administered Compound A HBr on blood pressure for the treatment of hypertension in male and female subjects ≥ 18 years of age.

Study design

[0137] The study consists of two parts. For enrollment into Part 1 of the study, a subject's value of plasma renin activity (PRA) must be ≤ 1 ng/mL/h based on morning measurement. If the value of PRA > 1 ng/mL/h based on morning measurement, then subjects may be eligible to enter Part 2 of the study.

[0138] For Part 1, 163 enrolled subjects ≥ 18 years of age were randomized into 6 equal treatment groups (1:1:1:1:1:1) to 12.5 mg BID, 25 mg BID, 12.5 mg QD, 50 mg QD, 100 mg QD, or placebo. After a review of interim clinical data, the 2 lowest dose levels (12.5 mg QD and 12.5

mg BID) were stopped for future randomization due to a lack of consistent meaningful reduction of blood pressure, but the patients randomized to that point remained in the study through completion. Thus, after the review of interim clinical data, subjects were randomized into 4 equal treatment groups (1:1:1:1) to 25 mg BID, 50 mg QD, 100 mg QD, or placebo.

[0139] For Part 2, 36 enrolled subjects ≥ 18 years of age were randomized (5:1) to either 100 mg QD Compound A HBr or placebo such that the Compound A HBr treatment group consisted of approximately 30 subjects and the placebo treatment group will consist of approximately 6 subjects.

[0140] Subjects orally administered the assigned study drug (Compound A HBr or placebo) according to the assigned dosing regimen for 8 weeks beginning on Study Day 1. All subjects in Part 1 (regardless of dosing group) received BID dosing to preserve the integrity of the blind; active drug is administered as the morning dose for all QD dose groups. Subjects returned to the research facility or were seen by the clinical investigator or approved home health care professional at the end of Study Weeks 1, 2, 3, 4, 5, 6, 7, and 8 (± 2 days) for protocol-defined efficacy and safety assessments and procedures, assessment of adverse events (AEs), and confirmation of compliance with study drug usage. Subjects also completed a telephone visit and blood pressure (BP) check at home approximately 3 days post last dose of study drug. Subjects attended up to 14 full clinic visits, including a pre-Screening visit, a Screening/start of Placebo Run-in visit, a second visit during Placebo Run-in, a clinic visit to initiate the ABPM procedure, a Randomization visit, 8 weekly visits during double-blind treatment, and an end-of-study visit scheduled 4 weeks after the last study treatment for final efficacy and safety assessments.

[0141] A schematic of the study design is shown in **Figure 1**.

Automated office blood pressure (AOBP) procedure

[0142] An automated oscillometric sphygmomanometer device was used to measure the subjects' systolic and diastolic blood pressure in office after approximately 5 minutes of rest in the seated position.

24-hour ambulatory blood pressure monitoring (ABPM) procedure

[0143] Ambulatory blood pressure monitoring was accomplished with an ambulatory blood pressure monitoring device that consists of a blood pressure cuff worn on a subject's arm attached to a small recording device that is typically attached to the subject's belt or waistband.

[0144] The ABPM device is worn for 24 hours. Throughout that period, the device records the subject's blood pressure at regular intervals, during the subject's routine daily activities and while they are sleeping. The ABPM thus provides a complete record of the subject's blood pressure over a 24-hour period.

[0145] 24-hour ABPM was measured in the clinic at baseline and Study Week 7. If, for any reason, the ABPM procedure was deemed a failure at the end of Study Week 7, it may have been repeated at Study Week 8 and therefore no imputation was employed regardless of use of rescue medications. Additionally, ABPM was also collected at the end of Study Week 4 in Part 2. If a repeat test was performed, it supersedes the original test results for that visit.

[0146] Specific derived variables based on ABPM measurements include mean 24-hour, mean Daytime, and mean Nighttime of SBP, DBP, and heart rate.

[0147] Change from baseline to Week 7 in 24-hour mean SBP (and DBP) based on ABPM will be analyzed using an ANCOVA with a term for treatment group and a baseline mean 24-hour value as a covariate.

[0148] The nighttime dip is defined as

$$100\% \times (\text{mean daytime SBP} - \text{mean nighttime SBP}) / \text{mean daytime SBP}$$

[0149] It is expressed as a percentage and is summarized by treatment group and visit using descriptive statistics. In addition, the number and percentage of subjects with nighttime dip in each of the dipper categories (Bloomfield & Park, 2015) is presented by treatment group and visit. The categories are:

- (a) < 10%
- (b) 10-20% inclusive
- (c) > 20%

Eligibility Criteria*Inclusion criteria*

[0150] The study was conducted using subjects meeting the following inclusion criteria:

- (a) Male and nonpregnant, nonlactating female subjects ≥ 18 years of age.
- (b) Automated office blood pressure (AOBP) with systolic blood pressure (SBP) ≥ 130 mm Hg
- (c) Background antihypertensive treatment of ≥ 2 drugs
- (d) Serum cortisol ≥ 18 mcg/dL

Exclusion criteria

[0151] Subjects were excluded from the study if they met any of the following exclusion criteria:

- (a) Concomitant use of epithelial sodium channel inhibitors or mineralocorticoid receptor antagonists
- (b) Subjects with hypokalemia
- (c) Subjects with hyperkalemia
- (d) Subjects with serum cortisol < 3 mcg/dL
- (e) Subjects with serum sodium < 135 mEq/L
- (f) Subjects with estimated glomerular filtration rate < 60 mL/min/1.73m²
- (g) Subjects with type 1 or uncontrolled (hemoglobin A1c $\geq 9\%$) type 2 diabetes mellitus
- (h) Subjects with body mass index > 40 kg/m²
- (i) Subjects with unstable angina
- (j) Subjects with SBP ≥ 175 mm Hg or diastolic blood pressure (DBP) ≥ 100 mm Hg for Part 1 and SBP ≥ 160 mm Hg or DBP ≥ 100 mm Hg for Part 2 at Pre-Screening, Screening/Start of Placebo Run-in, or Randomization
- (k) Subjects with a decrease in SBP ≥ 20 mm Hg or DBP ≥ 10 mm Hg from sitting to standing position at screening
- (l) Subjects who, in the opinion of the investigator, have suspected nonadherence to antihypertensive treatment

- (m) Subjects who, in the opinion of the investigator, have any major medical illness or symptoms
- (n) Subjects who, in the opinion of the investigator, have any acute or chronic medical or psychiatric condition
- (o) Subjects undergoing treatment with any of the following medications:
 - (i) Topical corticoids
 - (ii) Sympathomimetic decongestants
 - (iii) Theophylline
 - (iv) Phosphodiesterase type 5 inhibitors
 - (v) NSAIDs
 - (vi) Intramuscular steroids
 - (vii) Estrogen
 - (viii) Cytochromes
 - (ix) Strong CYP3A and CYP3A4 inducers
- (p) Subjects with known hypersensitivity to Compound A HBr or any of the excipients
- (q) Subjects who are night-shift workers

Arms and Interventions

[0152] The study contained the following arms and corresponding interventions:

Table 1

Arm	Intervention*
Placebo Comparator: Placebo (Part I) Placebo tablet(s) by mouth once or twice daily.	Other: Placebo (Part I) Placebo tablet(s) by mouth once or twice daily.
Experimental: Dose 1 (Part I) Compound A HBr tablet(s) by mouth once daily.	Drug: Compound A HBr (Part I) Tablet(s) containing 12.5 mg of Compound A HBr by mouth once daily.
Experimental: Dose 2 (Part I) Compound A HBr tablet(s) by mouth twice daily.	Drug: Compound A HBr (Part I) Tablet(s) containing 12.5 mg of Compound A HBr by mouth twice daily.

Arm	Intervention*
Experimental: Dose 3 (Part I) Compound A HBr tablet(s) by mouth twice daily.	Drug: Compound A HBr (Part I) Tablet(s) containing 25 mg of Compound A HBr by mouth twice daily.
Experimental: Dose 4 (Part I) Compound A HBr tablet(s) by mouth once daily.	Drug: Compound A HBr (Part I) Tablet(s) containing 50 mg of Compound A HBr once daily.
Experimental: Dose 5 (Part I) Compound A HBr tablet(s) by mouth once daily.	Drug: Compound A HBr (Part I) Tablet(s) containing 100 mg of Compound A HBr once daily.
Placebo Comparator: Placebo (Part II) Placebo tablet(s) by mouth once daily.	Other: Placebo (Part II) Placebo tablet(s) by mouth once daily.
Experimental: Dose (Part II) Compound A HBr tablet(s) by mouth once daily.	Drug: Compound A HBr (Part II) Tablet(s) containing 100 mg of Compound A HBr by mouth once daily.

Study Endpoints

Primary Endpoint

[0153] The primary endpoint is the change in office-measured (mean of last 2 of 5 unattended measurements using an automated oscillometric sphygmomanometer device after approximately 5 minutes of rest in the seated position) systolic blood pressure (SBP) from baseline to the end of Study Week 8.

Secondary Endpoint

[0154] Secondary endpoints of this study were:

- (a) Change in 24-hour ambulatory blood pressure monitoring (ABPM) parameters (systolic and diastolic) from baseline to the end of Study Week 7.
- (b) Change in office-measured SBP from baseline to the end of Study Weeks 1, 2, 3, 4, 5, 6, and 7.
- (c) Change in office-measured diastolic blood pressure (DBP) from baseline to the end of Study Weeks 1, 2, 3, 4, 5, 6, 7, and 8.

- (d) Proportion of subjects who achieve office-measured BP of $\leq 130/80$ mm Hg by the end of Study Week 8.

Pharmacodynamic Endpoints

[0155] Pharmacodynamics endpoints of this study were:

- (a) Change in plasma 11-deoxycortisol and PRA from baseline to the end of Study Week 4 and to end of follow up (i.e. end of Study Week 12 for Part 1 and end of Study 10 for Part 2).
- (b) Change in serum aldosterone, cortisol, and 11-deoxycorticosterone concentration from baseline to the end of Study Week 4 and to end of follow-up.

Pharmacokinetic Endpoints

[0156] Pharmacokinetic endpoints of this study are PK parameters, including, of area under the plasma concentration versus time curve (AUC), maximum plasma concentration (C_{max}), time to maximum concentration (T_{max}), and half-life (t_{1/2}) will be summarized descriptively for Randomization (baseline) and Study Weeks 1, 4, and 8

Safety endpoints

[0157] Safety endpoints of this study are:

- (a) Incidence and severity of all spontaneously reported adverse events (AEs)
- (b) Changes in vital signs (standing SBP, standing DBP, body temperature, heart rate, and respiratory rate)
- (c) Changes in electrocardiogram parameters (including cardiac intervals: PR, QRS, QT, and corrected QT interval using Fridericia's formula)
- (d) Changes in clinical laboratory assessments (hematology, chemistry, coagulation, and urinalysis)
- (e) Change in office-measured SBP from Study Week 8 (end-of-treatment period to end of follow up (i.e. end of Study Week 12 for Part 1 and end of Study 10 for Part 2).

Analysis methodology

[0158] The following analysis sets are defined in this study:

Full Analysis Set (FAS)

[0159] The FAS includes all randomized subjects who have received at least 1 dose of randomized study treatment (MLS-101 or placebo). The FAS will be the primary set for efficacy analyses. In analyses performed on the FAS, unless otherwise specified, subjects will be analyzed according to the randomized study treatment group.

Per Protocol Set (PPS or PP)

[0160] The Per Protocol Set includes all subjects in the FAS who have completed the Study Week 8 visit without any major protocol violations that could influence the validity of the data for the primary efficacy evaluations. In the analyses based on PPS, subjects will be analyzed according to the randomized study treatment group. All criteria to exclude subjects from the PPS will be made based on a blinded review of the data prior to the unblinding of the study.

[0161] A subject may be excluded from the Per Protocol Analysis Set if any of the following criteria are met:

- (a) Not meeting Inclusion/Exclusion criteria
- (b) Use of prohibited medications. Subjects using rescue medications will not be excluded from the PPS unless subjects have met other criteria excluding them from the PPS
- (c) Not compliant with the study drug
- (d) Out of window efficacy assessment at study Week 8 visit

[0162] Alternate criteria for exclusion from the Per Protocol Analysis Set were also applied to accommodate unforeseen events that occurred during the conduct of the study.

[0163] Analyses on Per Protocol Analysis Set will be of supportive purpose and limited to primary endpoint (i.e., “product Estimand”).

Safety Analysis Set (SAF)

[0164] The Safety Analysis Set includes all enrolled subjects who received at least one dose of study treatment (MLS-101 or placebo). In analyses performed on the Safety Analysis Set, subjects will be analyzed according to their actual treatment received.

PK/PD Analysis Set (PKPD)

[0165] PK/PD Analysis Set includes all subjects in the SAF who have sufficient data available for the analysis of pharmacokinetic and pharmacodynamic measurements. In the analyses based on PKPD, subjects will be analyzed according to the actual treatment received.

Definition of Baseline

[0166] Baseline is defined as the last available observed value of the parameter of interest prior to the first administration of the investigational medicinal product (IMP) for the double-blinded treatment period.

[0167] For AOBP measurements and any other clinical or laboratory variable for which there are replicate evaluations at the screening and baseline visits, baseline is defined as the mean of the last two non-missing values prior to first administration of the IMP for the double-blinded treatment period.

[0168] Change from baseline is calculated as: post-baseline result – baseline result.

[0169] Percentage change from baseline is calculated as: (change from baseline / baseline result) x 100%.

Summary of results

[0170] There was a dose-response relationship across the QD dose range, with doses of 50mg and 100mg QD associated with a mean reduction in AOBP measured systolic BP of -11 to -13mmHg (per-protocol, placebo-corrected, analysis of Part-1 100mg cohort = -10.3 mmHg, Full-analysis set combining Part-1 and Part-2 (interim) = -9.9 mmHg, N=58 active).

[0171] Once daily dosing was as effective as twice daily dosing, with results in the two BID cohorts no better than those in the 50mg and 100mg QD cohorts.

[0172] In a pooled analysis of 50mg QD, 100mg QD, 12.5mg BID and 25mg BID cohorts (N=103) 25% of subjects demonstrated a change in BPsys > -25mmHg and 41% a change > -15mmHg.

[0173] Using automated office blood pressure (AOBP), there was little difference in treatment response between individuals in Part 1 and available results from Part 2, suggesting PRA does not

appear to be a strong determinant of response (serum and urine aldosterone were also uninformative).

[0174] 24h ambulatory blood pressure measurements demonstrated overnight reduction of systolic BP of -11.5 ± 2.9 mmHg in the 100mg QD cohort, with an associated increase in night-time “BP-dipping”, consistent with persistent nocturnal benefit after morning dosing,

[0175] The pooled (Part 1 and Part 2) 100mg QD safety set (n=60) showed good safety and tolerability, with no effects on serum cortisol, few episodes of mild or moderate hyperkalemia and no episodes of severe hyperkalemia.

Automated Office Blood Pressure Results

[0176] A full analysis and safety set (FAS) analysis was conducted using all subjects with week 8 measurement. A per-protocol (PP) analysis was also conducted using all subjects completing treatment through the eighth week visit. Waterfall plots showing the AOBP change in systolic blood pressure at week 8 from the FAS analysis of placebo, 50mg QD and 100mg QD groups and the PP analysis of the 100 mg group is provided in **Figure 2**. Waterfall plots showing the AOBP change in systolic blood pressure at week 8 from the FAS analysis of 12.5mg QD, 12.5 mg BID, and 25 mg BID groups is provided in **Figure 3**. A modeled mean and per-protocol observed mean are also shown for each group.

[0177] Mean change in systolic blood pressure from baseline is shown in **Figure 4**. The figure provides a final analysis including both full analysis set (FAS, all evaluable subjects receiving at least one dose of Compound A HBr) and per-protocol (PP, only those receiving $\geq 75\%$ of study drug with week 8 visit). Part 2 data shows the interim average of last visit week 5-6.

[0178] A Compound A HBr dose-response was observed based on analysis of systolic AOBP change from baseline among the QD regimens. **Figure 5** shows the mean observed automated office blood-pressure change from baseline at week 8 for QD dosing regimens. BID per-protocol cohorts are shown on the far right of this graph.

[0179] An analysis was conducted in which the change in systolic blood pressure from baseline at week 8 were pooled for the 50 mg QD, 100 mg QD, 12.5 mg BID, and 25 mg BID cohorts and then separated into quartiles based on degree of systolic blood pressure response. **Figure 6** is a graph showing the systolic blood pressure change from baseline at week 8 for the pooled cohorts,

the lowest response quartile, the highest response quartile, and placebo. 25% of subjects achieved $> -23\text{mmHg}$ fall in systolic blood pressure, with mean reduction of $-33.4 \pm 1.5 \text{ mmHg}$. 41% of subjects achieved a $\geq 15 \text{ mmHg}$ fall in systolic blood pressure.

[0180] Figure 7 is a waterfall plot showing change in systolic blood pressure from placebo and 100 mg QD groups pooled from both Parts 1 and 2. Part 2 data from interim snapshot with all subjects randomized and average last visit week 5-6, minimum week 2.

Analysis of factors affecting change in blood pressure

[0181] An analysis was conducted to identify factors affecting the degree of blood pressure reduction in hypertensive subjects. As summarized in the table below, it was discovered that Compound A HBr is particularly effective at reducing the blood pressure of individuals with a body mass index (BMI) of greater than 30. This effect was observed across dosing cohorts. A BMI of above 30 is considered to be in the obesity range. Similarly, a waist-hip ratio of greater than 0.90 in males and 0.85 in females is considered to be in the obesity range. Thus, it is inferred that Compound A HBr is particularly effective at reducing the blood pressure of males with a waist-hip ratio of greater than 0.90 and females with a waist-hip ratio of greater than 0.85.

Table 2

Difference from placebo (* $p < 0.05$)		12.5mg QD	50mg QD	100mg QD	12.5mg BID	25mg BID
Gender (N)	Male (N)	-2.3 (11)	-8.3 (13)	-12.4 (12)	-13.8 (8)	-9.5 (11)
	Female (N)	-0.2 (12)	-11.3 (15)	-5.1 (18)	-3.79 (14)	-5.18 (19)
Age (N)	<65 (N)	-0.3 (10)	-10.2 (13)	-15.7 (8)	-5.4 (6)	-8.5 (13)
	65-79 (N)	1.1 (10)	-8.8 (13)	-1.6 (18)	-1.5 (13)	-2.4 (15)
Race (N)	Black (N)	6.75 (11)	-6.9 (8)	-7.0 (15)	5.57 (7)	-10.1 (7)
	Other (N)	-7.5 (12)	-12.1 (20)	-9.2 (15)	-14.7 (15)	-7.2 (23)
BMI	25-30 (N)	-1.4 (8)	2.0 (11)	-2.6 (10)	-3.5 (4)	-1.1 (10)
	>30 (N)	-2.5 (12)	-16.6* (15)	-13.2* (15)	-10.1 (16)	-9.1 (15)
Baseline BP _{sys}	Low tertile	-10.7	-8.3	-11.8	3.8	-8.8
	Middle tertile	9.3	-11.9	-11.8	-9.7	-4.0
	High tertile	-3.6	-20.6*	-9.7	-9.7	-5.6
Background hypertension therapy	2 medications (N)**	1.8 (14)	-3.7 (20)	-7.5 (14)	-1.2 (7)	1.4 (14)
	3+ medications (N)	-6.0 (9)	-19.1* (8)	-9.6 (16)	-12.2* (15)	-15.8* (16)
Thiazide	No (N)	2.6 (11)	-4.3 (12)	-3.3 (13)	-1.4 (9)	-4.7 (12)
	Yes (N)	-5.3 (12)	-13.2* (16)	-11.4* (17)	-10.6 (13)	-8.3 (18)

[0182] All values determined using least squares analysis of modeled means using all available information. **Difference in effect between 2 and 3+ background due to an imbalance in placebo response.

Ambulatory Blood Pressure (ABPM) Results

[0183] A graph showing an example of ambulatory 24-hour blood pressure monitoring is providing in **Figure 9**. The graph shows the 24-hour ambulatory blood pressure (systolic) of a subject receiving Compound A HBr 100mg QD versus baseline, showing an average 24-hour blood pressure reduction and restoration of normal nocturnal dipping pattern.

[0184] A graph showing the change in systolic blood pressure at week 8 relative to baseline as measured using the ABPM full analysis set is provided in **Figure 10**. Waterfall plots showing the 24-hour average and overnight average ABPM change at 8 weeks relative to baseline is provided in **Figure 11**. 100 mg QD dose levels provide excellent 24-hour blood pressure reduction. Overnight blood pressure reduction from the 100 mg QD dose level appears to be superior to 25 mg BID.

[0185] As shown in the summary table below, the most consistent benefit across all metrics was observed in the 100mg QD cohort.

Table 3

Change in BP mmHg Week 8, Full Analysis Set							
Mean (scm)		Placbo	12.5mg QD	50mg QD	100mg QD	12.5mg BID	25mg BID
AOBP	N	30	22	28	30	22	30
	BP _{sys}	-4.3 (2.6)	-5.7 (3.1)	-13.9 (2.6)	-12.2 (2.7)	-11.3 (3.1)	-11.0 (2.6)
	BP _{dias}	-1.3 (1.8)	-6.1 (1.8)	-8.1 (1.7)	-4.76 (1.5)	-6.1 (1.8)	-3.83 (2.1)
ABPM	N	30	23	28	30	16	30
ABPM (24h)	BP _{sys}	-0.6 (1.9)	-5.2 (3.4)	-1.8 (3.0)	-8.9 (2.2)	-5.7 (3.2)	-8.7 (2.9)
	BP _{dias}	-1.4 (1.0)	-2.3 (1.7)	-3.0 (1.6)	-5.9 (1.5)	-5.4 (2.2)	-6.1 (1.8)
	BP _{mean}	-1.0 (1.4)	-3.7 (2.6)	-2.4 (2.2)	-7.4 (1.8)	-5.5 (2.7)	-7.4 (2.3)
ABPM (night)	BP _{sys}	-3.3 (2.3)	-5.4 (4.2)	2.4 (4.2)	-11.5 (2.5)	-7.5 (4.0)	-6.0 (2.8)
Dip (%)	<10%	63	64	78	46	69	79
	10-20%	37	36	21	46	31	17
	>20%	0	0	0	8	0	4

[0186] Night-time dip defined as $100\% \times (24\text{-hour ambulatory Daytime SBP} - 24\text{-hour ambulatory monitoring Night-time SBP}) / 24\text{-hour ambulatory monitoring Daytime}$

Safety

[0187] No serious adverse events (SAEs) related to the study medication were observed in the trial. Adverse events requiring drug discontinuation or dose reduction, showing incidence in Part 1 versus incidence Part 2 is provided in Table 4 below.

Table 4

		Total Placebo	Total active	Part 1 All active	Part 1 100mg QD	Part 2 100mg QD	100mg QD Pooled
	N	35	190	159	29	31	60
Study drug discontinuation	Hypotension	0	3 (1.6%)	2 (1.2%)	1 (3.4%)	1 (2.8%)	2 (3.3%)
	Hyponatremia	0	1 (0.5%)	0	0	1 (3.4%)	1 (1.7%)
	Hyperkalemia	0	6 (3.2%)	6 (3.8%)	2 (6.9%)	0	2 (3.3%)
	Other possibly related	0	1 (0.5%)	1 (0.6%)	1 (3.4%)	0	1 (1.7%)
	Other unrelated	0	12 (6.3%)	11 (6.9%)	3 (6.0%)	1 (2.8%)	4 (6.7%)
Dose titration	Hyperkalemia	0	7 (4.1%)	6 (3.8%)	1 (3.4%)	1 (3.2%)	2 (3.3%)
	Hyponatremia	0	1 (0.5%)	0	0	1 (3.2%)	1 (1.7%)
	Other possibly related	0	0	0	0	0	0
	Other unrelated	1 (1.4%)	1 (0.5%)	1 (0.6%)	0	0	0

Serum potassium

[0188] Change in group mean serum potassium (K⁺) is shown in the table below.

Table 5

	Part 1	Part 2	Pooled
Mean (mMol/L)	+0.50	+0.23	+0.35
SD	0.96	0.51	0.75
N	26*	31	57
SEM	0.19	0.09	0.10

[0189] Number of individuals in the 100mg QD cohorts with verified or multiple increased serum potassium above normal range during treatment is shown in the table below.

Table 6

Serum K ⁺	5.2-5.5mMol/L	5.6-6.0mMol/L	6.1-6.5mMol/L	>6.5mMol/L
Part 1	5 (18.5%)	3 (10.7%)	0	1*
Part 2	1 (4%)	0	0	0
Pooled	6 (10.3%)	3 (5.2%)	0	0

[0190] *Measure was an isolated incident not verified by repeat measurement with study drug discontinuation (protocol deviation).

Change in estimated glomerular filtration rate (eGFR)

[0191] A dose-dependent and reversible reduction in eGFR was observed. This phenomenon has been reported with ACE/ARB and more recently SGLT2 inhibition due to reduced intra-glomerular pressure and felt to attenuate progression of hypertensive nephropathy. A graph showing the change in estimated glomerular filtration rate (eGFR) in different dosing cohorts is provided in **Figure 8**.

Example 2

[0192] A complete analysis of the study described in Example 1 was performed. This complete analysis confirmed the findings described above in Example 1 as follows.

Summary of results

[0193] Lorundrostat was effective at lowering BP in individuals with inadequately treated or treatment resistant hypertension.

[0194] There was a dose- and exposure-response relationship, with mean placebo-adjusted reduction in SBP of 9.58 mmHg and 7.81 mmHg seen at doses of 50 mg QD and 100 mg QD, respectively.

[0195] 24-hour ABPM, central BP and nighttime SBP values confirmed the reduction in SBP seen with AOBP, most prominently in the 100 mg QD dose cohort.

[0196] The safety dataset lorundrostat was safe and well tolerated, with no effects on serum cortisol and an expected modest increase in serum potassium with relatively few episodes of clinically meaningful hyperkalemia.

[0197] The results demonstrate a clinically meaningful and statistically significant placebo-adjusted reduction in AOBP SBP of 9.58 mmHg ($p=0.0114$) and 7.81 mmHg ($p=0.0422$) in the 50 mg and 100 mg QD cohorts, respectively, in Part 1. The reduction in AOBP SBP observed in Part 2 for the 100 mg QD cohort was similar to that observed for the same dose in Part 1 (-11.5 mmHg, $p=0.8426$).

[0198] The reduction in AOBP SBP was validated and confirmed by comparable reductions in 24-hour ABPM SBP. The ABPM data further demonstrated the benefits of lorundrostat in reducing both central and nighttime SBP.

[0199] Sub-group analyses highlighted statistically and clinically significant reductions in AOBP SBP in subjects with a BMI >30 kg/m², those in the upper tertile of baseline AOBP SBP, and those taking thiazide diuretics.

[0200] Pharmacodynamic responses demonstrated dose-dependent reduction in serum aldosterone levels and a commensurate increase in plasma renin activity. 11-deoxycorticosterone levels were unaffected. Morning serum cortisol levels were modestly increased. No adrenocortical

insufficiency occurred during the trial. Due to supply chain disruption, the ability to perform ACTH stimulation testing was limited during the first part of the trial. However, the majority of subjects in Part 2 dosed with 100 mg QD, the maximum dose tested, had ACTH-stimulation testing performed at Baseline and after 8 weeks of treatment. There were no individuals with abnormal ACTH-stimulation results.

[0201] Decreases in eGFR were observed in all treatment groups with greater decreases apparent for lorundrostat treatment groups compared with placebo.

Primary Efficacy Endpoint: Change from Baseline at Week 8 in Seated Automated Office-measured Systolic Blood Pressure

[0202] The results of a Mixed Model Repeated Measures (MMRM) analysis of the primary efficacy endpoint, change in seated AOBP SBP from Baseline to Week 8, is presented in **Figure 12** and **Table 7** for Part 1 and in **Figure 13** and **Table 8** for the 100 mg QD dose cohorts from Part 1 and Part 2.

[0203] At Week 8, a statistically significant reduction in modelled AOBP SBP from baseline was detected in the 50 mg QD cohort (least square mean [LSM] difference: -9.58 mmHg; $p=0.0114$) and 100 mg QD cohort (LSM difference: -7.81 mmHg; $p=0.0422$) in Part 1 (**Figure 12** and **Table 7**). While the 12.5 mg BID, 25 mg BID and 12.5 mg QD cohorts exhibited reductions in BP that were greater than placebo (placebo adjusted reductions of -7.2 mmHg, -6.97 mmHg, and -1.53 mmHg, respectively), none of these demonstrated statistical significance. The results were similar for the sensitivity analysis using the FAS, the analysis using the PPS, and the analysis using the additional estimand.

[0204] The change in SBP from baseline to Week 8 was similar for the 100 mg QD cohorts in Part 1 and Part 2 (LSM difference: 0.74 mmHg; $p=0.8426$) (**Figure 13** and **Table 8**). Further, no statistically significant appreciable difference in AOBP SBP change from baseline was seen between subjects who received lorundrostat 100 mg QD in Parts 1 and 2 combined who had a baseline PRA of <1 ng/mL/h versus those with a baseline PRA of ≥ 1 ng/mL/h (**Table 9**).

[0205] Boxplots of the mean changes in measured AOBP SBP from baseline to Week 8 are presented in **Figure 14** for Part 1 and in **Figure 15** for Part 2.

Table 7: Modelled (MMRM) Least Square Mean (SEM) Change from Baseline at Week 8 in Seated Automated Office-Measured Systolic Blood Pressure (mmHg), Part 1 (Full Analysis Set)

	Placebo (N=30)	12.5 mg BID (N=22)	25 mg BID (N=30)	12.5 mg QD (N=23)	50 mg QD (N=28)	100 mg QD (N=30)
Week 8						
n	29	19	28	19	28	25
LSM (SEM)	-4.10 (2.62)	-11.30 (3.15)	-11.07 (2.65)	-5.63 (3.16)	-13.69 (2.67)	-11.92 (2.77)
90% CI	-8.44; 0.23	-16.52; -6.08	-15.46; -6.69	-10.86; -0.41	-18.11; -9.27	-16.50; -7.33
LSM Δ from Placebo		-7.2	-6.97	-1.53	-9.58	-7.81
90% CI		-13.98; -0.41	-13.13; -0.80	-8.32; 5.27	-15.77; -3.39	-14.12; -1.50
p-value		0.0813	0.0634	0.7103	0.0114	0.0422

[0206] Analysis used a MMRM approach with fixed effects for categorical terms for treatment, week, and treatment by week interaction, and baseline SBP as a fixed continuous covariate. No adjustment for multiplicity was implemented.

[0207] Abbreviations: BID, twice daily; CI, confidence interval; Δ, difference; LSM, least square mean; mg, milligrams; mmHg, millimeters of mercury; MMRM, mixed model repeated measures; QD, once daily; SBP, systolic blood pressure; SEM, standard error of the mean.

Table 8: Modelled (MMRM) Least Square Mean (SEM) Change from Baseline at Week 8 in Seated Automated Office-Measured Systolic Blood Pressure (mmHg), Parts 1 & 2 (Full Analysis Set)

	100 mg QD Part 1 (N=30)	100 mg QD Part 2 (N=31)
Week 8		
n	25	30
LSM (SEM)	-12.08 (2.68)	-11.35 (2.48)
90% CI	-16.56; -7.61	-15.49; -7.20
LSM Δ with Placebo		0.74
90% CI		-5.43; 6.90
p-value		0.8426

[0208] Analysis used a MMRM approach with fixed effects for categorical terms for treatment, week, and treatment by week interaction, and baseline SBP as a fixed continuous covariate. No adjustment for multiplicity was implemented.

[0209] Abbreviations: CI, confidence interval; Δ, difference; LSM, least square mean; mg, milligrams; mmHg, millimeters of mercury; MMRM, mixed model repeated measures; QD, once daily; SBP, systolic blood pressure; SEM, standard error of the mean.

Table 9: Modelled (ANCOVA) Least Square Mean (SEM) Change from Baseline at Week 4 and Week 8 in Seated Automated Office-Measured Systolic Blood Pressure (mmHg) in Subjects Randomized to 100 mg QD in Parts 1 & 2, according to PRA level at Baseline (Full Analysis Set)

FAS Randomized to 100 mg QD, Part 1 and Part 2 Combined	PRA Baseline < 1 ng/mL/h (N=27)	PRA Baseline ≥ 1 ng/mL/h (N=34)
Week 4		
n	22	28
LSM (SEM)	-15.42 (3.12)	-15.24 (2.75)
90% CI	-20.66; -10.18	-19.86; -10.62
LSM Δ with PRA Baseline < 1 ng/mL/h		0.18
90% CI		-6.97; 7.33
p-value		0.9663
Week 8		
n	22	33
LSM (SEM)	-11.27 (3.13)	-13.34 (2.52)
90% CI	-16.51; -6.02	-17.55; -9.12
LSM Δ with PRA Baseline < 1 ng/mL/h		-2.07
90% CI		-9.04; 4.90
p-value		0.6213

[0210] Analysis used an ANCOVA model with binary baseline PRA (<1 ng/mL/h versus ≥1 ng/mL/h) as a factor and baseline SBP as a covariate, in the subset of subjects randomized to receive 100 mg QD. The two ANCOVA models (Week 4 and Week 8) were run separately.

[0211] Abbreviations: ANCOVA, analysis of covariance; CI, confidence interval; Δ, difference; FAS, Full Analysis Set; h, hour; LSM, least square mean; mg, milligrams; mL, milliliter; mmHg, millimeters of mercury; ng, nanograms; PRA, plasma renin activity; QD, once daily; SBP, systolic blood pressure; SEM, standard error mean.

Secondary Efficacy Endpoints

Change from Baseline at Week 8 in Seated Automated Office-measured Diastolic Blood Pressure

[0212] At Week 4, statistically significant reductions in modelled AOBP DBP from baseline were detected across all cohorts in Part 1 except 12.5 mg QD. At Week 8, a statistically significant reduction in modelled AOBP DBP from baseline was detected in the 50 mg QD cohort only (LSM difference: -5.46 mmHg; p=0.0224), although all lorundrostat dose groups exhibited greater numerical declines than placebo (Table 10). The change in DBP from baseline to Week 8 was not statistically different between the 100 mg QD cohorts in Part 1 and Part 2 (LSM difference: 0.98 mmHg; p=0.6406) (Table 11).

Table 10: Modelled (MMRM) Least Square Mean (SEM) Change from Baseline at Weeks 4 and 8 in Seated Automated Office-Measured Diastolic Blood Pressure (mmHg) by Dose, Part 1 (Full Analysis Set)

	Placebo (N=30)	12.5 mg BID (N=22)	25 mg BID (N=30)	12.5 mg QD (N=23)	50 mg QD (N=28)	100 mg QD (N=30)
Week 4						
n	28	19	27	21	28	25
LSM (SEM)	-0.54 (1.40)	-5.02 (1.67)	-6.47 (1.41)	-2.50 (1.60)	-4.49 (1.41)	-6.96 (1.48)
90% CI	-2.85; 1.78	-7.78; -2.25	-8.81; -4.14	-5.15; 0.15	-6.82; -2.15	-9.40; -4.51
LSM Δ with Placebo		-4.48	-5.94	-1.96	-3.95	-6.42
90% CI		-8.09; -0.87	-9.24; -2.63	-5.48; 1.55	-7.22; -0.68	-9.80; -3.04
p-value		0.0418	0.0034	0.3569	0.0476	0.002
Week 8						
n	29	19	28	19	28	25
LSM (SEM)	-1.63 (1.66)	-5.47 (2.02)	-4.12 (1.68)	-3.76 (2.02)	-7.09 (1.70)	-5.75 (1.77)
90% CI	-4.38; 1.11	-8.81; -2.14	-6.91; -1.33	-7.10; -0.42	-9.90; -4.29	-8.68; -2.82
LSM Δ with Placebo		-3.84	-2.49	-2.12	-5.46	-4.11
90% CI		-8.16; 0.49	-6.41; 1.44	-6.45; 2.20	-9.37; -1.54	-8.14; -0.08
p-value		0.1440	0.2964	0.4172	0.0224	0.0934

[0213] Analysis used a MMRM approach with fixed effects for categorical terms for treatment, week, and treatment by week interaction, and baseline DBP as a fixed continuous covariate. P-values ≤ 0.05 are bolded. Abbreviations: BID, twice daily; CI, confidence interval; Δ, difference; DBP, diastolic blood pressure; LSM, least square mean; mmHg, millimeters of mercury; QD, once daily; SEM, standard error mean.

Table 11: Modelled (MMRM) Least Square Mean (SEM) Change from Baseline at Weeks 4 and 8 in Seated Automated Office-Measured Diastolic Blood Pressure (mmHg) by Dose in Subjects Randomized to 100 mg QD, Parts 1 & 2 (Full Analysis Set)

FAS Randomized to 100 mg QD, Part 1 and Part 2 Combined	100 mg QD Part 1 (N=30)	100 mg QD Part 2 (N=31)
Week 4		
n	25	26
LSM (SEM)	-5.88 (1.49)	-6.30 (1.44)
90% CI	-8.38; -3.38	-8.71; -3.89
LSM Δ with 100 mg QD Part 1		-0.43
90% CI		-3.90; 3.05
p-value		0.8384
Week 8		
n	25	30
LSM (SEM)	-4.57 (1.53)	-5.55 (1.42)
90% CI	-7.13; -2.01	-7.93; -3.18
LSM Δ with 100 mg QD Part 1		-0.98
90% CI		-4.47; 2.51
p-value		0.6406

[0214] Analysis used a MMRM approach with fixed effects for categorical terms for treatment, week, and treatment by week interaction, and baseline DBP as a fixed continuous covariate. Abbreviations: CI, confidence interval; Δ, difference; DBP, diastolic blood pressure; FAS, Full Analysis Set; LSM, least square mean; mg, milligrams; mmHg, millimeters of mercury; MMRM, mixed model repeated measures; QD, once daily; SEM, standard error mean.

Change from Baseline to Week 8 in Seated Automated Office-measured Blood Pressure Parameters

[0215] Mean SBP decreased over the first 4 to 5 weeks of treatment, including in the placebo arm (Table 12 and Table 13). The reductions in mean DBP (Table 14 and Table 15) were smaller than those observed for SBP, and the change from baseline in the placebo group was marginal. In general, the reductions in BP reached a plateau at around 4 weeks of treatment.

Table 12: Summary of Mean (SD) Change from Baseline in Seated Automated Office-Measured Systolic Blood Pressure (mmHg) by Study Visit, Part 1 (Full Analysis Set)

Visit	Placebo (N=30)	12.5 mg BID (N=22)	25 mg BID (N=30)	12.5 mg QD (N=23)	50 mg QD (N=28)	100 mg QD (N=30)
BL	142.70 (10.24)	144.57 (10.53)	140.93 (9.61)	147.09 (11.63)	141.82 (10.86)	143.80 (11.98)
Week 1 CFB	139.83 (10.84) -2.87 (10.24)	135.68 (14.48) -8.89 (11.51)	134.37 (14.17) -6.57 (10.78)	141.43 (15.98) -5.65 (13.96)	133.50 (12.23) -8.32 (14.27)	144.41 (14.54) 0.06 (12.66)
Week 2 CFB	143.04 (11.33) -0.21 (11.65)	132.59 (14.70) -11.98 (13.02)	134.57 (17.75) -6.37 (13.43)	143.73 (17.32) -1.86 (16.36)	132.29 (10.55) -9.54 (13.78)	139.04 (18.22) -5.64 (16.38)
Week 3 CFB	142.04 (13.94) -0.46 (15.13)	137.70 (15.37) -5.80 (9.60)	136.34 (19.78) -5.34 (18.35)	142.80 (18.14) -4.15 (13.14)	132.32 (13.45) -9.50 (16.67)	136.56 (14.68) -9.20 (11.37)
Week 4 CFB	139.86 (12.10) -3.39 (12.65)	132.95 (15.79) -10.71 (12.27)	131.85 (13.59) -9.63 (12.34)	143.00 (18.03) -3.95 (15.74)	132.75 (11.85) -9.07 (15.77)	129.76 (12.66) -14.60 (11.66)
Week 5 CFB	142.29 (14.76) -0.96 (12.68)	131.44 (13.13) -12.53 (13.34)	132.25 (16.30) -9.16 (15.72)	144.21 (13.11) -3.53 (12.49)	134.27 (15.39) -8.38 (15.19)	130.96 (14.84) -13.40 (16.59)
Week 6 CFB	139.89 (11.93) -3.70 (13.86)	129.79 (15.24) -14.00 (14.80)	134.32 (13.96) -7.09 (11.66)	139.00 (16.95) -8.64 (16.52)	131.11 (12.49) -10.72 (14.86)	138.73 (14.13) -6.62 (15.69)
Week 7 CFB	137.81 (13.53) -5.78 (13.89)	131.89 (11.93) -11.76 (13.06)	130.74 (15.42) -11.00 (13.60)	136.56 (19.58) -11.08 (19.26)	133.19 (16.39) -7.69 (18.91)	134.32 (18.32) -11.04 (16.75)
Week 8 CFB	139.14 (14.15) -4.09 (11.71)	131.89 (12.93) -13.79 (17.70)	131.29 (16.59) -10.13 (14.02)	140.78 (22.01) -6.86 (19.85)	128.64 (13.69) -13.18 (17.17)	131.28 (14.13) -14.08 (13.26)

[0216] Baseline was defined as the average of the last two non-missing values prior to first dose of study treatment including unscheduled visits. Abbreviations: BID, twice daily; BL, baseline; CFB, change from baseline; mmHg, millimeters of mercury; QD, once daily; SD, standard deviation.

Table 13: Summary of Mean (SD) Change from Baseline in Seated Automated Office-Measured Systolic Blood Pressure (mmHg) by Study Visit, Part 2 (Full Analysis Set)

Visit	Placebo (N=6)	100 mg QD (N=31)
Baseline	132.92 (8.38)	140.35 (8.62)
Week 1 CFB	126.67 (15.87) -6.25 (9.67)	129.00 (18.15) -11.35 (15.60)
Week 2 CFB	131.83 (15.66) -1.08 (9.23)	131.33 (14.99) -8.80 (13.86)
Week 3 CFB	130.17 (11.03) -2.75 (7.52)	131.52 (16.81) -8.76 (15.67)
Week 4 CFB	136.17 (18.70) 3.25 (10.93)	125.44 (17.18) -16.04 (17.07)
Week 5 CFB	125.00 (12.41) -7.92 (6.41)	127.92 (20.63) -12.87 (19.31)
Week 6 CFB	127.00 (10.30) -5.92 (9.37)	127.58 (17.26) -13.29 (16.80)
Week 7 CFB	127.83 (17.10) -5.08 (13.25)	128.75 (14.28) -11.66 (16.54)
Week 8 CFB	128.33 (18.86) -4.58 (11.18)	129.30 (15.44) -11.20 (15.71)

[0217] Baseline was defined as the average of the last two non-missing values prior to first dose of study treatment including unscheduled visits. Abbreviations: CFB, change from baseline; mmHg, millimeters of mercury; QD, once daily; SD, standard deviation.

Table 14: Summary of Mean (SD) Change from Baseline in Seated Automated Office-Measured Diastolic Blood Pressure (mmHg) by Study Visit, Part 1 (Full Analysis Set)

Visit	Placebo (N=30)	12.5 mg BID (N=22)	25 mg BID (N=30)	12.5 mg QD (N=23)	50 mg QD (N=28)	100 mg QD (N=30)
BL	83.37 (8.76)	81.55 (7.58)	78.92 (7.95)	82.39 (10.65)	84.88 (6.37)	78.87 (9.60)
Week 1 CFB	81.93 (8.93) -1.43 (7.41)	75.59 (8.32) -5.95 (6.17)	76.70 (9.28) -2.22 (5.68)	85.26 (13.88) 2.87 (12.31)	80.54 (7.58) -4.34 (8.86)	79.70 (11.07) 0.98 (8.29)
Week 2 CFB	83.50 (10.75) 0.00 (7.89)	74.23 (10.15) -7.32 (9.14)	76.50 (10.74) -2.42 (8.03)	81.23 (9.21) 0.68 (8.89)	78.96 (8.27) -5.91 (7.38)	76.36 (11.90) -2.14 (9.60)
Week 3 CFB	83.07 (10.25) -0.04 (10.23)	79.95 (9.17) -0.93 (7.51)	78.72 (15.35) -0.55 (14.99)	81.80 (13.73) -1.20 (9.13)	81.04 (9.15) -3.84 (8.83)	72.84 (10.83) -5.48 (9.36)
Week 4 CFB	82.29 (9.68) -1.21 (6.86)	75.79 (10.69) -4.18 (10.21)	73.26 (7.79) -5.80 (7.01)	81.20 (14.03) -1.80 (9.84)	79.57 (8.36) -5.30 (8.33)	71.60 (8.62) -6.36 (6.75)
Week 5 CFB	82.61 (9.05) -0.89 (7.34)	73.50 (10.13) -7.00 (7.81)	76.29 (9.91) -2.82 (8.82)	83.74 (14.32) 0.82 (14.46)	78.58 (7.53) -6.10 (7.22)	72.60 (11.27) -5.36 (8.12)
Week 6 CFB	84.37 (13.27) 0.87 (13.94)	74.95 (10.29) -6.47 (6.39)	76.04 (10.57) -3.07 (8.82)	79.06 (13.07) -4.17 (10.04)	78.63 (8.17) -6.26 (8.48)	74.77 (10.12) -3.33 (7.96)
Week 7 CFB	79.81 (8.39) -3.69 (6.06)	74.21 (9.64) -5.76 (7.62)	73.89 (10.76) -4.87 (8.84)	77.11 (12.74) -6.11 (12.05)	80.88 (11.41) -3.75 (11.03)	73.48 (11.08) -4.12 (8.55)
Week 8 CFB	81.28 (9.42) -2.24 (8.37)	75.21 (10.07) -5.84 (8.78)	75.43 (13.06) -3.68 (11.71)	81.44 (17.24) -1.78 (13.33)	76.82 (9.82) -8.05 (9.13)	73.00 (9.43) -5.46 (7.85)

[0218] Baseline was defined as the average of the last two non-missing values prior to first dose of study treatment including unscheduled visits. Abbreviations: BID, twice daily; CFB, change from baseline; mmHg, millimeters of mercury; QD, once daily; SD, standard deviation.

Table 15: Summary of Mean (SD) Change from Baseline in Seated Automated Office-Measured Diastolic Blood Pressure (mmHg) by Study Visit, Part 2 (Full Analysis Set)

Visit	Placebo (N=6)	100 mg QD (N=31)
Baseline	78.25 (7.58)	78.05 (7.64)
Week 1 CFB	79.33 (12.69) 1.08 (7.91)	72.19 (8.84) -5.85 (11.04)
Week 2 CFB	75.67 (10.60) -2.58 (6.14)	73.10 (7.88) -5.13 (8.47)
Week 3 CFB	76.50 (10.65) -1.75 (8.20)	73.72 (7.97) -4.76 (8.11)
Week 4 CFB	77.33 (10.67) -0.92 (7.30)	71.36 (8.29) -6.92 (10.16)
Week 5 CFB	72.83 (11.48) -5.42 (6.79)	71.31 (9.19) -6.35 (9.99)
Week 6 CFB	77.17 (12.12) -1.08 (6.88)	70.65 (8.56) -7.25 (7.83)
Week 7 CFB	72.17 (9.06) -6.08 (4.28)	71.61 (9.29) -6.13 (8.05)
Week 8 CFB	76.17 (10.98) -2.08 (8.19)	72.17 (8.40) -5.68 (10.78)

[0219] Baseline was defined as the average of the last two non-missing values prior to first dose of study treatment including unscheduled visits. Abbreviations: CFB, change from baseline; mmHg, millimeters of mercury; QD, once daily; SD, standard deviation.

Proportion of Subjects with Seated Automated Office-Measured Diastolic Blood Pressure $\leq 130/80$ mmHg

[0220] Overall, six subjects in Part 1 and three subjects in Part 2 had AOBP at or below the AHA cut-point for hypertension (130/80 mmHg) at baseline (Table 16 and Table 17). By Week 8 the proportion of subjects with AOBP $\leq 130/80$ mmHg across all doses in Part 1 ranged from 23.3% for the Placebo cohort to 43.3% for the 25 mg BID cohort (**Figure 16**). In Part 2, 54.8% of the 100 mg QD cohort achieved this treatment goal compared to 30% in the 100 mg QD cohort of Part 1 (**Figure 17**).

Table 16: Proportion of Subjects with Seated Automated Office-Measured SBP/DBP $\leq$ 130/80 mmHg at Week 8, Part 1 (Full Analysis Set)

Visit		Placebo (N=30)	12.5 mg BID (N=22)	25 mg BID (N=30)	12.5 mg QD (N=23)	50 mg QD (N=28)	100 mg QD (N=30)
Baseline	SBP/DBP $\leq$ 130/80 mmHg						
	Yes, n (%)	1 (3.3)	1 (4.5)	3 (10.0)	0	0	1 (3.3)
	No, n (%)	29 (96.7)	21 (95.5)	27 (90.0)	23 (100)	28 (100)	29 (96.7)
Week 8	SBP/DBP $\leq$ 130/80 mmHg						
	Yes, n (%)	7 (23.3)	7 (31.8)	13 (43.3)	6 (26.1)	12 (42.9)	9 (30.0)
	No, n (%)	23 (76.7)	15 (68.2)	17 (56.7)	17 (73.9)	16 (57.1)	21 (70.0)

[0221] Baseline was defined as the average of the last two non-missing values prior to first dose of study treatment including unscheduled visits. Abbreviations: BID, twice daily; DBP, diastolic blood pressure; mmHg, millimeters of mercury; QD, once daily; SBP, systolic blood pressure.

Table 17: Proportion of Subjects with Seated Automated Office-Measured SBP/DBP $\leq$ 130/80 mmHg at Week 8, Part 2 (Full Analysis Set)

Visit		Placebo (N=6)	100 mg QD (N=31)
Baseline	SBP/DBP $\leq$ 130/80 mmHg		
	Yes, n (%)	1 (16.7)	2 (6.5)
	No, n (%)	5 (83.3)	29 (93.5)
Week 8	SBP/DBP $\leq$ 130/80 mmHg		
	Yes, n (%)	3 (50.0)	17 (54.8)
	No, n (%)	3 (50.0)	14 (45.2)

[0222] Baseline was defined as the average of the last two non-missing values prior to first dose of study treatment including unscheduled visits. Abbreviations: DBP, diastolic blood pressure; mmHg, millimeters of mercury; QD, once daily; SBP, systolic blood pressure.

Time to First Occurrence of Seated Automated Office-measured SBP/DBP $\leq$ 130/80 mmHg

[0223] With the exception of subjects assigned to the Placebo group, the majority of subjects who achieved SBP/DBP of 130/80 mmHg did so between Weeks 2 and 4 of treatment in both Part 1 and Part 2 (**Figure 18** and **Figure 19**).

Change from Baseline at End of Treatment in 24-hour Ambulatory Blood Pressure Monitoring Parameters

[0224] The modelled changes in ABPM parameters (24-hour SBP, DBP, MAP, central SBP, central DBP and central MAP; daytime SBP, DBP and MAP; nighttime SBP and DBP) demonstrated a consistent AHT effect (Table 18 and Table 19). The results are compatible with those reported for AOBP parameters (SBP and DBP).

[0225] The changes from baseline to EoT in measured 24-hour, daytime and nighttime mean ABPM SBP, DBP and MAP are summarized in Table 20 and . The changes from baseline in mean 24-hour ABPM SBP and DBP at EoT were numerically smaller than those reported for AOBP which is an expected finding for the different modes of measurement.

Table 18: Modelled (ANCOVA) Least Square Mean Change from Baseline at End of Treatment in 24-hour ABPM Parameters, Part 1 (Full Analysis Set; Post-hoc Analysis)

24-hr ABPM Parameter	Statistic	12.5 mg BID (N=22)	25 mg BID (N=30)	12.5 mg QD (N=23)	50 mg QD (N=28)	100 mg QD (N=30)
24-hr SBP (mmHg)	LSM Δ with Placebo	-4.76	-8.04	-1.5	-3.85	-5.33
	p-value	0.2181	0.0181	0.7043	0.2496	0.1256
24-hr DBP (mmHg)	LSM Δ with Placebo	-4.24	-5.13	-1.44	-2.74	-5.23
	p-value	0.0742	0.0139	0.5504	0.18	0.0141
24-hr Mean MAP (mmHg)	LSM Δ with Placebo	-4.58	-6.68	-1.62	-3.48	-5.45
	p-value	0.1268	0.0113	0.5951	0.1785	0.0422
Daytime Mean SBP (mmHg)	LSM Δ with Placebo	-4.96	-8.76	-2.14	-6.85	-4.12
	p-value	0.2038	0.0109	0.5918	0.0424	0.2409
Daytime Mean DBP (mmHg)	LSM Δ with Placebo	-4.19	-5.64	-2.47	-4.18	-4.98
	p-value	0.0828	0.0079	0.3155	0.0443	0.0216
Nighttime Mean SBP (mmHg)	LSM Δ with Placebo	-3.9	-4.66	-0.21	2.37	-7.36
	p-value	0.421	0.2823	0.9675	0.576	0.0931
Nighttime Mean DBP (mmHg)	LSM Δ with Placebo	-3.92	-3.28	-1.53	0.15	-5.68
	p-value	0.2022	0.2336	0.6328	0.9556	0.0427
Mean Central SBP (mmHg)	LSM Δ with Placebo	-7.19	-10.19	1.92	-5.46	-7.79
	p-value	0.1148	0.0069	0.6616	0.1481	0.0409
Mean Central DBP (mmHg)	LSM Δ with Placebo	-4.85	-7.36	-1.29	-2.58	-7.01
	p-value	0.1123	0.0037	0.6623	0.3068	0.0063
Mean Central Mean BP (mmHg)	LSM Δ with Placebo	-6.08	-8.87	0.06	-4.11	-7.77
	p-value	0.1029	0.0041	0.9875	0.1826	0.0126

[0226] P-values in bold indicate p<0.05.

Table 19: Modelled (ANCOVA) Least Square Mean Change from Baseline at End of Treatment in 24-hour ABPM Parameters in Subjects Randomized to 100 mg QD, Parts 1 & 2 (Full Analysis Set; Post-hoc Analysis)

24-hr ABPM Parameter	Statistic	100 mg QD Part 2 (N=31)
24-hr Mean SBP (mmHg)	LSM Δ with 100 mg QD Part 1 p-value	4.13 0.3145
24-hr Mean DBP (mmHg)	LSM Δ with 100 mg QD Part 1 p-value	4.26 0.0984
24-hr Mean AP (mmHg)	LSM Δ with 100 mg QD Part 1 p-value	3.33 0.2967
Daytime Mean SBP (mmHg)	LSM Δ with 100 mg QD Part 1 p-value	1.64 0.705
Daytime Mean DBP (mmHg)	LSM Δ with 100 mg QD Part 1 p-value	3.92 0.1326
Nighttime Mean SBP (mmHg)	LSM Δ with 100 mg QD Part 1 p-value	8.91 0.0422
Nighttime Mean DBP (mmHg)	LSM Δ with 100 mg QD Part 1 p-value	5.04 0.0755
Mean Central SBP (mmHg)	LSM Δ with 100 mg QD Part 1 p-value	4.68 0.2716
Mean Central DBP (mmHg)	LSM Δ with 100 mg QD Part 1 p-value	4.53 0.1211
Mean Central Mean BP (mmHg)	LSM Δ with 100 mg QD Part 1 p-value	3.98 0.2521

[0227] P-values in bold indicate p<0.05.

Table 20: Measured Mean (SD) Change from Baseline to End of Treatment in 24-hour Ambulatory Blood Pressure Monitoring Parameters, Part 1 (Full Analysis Set)

	Visit	Placebo (N=30)	12.5 mg BID (N=22)	25 mg BID (N=30)	12.5 mg QD (N=23)	50 mg QD (N=28)	100 mg QD (N=30)
24-hr Mean SBP (mmHg)	BL	138.30 (12.62)	139.86 (11.90)	138.97 (15.30)	142.82 (8.61)	133.14 (16.48)	143.41 (14.56)
	EoT	137.85 (12.49)	133.19 (14.86)	129.69 (12.57)	139.00 (16.31)	131.36 (15.58)	135.04 (11.25)
	CFB	-0.81 (10.73)	-5.69 (12.90)	-8.73 (15.67)	-5.20 (16.55)	-1.79 (15.82)	-8.88 (11.90)
24-hr Mean DBP (mmHg)	BL	83.83 (8.62)	82.50 (8.53)	81.97 (10.86)	82.45 (6.46)	80.75 (10.87)	82.38 (10.96)
	EoT	82.62 (9.70)	77.63 (11.03)	76.50 (10.59)	79.93 (7.33)	77.75 (9.33)	75.92 (8.42)
	CFB	-1.62 (5.79)	-5.38 (8.59)	-6.12 (9.77)	-2.27 (8.35)	-3.00 (8.52)	-5.92 (8.44)
24-hr Mean MAP (mmHg)	BL	111.07 (9.76)	111.18 (9.36)	110.47 (12.25)	112.64 (5.46)	106.95 (13.03)	112.90 (11.32)
	EoT	110.23 (10.11)	105.41 (12.62)	103.10 (10.92)	109.47 (10.81)	104.55 (11.74)	105.48 (8.26)
	CFB	-1.21 (7.66)	-5.53 (10.63)	-7.42 (12.49)	-3.73 (12.21)	-2.39 (11.80)	-7.40 (10.04)
Daytime Mean SBP (mmHg)	BL	140.43 (11.30)	140.64 (12.35)	142.40 (16.83)	144.55 (8.48)	136.86 (14.62)	145.66 (14.64)
	EoT	140.73 (12.54)	135.38 (14.97)	132.58 (13.62)	141.13 (15.62)	132.32 (14.36)	139.42 (11.65)
	CFB	0.42 (12.23)	-4.06 (14.48)	-9.08 (17.41)	-4.80 (15.10)	-4.54 (13.59)	-7.08 (12.60)
Daytime Mean DBP (mmHg)	BL	85.77 (9.53)	83.59 (8.59)	84.70 (11.74)	84.36 (6.49)	83.61 (9.34)	84.03 (11.04)
	EoT	85.19 (9.86)	79.69 (10.81)	79.04 (10.41)	81.53 (6.79)	79.50 (9.08)	78.79 (9.44)
	CFB	-0.92 (6.75)	-4.25 (9.64)	-6.23 (10.43)	-2.60 (8.43)	-4.11 (6.81)	-4.96 (8.74)
Nighttime Mean SBP (mmHg)	BL	133.07 (16.86)	135.18 (13.57)	129.50 (13.89)	136.32 (12.38)	127.22 (16.95)	135.96 (15.36)
	EoT	130.58 (14.77)	126.81 (16.69)	123.92 (12.17)	132.00 (18.11)	129.54 (21.68)	124.50 (14.93)
	CFB	-3.46 (12.79)	-7.50 (16.17)	-5.96 (15.37)	-5.43 (20.36)	2.44 (22.25)	-11.48 (13.87)
Nighttime Mean DBP (mmHg)	BL	78.77 (8.07)	77.95 (9.66)	74.10 (9.84)	78.05 (7.91)	73.85 (11.94)	77.21 (13.13)
	EoT	76.88 (10.89)	72.44 (12.25)	71.38 (11.94)	74.29 (9.59)	74.25 (13.08)	69.00 (9.04)
	CFB	-2.46 (9.51)	-6.00 (10.17)	-4.13 (10.86)	-3.21 (9.55)	0.00 (12.34)	-6.57 (9.97)

Table 21: Measured Mean (SD) Change from Baseline to End of Treatment in 24-hour Ambulatory Blood Pressure Monitoring Parameters, Part 2 (Full Analysis Set)

	Visit	Placebo (N=6)	100 mg QD (N=31)
24-hr Mean SBP (mmHg)	Baseline	137.50 (16.01)	131.06 (13.09)
	EoT	128.83 (15.66)	132.59 (16.72)
	CFB	-8.67 (7.34)	2.30 (16.68)
24-hr Mean DBP (mmHg)	Baseline	80.00 (9.53)	76.42 (8.92)
	EoT	75.00 (10.64)	77.07 (11.15)
	CFB	-5.00 (3.10)	1.33 (10.97)
24-hr Mean MAP (mmHg)	Baseline	108.75 (10.73)	103.74 (10.18)
	EoT	101.92 (12.28)	104.83 (12.95)
	CFB	-6.83 (4.32)	1.81 (13.46)
Daytime Mean SBP (mmHg)	Baseline	139.33 (16.19)	133.71 (12.56)
	EoT	130.33 (14.50)	135.22 (16.83)
	CFB	-9.00 (9.53)	2.41 (17.69)
Daytime Mean DBP (mmHg)	Baseline	81.00 (10.00)	78.52 (8.81)
	EoT	76.83 (10.91)	79.41 (11.01)
	CFB	-4.17 (3.06)	1.67 (10.63)
Nighttime Mean SBP (mmHg)	Baseline	132.83 (17.63)	124.94 (16.29)
	EoT	124.50 (20.04)	126.04 (18.97)
	CFB	-8.33 (8.07)	1.52 (16.44)
Nighttime Mean DBP (mmHg)	Baseline	76.83 (10.34)	71.16 (10.77)
	EoT	69.83 (11.20)	71.85 (12.27)
	CFB	-7.00 (5.18)	1.04 (12.49)

[0228] In many of the treatment cohorts, the proportion of subjects achieving a nighttime dip in ABPM SBP of $\geq 10\%$ increased from baseline to the last post-baseline assessment (Table 22 and Table 23).

Table 22: Proportion of Subjects with Nighttime Dip in 24-hour Systolic Ambulatory Blood Pressure, Part 1 (Full Analysis Set)

Visit	Category	Placebo (N=30)	12.5 mg BID (N=22)	25 mg BID (N=30)	12.5 mg QD (N=23)	50 mg QD (N=28)	100 mg QD (N=30)
Baseline	<10%, n (%)	20 (66.7)	18 (81.8)	19 (63.3)	15 (68.2)	18 (66.7)	20 (71.4)
	10–20%, n (%)	9 (30.0)	4 (18.2)	9 (30.0)	7 (31.8)	9 (33.3)	7 (25.0)
	> 20%, n (%)	1 (3.3)	0	2 (6.7)	0	0	1 (3.6)
EoT	<10%, n (%)	16 (61.5)	11 (68.8)	19 (79.2)	9 (64.3)	22 (78.6)	11 (45.8)
	10–20%, n (%)	10 (38.5)	5 (31.3)	4 (16.7)	5 (35.7)	6 (21.4)	11 (45.8)
	>20%, n (%)	0	0	1 (4.2)	0	0	2 (8.3)

[0229] Nighttime Dip was defined as $100\% \times (24\text{-hour ABPM Mean Daytime SBP} - 24\text{-hour ABPM Mean Nighttime SBP}) / 24\text{-hour ABPM Mean Daytime SBP}$.

Table 23: Proportion of Subjects with Nighttime Dip in 24-hour Systolic Ambulatory Blood Pressure, Part 2 (Full Analysis Set)

Visit	Category	Placebo (N=6)	100 mg QD (N=31)
Baseline	<10%, n (%)	4 (66.7)	19 (61.3)
	10–20%, n (%)	2 (33.3)	11 (35.5)
	>20%, n (%)	0	1 (3.2)
Week 4	<10%, n (%)	6 (100)	18 (72.0)
	10–20%, n (%)	0	6 (24.0)
	>20%, n (%)	0	1 (4.0)
EoT	<10%, n (%)	4 (66.7)	18 (66.7)
	10–20%, n (%)	2 (33.3)	9 (33.3)
	>20%, n (%)	0	0

[0230] The Nighttime Dip was defined as $100\% \times (24\text{-hour ABPM Mean Daytime SBP} - 24\text{-hour ABPM Mean Nighttime SBP}) / 24\text{-hour ABPM Mean Daytime SBP}$.

Analysis of factors affecting change in blood pressure

[0231] An analysis was conducted to identify factors affecting the degree of blood pressure reduction in hypertensive subjects. As shown in the tables below, it was discovered that Lorundrostat is particularly effective at reducing the blood pressure of individuals with a body mass index (BMI) of greater than 30. This effect was observed across dosing cohorts.

[0232] Further, as shown in the tables below, it was discovered that Lorundrostat is particularly effective at reducing the blood pressure of individuals who were receiving a thiazide diuretic as one of their background hypertension medications. This effect was observed across dosing cohorts.

[0233] There was no apparent consistent difference between mean change from baseline in AOBP SBP at Week 8 when summarized by sex (Male, Female) age (<65, 65–79, ≥80 years), race (Black or African American, Other), number of AHT medications at baseline (2, ≥3), or use of concomitant angiotensin converting enzyme inhibitors (ACEi) or ARBs in Part 1 (Table 24) or Part 2 (Table 25).

[0234] Using pooled data from low renin subjects (Part-1) from the lorundrostat 25mg BID, 50mg QD and 100mg QD cohorts, the relationship between median baseline body mass index (BMI) and serum leptin (ng/dl) and the relationship between BMI at baseline and mean change in systolic BP (mmHg), measured by AOBP, at week 8 compared to baseline were analyzed (Figure 26 and Figure 27). Each of these cohorts demonstrated significant reduction in median serum aldosterone at week 4 compared to baseline. Treated as continuous variables, there was a strong

relationship between increasing BMI and increasing serum leptin. Treated as continuous variables there was a strong relationship between BMI and reduction in BP. These two associations support the postulate that elevated serum leptin is associated with a larger reduction in BP. These data are consistent with the hypothesis that increased production of leptin in the setting of visceral obesity contributes to the increase in aldosterone-mediated hypertension. They further support the hypothesis that inhibition of aldosterone synthesis abrogates the stimulatory effect of leptin on aldosterone production.

Table 24: Mean (SD) Change from Baseline at Week 8 in Automated Office-Measured Systolic Blood Pressure, by Subgroup, Part 1 (Full Analysis Set)

	Sub-group	Visit	Placebo (N=30)	12.5 mg BID (N=22)	25 mg BID (N=30)	12.5 mg QD (N=23)	50 mg QD (N=28)	100 mg QD (N=30)
Sex	Male	n	13	8	11	11	13	12
		BL	145.23 (11.27)	146.50 (13.29)	138.18 (8.02)	147.45 (14.10)	142.04 (11.51)	142.79 (13.06)
		Wk8	142.92 (10.00)	134.40 (9.42)	128.82 (16.45)	145.56 (26.10)	132.08 (15.20)	129.60 (11.45)
	CFB	-3.79 (8.91)	-17.50 (15.84)	-9.36 (13.49)	-4.50 (26.71)	-9.96 (15.67)	-15.45 (15.48)	
	Female	n	17	14	19	12	15	18
		BL	140.76 (9.24)	143.46 (8.97)	142.53 (10.29)	146.75 (9.45)	141.63 (10.68)	144.47 (11.54)
Wk8		136.47 (16.22)	131.00 (14.17)	132.88 (16.99)	136.00 (17.23)	125.67 (11.97)	132.40 (15.95)	
CFB	-4.29 (13.61)	-12.46 (18.69)	-10.62 (14.75)	-9.22 (10.54)	-15.97 (18.44)	-13.17 (12.05)		
Age (yr)	<65	n	17	6	14	10	15	9
		BL	140.68 (9.44)	139.08 (9.02)	140.39 (6.49)	149.30 (15.40)	140.73 (11.21)	147.00 (12.65)
		Wk8	139.06 (14.69)	132.17 (11.13)	127.38 (13.07)	144.88 (25.16)	129.27 (14.04)	129.33 (20.63)
	CFB	-2.44 (11.56)	-6.92 (7.84)	-12.31 (13.78)	-5.75 (22.93)	-11.47 (16.60)	-22.75 (14.75)	
	65-79	n	12	13	15	10	13	17
		BL	146.29 (10.92)	147.23 (10.81)	140.17 (11.19)	144.45 (8.83)	143.08 (10.76)	142.26 (12.30)
		Wk8	138.58 (14.47)	135.73 (11.26)	133.86 (19.37)	135.63 (15.23)	127.92 (13.82)	133.73 (12.53)
	CFB	-7.71 (11.04)	-12.77 (19.08)	-7.82 (14.88)	-8.50 (14.04)	-15.15 (18.27)	-9.53 (11.49)	
	≥80	n	1	3	1	3	0	4
		BL	134.00 (NE)	144.00 (11.14)	160.00 (NE)	148.50 (2.78)		143.13 (10.41)
		Wk8	147.00 (NE)	110.00 (1.41)	146.00 (NE)	145.00 (42.43)		125.00 (8.04)
	CFB	13.00 (NE)	-40.00 (4.24)	-14.00 (NE)	-4.75 (39.95)		-18.13 (12.34)	
Race	Black or AA	n	16	7	7	11	8	15
		BL	142.28 (10.81)	145.14 (9.03)	137.29 (7.54)	146.86 (14.31)	142.69 (15.03)	145.43 (10.76)
		Wk8	137.00 (16.33)	137.71 (13.50)	124.00 (15.68)	147.50 (22.06)	130.38 (14.12)	129.92 (16.18)
	CFB	-5.28 (13.58)	-7.43 (20.17)	-13.29 (15.91)	-1.44 (16.04)	-12.31 (18.13)	-17.13 (11.55)	
	Other	n	14	15	23	12	20	15
		BL	143.18 (9.92)	144.30 (11.46)	142.04 (10.04)	147.29 (9.18)	141.48 (9.17)	142.17 (13.25)
Wk8		141.77 (10.95)	128.50 (11.84)	133.71 (16.53)	135.40 (21.55)	127.95 (13.83)	132.54 (12.47)	
CFB	-2.62 (9.21)	-17.50 (15.80)	-9.07 (13.59)	-11.20 (22.29)	-13.53 (17.25)	-11.27 (14.54)		
AHTs	2	n	17	7	14	14	20	14
		BL	142.38 (11.91)	144.00 (14.58)	143.54 (9.04)	150.32 (13.04)	139.88 (9.41)	140.39 (9.10)
		Wk8	135.44 (15.09)	136.33 (11.76)	136.92 (18.45)	142.80 (25.41)	129.60 (13.98)	124.82 (13.25)
	CFB	-7.88 (10.12)	-8.33 (13.28)	-6.15 (13.68)	-9.70 (21.49)	-10.28 (15.34)	-17.95 (15.83)	
	≥3	n	13	15	16	9	8	16
		BL	143.12 (7.99)	144.83 (8.66)	138.66 (9.79)	142.06 (7.00)	146.69 (13.31)	146.78 (13.61)
Wk8		143.69 (11.90)	129.85 (13.37)	126.40 (13.57)	138.25 (18.26)	126.25 (13.56)	136.36 (13.05)	
CFB	0.58 (12.21)	-16.31 (19.35)	-13.57 (13.83)	-3.31 (18.37)	-20.44 (20.36)	-11.04 (10.45)		
ACEi/ ARB	Yes	n	22	17	27	18	20	23
		BL	145.09 (10.31)	143.97 (10.62)	140.72 (8.88)	147.78 (11.24)	143.40 (11.57)	144.89 (13.29)
		Wk8	140.64 (14.76)	132.00 (12.59)	132.20 (15.32)	141.50 (23.12)	127.65 (14.07)	134.90 (13.12)
	CFB	-4.45 (12.63)	-12.47 (17.09)	-9.04 (14.04)	-6.39 (16.84)	-15.75 (17.46)	-11.68 (13.23)	
	No	n	8	5	3	5	8	7
		BL	136.13 (6.93)	146.60 (11.17)	142.83 (17.55)	144.60 (14.05)	137.88 (8.19)	140.21 (5.08)
Wk8		134.43 (11.70)	131.50 (16.22)	123.67 (28.36)	138.25 (20.45)	131.13 (13.27)	116.80 (7.19)	
CFB	-2.93 (8.89)	-18.75 (21.77)	-19.17 (12.25)	-8.50 (31.61)	-6.75 (15.62)	-23.70 (8.89)		

[0235] Abbreviations: AA, African American; ARB, angiotensin receptor blocker; ACEi, angiotensin converting enzyme inhibitor; AHT, antihypertensive; BID, twice daily; BL, baseline;

CFB change from baseline; mg, milligrams; QD, once daily; SD, standard deviation; Wk8, Week 8; yr, years.

Table 25: Mean (SD) Change from Baseline at Week 8 in Automated Office-Measured Systolic Blood Pressure, by Subgroup, Part 2 (Full Analysis Set)

	Sub-group	Visit	Placebo (N=6)	100 mg QD (N=31)
Sex	Male	n	2	10
		BL	130.50 (12.02)	143.40 (11.39)
		Wk8	122.50 (28.99)	132.10 (10.89)
		CFB	-8.00 (16.97)	-11.30 (17.09)
	Female	n	4	21
		BL	134.13 (7.94)	138.90 (6.80)
		Wk8	131.25 (16.70)	127.90 (17.36)
		CFB	-2.88 (10.04)	-11.15 (15.43)
Age (yr)	<65	n	4	8
		BL	135.88 (8.09)	133.94 (5.73)
		Wk8	134.50 (17.62)	120.88 (19.85)
		CFB	-1.38 (10.64)	-13.06 (20.62)
	65-79	n	2	22
		BL	127.00 (7.07)	142.20 (8.40)
		Wk8	116.00 (19.80)	132.81 (12.82)
		CFB	-11.00 (12.73)	-9.69 (13.82)
	≥80	n	0	1
		BL		151.00 (NE)
		Wk8		123.00 (NE)
		CFB		-28.00 (NE)
Race	Black or AA	n	2	6
		BL	136.25 (13.08)	141.67 (7.70)
		Wk8	139.00 (22.63)	125.83 (7.96)
		CFB	2.75 (9.55)	-15.83 (11.63)
	Other	n	4	25
		BL	131.25 (6.99)	140.04 (8.94)
		Wk8	123.00 (17.57)	130.17 (16.82)
		CFB	-8.25 (11.15)	-10.04 (16.57)
AHTs	2	n	4	20
		BL	128.25 (4.79)	138.10 (7.83)
		Wk8	118.00 (11.92)	127.84 (16.77)
		CFB	-10.25 (8.66)	-10.37 (15.86)
	≥3	n	2	11
		BL	142.25 (4.60)	144.45 (8.81)
		Wk8	149.00 (8.49)	131.82 (13.19)
		CFB	6.75 (3.89)	-12.64 (16.10)
ACEi/ ARB	Yes	n	5	30
		BL	134.10 (8.79)	140.53 (8.71)
		Wk8	129.40 (20.89)	129.24 (15.71)
		CFB	-4.70 (12.50)	-11.45 (15.92)
	No	n	1	1
		BL	127.00 (NE)	135.00 (NE)
		Wk8	123.00 (NE)	131.00 (NE)
		CFB	-4.00 (NE)	-4.00 (NE)

[0236] Abbreviations: AA, African American; ARB, angiotensin receptor blocker; ACEi, angiotensin converting enzyme inhibitor; AHT, antihypertensive; BL, baseline; CFB change from baseline; mg, milligrams; NE, not evaluable; QD, once daily; SD, standard deviation; Wk8, Week 8; yr, years.

[0237] There was an apparent increase in the AHT effect of lorundrostat with increasing BMI (Table 26) that was most apparent in the 100 mg QD dose cohorts in Part 1 (Table 26) and Part 2 (Table 27). Exploratory analysis using MMRM resulted in a placebo-adjusted reduction in AOBP SBP of -16.7 mmHg ($p=0.0023$) in the Part 1 50 mg QD cohort and -12.3 mmHg ($p=0.0297$) in the Part 1 100 mg QD cohort (data not shown).

Table 26: Mean (SD) Change from Baseline at Week 8 in Automated Office-Measured Systolic Blood Pressure, by BMI at Baseline, Part 1 (Full Analysis Set)

Sub-group	Visit	Placebo (N=30)	12.5 mg BID (N=22)	25 mg BID (N=30)	12.5 mg QD (N=23)	50 mg QD (N=28)	100 mg QD (N=30)
<25 kg/m ²	n	1	2	4	3	1	5
	BL	164.00 (NE)	139.75 (10.96)	144.38 (12.41)	150.00 (4.92)	156.00 (NE)	144.90 (18.74)
	Wk8	159.00 (NE)	150.00 (NE)	126.25 (18.52)	137.00 (NE)	118.00 (NE)	146.00 (18.33)
	CFB	-5.00 (NE)	2.50 (NE)	-18.13 (15.56)	-11.50 (NE)	-38.00 (NE)	-7.83 (17.47)
25–30 kg/m ²	n	13	4	10	8	11	10
	BL	146.19 (11.88)	149.38 (10.16)	137.00 (8.59)	141.06 (6.90)	139.09 (10.46)	139.95 (8.19)
	Wk8	138.62 (14.65)	125.50 (14.89)	134.11 (15.72)	134.14 (18.96)	136.64 (14.70)	129.67 (10.05)
	CFB	-7.58 (8.31)	-23.88 (24.55)	-4.89 (13.17)	-7.71 (19.07)	-2.45 (15.21)	-11.17 (11.94)
>30 kg/m ²	n	16	16	15	12	15	14
	BL	138.53 (5.52)	143.97 (10.82)	142.07 (9.48)	150.38 (13.97)	143.40 (11.05)	146.79 (11.75)
	Wk8	138.27 (13.68)	132.43 (11.93)	130.93 (17.43)	145.80 (24.73)	124.13 (10.98)	129.00 (15.28)
	CFB	-1.00 (13.91)	-12.07 (15.48)	-11.13 (13.83)	-5.80 (22.31)	-19.27 (15.13)	-18.50 (13.40)

[0238] Abbreviations: BID, twice daily; BL, baseline; CFB, change from baseline; NE, not evaluable; QD, once daily; SD, standard deviation; Wk8, Week 8.

Table 27: Mean (SD) Change from Baseline at Week 8 in Automated Office-Measured Systolic Blood Pressure, by BMI at Baseline, Part 2 (Full Analysis Set)

Sub-group	Visit	Placebo (N=6)	100 mg QD (N=31)
<25 kg/m ²	n	1	2
	BL	132.00 (NE)	136.50 (2.12)
	Wk8	117.00 (NE)	130.00 (1.41)
	CFB	-15.00 (NE)	-6.50 (3.54)
25-30 kg/m ²	n	0	15
	BL		141.40 (7.98)
	Wk8		126.80 (17.49)
	CFB		-14.60 (15.76)
>30 kg/m ²	n	5	14
	BL	133.10 (9.36)	139.79 (9.93)
	Wk8	130.60 (20.16)	132.08 (14.23)
	CFB	-2.50 (11.12)	-8.00 (16.62)

[0239] Abbreviations: BL, baseline; CFB, change from baseline; NE, not evaluable; QD, once daily; SD, standard deviation; Wk8, Week 8.

[0240] There was an apparent increase in the AHT effect of lorundrostat with increasing baseline AOBP SBP in both Part 1 and Part 2 (Table 28 and Table 29, respectively). It should be noted that a greater AHT effect with increasing baseline AOBP SBP was also observable in the Part 1 placebo cohort and only the 50 mg QD cohort in Part 1 demonstrated a statistically significant placebo-adjusted reduction in AOBP SBP from baseline at Week 8 (-19.9 mmHg, p=0.0113).

Table 28: Mean (SD) Change from Baseline at Week 8 in Automated Office-Measured Systolic Blood Pressure, by Systolic Blood Pressure Tertile at Baseline, Part 1 (Full Analysis Set)

Sub-group	Visit	Placebo (N=30)	12.5 mg BID (N=22)	25 mg BID (N=30)	12.5 mg QD (N=23)	50 mg QD (N=28)	100 mg QD (N=30)
Low	n	10	5	11	8	12	10
	BL	133.75 (3.16)	132.80 (4.72)	131.91 (4.93)	135.13 (1.71)	132.83 (3.43)	132.15 (6.41)
	Wk8	131.11 (13.06)	132.25 (10.34)	120.70 (13.06)	131.17 (12.77)	130.25 (12.04)	129.86 (9.26)
	CFB	-3.33 (12.89)	-0.75 (5.48)	-12.50 (13.48)	-3.75 (13.24)	-2.58 (12.54)	-4.71 (8.58)
Middle	n	12	10	11	4	8	9
	BL	141.08 (2.64)	141.90 (3.14)	140.86 (2.56)	144.88 (0.85)	140.63 (1.73)	140.94 (2.14)
	Wk8	139.50 (13.81)	131.75 (14.00)	135.45 (15.29)	143.33 (22.23)	127.63 (13.35)	124.56 (13.30)
	CFB	-1.58 (13.38)	-10.56 (16.34)	-5.41 (14.64)	-1.17 (21.80)	-13.00 (14.05)	-16.39 (13.97)
High	n	8	7	8	11	8	11
	BL	156.31 (8.92)	156.79 (7.57)	153.44 (5.64)	156.59 (8.92)	156.50 (6.88)	156.73 (6.96)
	Wk8	147.63 (11.86)	131.86 (14.81)	139.86 (16.99)	146.33 (26.41)	127.25 (17.59)	139.11 (15.36)
	CFB	-8.69 (6.44)	-24.93 (18.46)	-14.14 (13.63)	-10.83 (23.91)	-29.25 (14.31)	-19.06 (12.91)

[0241] Abbreviations: BID, twice daily; BL, baseline; CFB, change from baseline; QD, once daily; SD, standard deviation; Wk8, Week 8.

Table 29: Mean (SD) Change from Baseline at Week 8 in Automated Office-measured Systolic Blood Pressure, by Systolic Blood Pressure Tertile at Baseline, Part 2 (Full Analysis Set)

Sub-group	Visit	Placebo (N=6)	100 mg QD (N=31)
Low	n	4	10
	BL	128.25 (4.79)	132.10 (3.28)
	Wk8	118.00 (11.92)	124.11 (19.94)
	CFB	-10.25 (8.66)	-7.56 (19.91)
Middle	n	1	10
	BL	139.00 (NE)	138.65 (1.20)
	Wk8	143.00 (NE)	130.60 (16.91)
	CFB	4.00 (NE)	-8.05 (16.54)
High	n	1	11
	BL	145.50 (NE)	149.41 (7.12)
	Wk8	155.00 (NE)	132.36 (8.91)
	CFB	9.50 (NE)	-17.05 (9.63)

[0242] Abbreviations: BL, baseline; CFB, change from baseline; NE, not evaluable; QD, once daily; SD, standard deviation; Wk8, Week 8.

[0243] There also appeared to be a greater reduction in AOBP SBP from baseline in subjects with concomitant use of thiazide diuretics in Part 1 (Table 30), but this was not as apparent in Part 2 (Table 31). In Part 1, statistically significant placebo-adjusted reductions in AOBP SBP at Week 8 were achieved in the 12.5 mg BID and 50 mg QD cohorts with mean changes of -10.7 mmHg (p=0.047) and -12.9 mmHg (p=0.0108), respectively.

Table 30: Mean (SD) Change from Baseline at Week 8 in Automated Office-Measured Systolic Blood Pressure, by Thiazide Diuretic Use at Baseline [Yes/No], Part 1 (Full Analysis Set)

Sub-group	Visit	Placebo (N=30)	12.5 mg BID (N=22)	25 mg BID (N=30)	12.5 mg QD (N=23)	50 mg QD (N=28)	100 mg QD (N=30)
Yes	n	16	13	18	12	16	17
	BL	142.84 (8.18)	145.69 (9.02)	141.64 (9.28)	141.46 (8.43)	144.94 (12.46)	144.88 (10.09)
	Wk8	139.81 (13.46)	127.58 (11.07)	130.53 (17.84)	132.44 (14.02)	127.63 (14.08)	128.27 (16.26)
	CFB	-3.03 (12.33)	-19.25 (16.90)	-10.65 (14.39)	-7.89 (14.31)	-17.31 (17.91)	-17.37 (14.74)
No	n	14	9	12	11	12	13
	BL	142.54 (12.51)	142.94 (12.82)	139.88 (10.41)	153.23 (11.82)	137.67 (6.71)	142.38 (14.38)
	Wk8	138.31 (15.47)	139.29 (13.28)	132.45 (15.21)	149.11 (26.02)	130.00 (13.65)	135.80 (9.10)
	CFB	-5.38 (11.25)	-4.43 (15.93)	-9.32 (14.08)	-5.83 (25.10)	-7.67 (15.11)	-9.15 (9.27)

[0244] Abbreviations: BID, twice daily; BL, baseline; CFB, change from baseline; QD, once daily; Wk8, Week 8.

Table 31: Mean (SD) Change from Baseline at Week 8 in Automated Office-Measured Systolic Blood Pressure, by Thiazide Diuretic Use at Baseline [Yes/No], Part 2 (Full Analysis Set)

Sub-group	Visit	Placebo (N=6)	100 mg QD (N=31)
Yes	n	5	19
	BL	135.10 (7.21)	141.89 (8.86)
	Wk8	133.60 (15.39)	131.72 (11.71)
	CFB	-1.50 (9.22)	-10.50 (13.87)
No	n	1	12
	BL	122.00 (NE)	137.92 (7.98)
	Wk8	102.00 (NE)	125.67 (19.81)
	CFB	-20.00 (NE)	-12.25 (18.73)

[0245] Abbreviations: BL, baseline; CFB, change from baseline; NE, not evaluable; QD, once daily; Wk8, Week 8.

[0246] There was no apparent consistent difference between mean change from baseline in AOBP DBP at Week 8 when summarized by sex (male, female), age (<65, 65-79, ≥80 years), race (Black or African American, Other), BMI (<25, 25–30, >30 kg/m²), seated AOBP DBP at baseline, number of AHT medications at baseline (2, ≥3), or use of concomitant ACEi or ARBs in Part 1 (Table 32) or Part 2 (Table 33).

Table 32: Mean (SD) Change from Baseline at Week 8 in Automated Office-Measured Diastolic Blood Pressure, by Subgroup, Part 1 (Full Analysis Set)

Category	Sub-group	Visit	Placebo (N=30)	12.5 mg BID (N=22)	25 mg BID (N=30)	12.5 mg QD (N=23)	50 mg QD (N=28)	100 mg QD (N=30)
Sex	Male	n	13	8	11	11	13	12
		BL	85.42 (6.00)	85.44 (10.67)	78.45 (9.55)	86.27 (12.87)	84.88 (8.36)	84.29 (7.81)
		Wk8	84.92 (8.22)	78.40 (9.63)	72.82 (9.34)	87.78 (21.70)	78.15 (6.52)	76.20 (6.81)
		CFB	-1.04 (9.31)	-7.50 (5.61)	-5.64 (7.70)	1.28 (17.06)	-6.73 (7.65)	-8.15 (8.28)
	Female	n	17	14	19	12	15	18
		BL	81.79 (10.30)	79.32 (4.13)	79.18 (7.14)	78.83 (6.89)	84.87 (4.28)	75.25 (9.11)
		Wk8	78.71 (9.59)	74.07 (10.32)	77.12 (15.02)	75.11 (8.40)	75.67 (12.10)	70.87 (10.51)
		CFB	-3.09 (7.82)	-5.25 (9.78)	-2.41 (13.79)	-4.83 (8.08)	-9.20 (10.37)	-3.67 (7.27)
Age (yr)	<65	n	17	6	14	10	15	9
		BL	87.06 (7.30)	84.83 (5.48)	83.29 (5.64)	84.85 (14.74)	87.87 (4.25)	86.39 (5.68)
		Wk8	84.56 (7.83)	79.17 (9.58)	76.54 (7.57)	82.63 (20.67)	80.53 (9.93)	78.33 (9.69)
		CFB	-3.00 (7.04)	-5.67 (5.02)	-6.69 (8.06)	-2.19 (9.98)	-7.33 (9.30)	-8.67 (10.16)
	65-79	n	12	13	15	10	13	17
		BL	78.13 (8.59)	81.81 (7.33)	74.73 (7.97)	81.50 (5.98)	81.42 (6.79)	76.85 (8.73)
		Wk8	76.92 (10.29)	76.18 (7.87)	74.71 (17.26)	77.25 (5.52)	72.54 (8.04)	72.80 (7.89)
		CFB	-1.21 (10.43)	-3.18 (7.91)	-0.46 (14.22)	-5.06 (7.49)	-8.88 (9.23)	-4.37 (7.01)
	≥80	n	1	3	1	3	0	4
		BL	83.50 (NE)	73.83 (9.17)	80.50 (NE)	77.17 (5.77)		70.50 (10.56)
		Wk8	81.00 (NE)	58.00 (7.07)	71.00 (NE)	93.50 (37.48)		65.75 (11.73)
		CFB	-2.50 (NE)	-21.00 (9.90)	-9.50 (NE)	13.00 (37.48)		-4.75 (8.03)
Race	Black or AA	n	16	7	7	11	8	15
		BL	85.81 (8.77)	78.93 (5.16)	83.21 (7.11)	84.95 (13.98)	88.13 (3.96)	79.20 (9.98)
		Wk8	83.69 (10.16)	79.14 (8.49)	75.43 (10.05)	85.00 (19.41)	83.25 (8.88)	71.92 (10.83)
		CFB	-2.13 (9.04)	0.21 (7.03)	-7.79 (9.03)	-0.69 (7.56)	-4.88 (8.84)	-7.38 (7.65)
	Other	n	14	15	23	12	20	15
		BL	80.57 (8.17)	82.77 (8.36)	77.61 (7.87)	80.04 (6.05)	83.58 (6.76)	78.53 (9.54)
		Wk8	78.31 (7.80)	72.92 (10.54)	75.43 (14.14)	78.60 (15.76)	74.25 (9.14)	74.00 (8.26)
		CFB	-2.38 (7.82)	-9.38 (7.89)	-2.31 (12.36)	-2.65 (17.00)	-9.33 (9.15)	-3.69 (7.91)
BMI (kg/m ²)	<25	n	1	2	4	3	1	5
		BL	89.00 (NE)	74.75 (15.91)	77.50 (3.56)	74.17 (3.51)	85.50 (NE)	81.00 (10.52)
		Wk8	83.00 (NE)	92.00 (NE)	69.25 (9.50)	73.00 (NE)	61.00 (NE)	78.33 (19.14)
		CFB	-6.00 (NE)	6.00 (NE)	-8.25 (7.63)	-1.50 (NE)	-24.50 (NE)	-0.67 (7.01)
	25-30	n	13	4	10	8	11	10
		BL	80.38 (8.06)	79.75 (3.88)	76.85 (10.34)	82.00 (5.76)	84.77 (7.28)	79.70 (11.37)
		Wk8	77.77 (10.02)	71.75 (9.07)	78.89 (20.58)	76.00 (6.22)	80.27 (6.29)	72.67 (9.33)
		CFB	-2.62 (9.24)	-8.00 (7.56)	1.11 (16.18)	-4.64 (7.81)	-4.50 (8.75)	-6.50 (7.61)
	>30	n	16	16	15	12	15	14
		BL	85.44 (9.06)	82.84 (7.20)	80.33 (7.20)	84.71 (13.38)	85.73 (5.35)	77.96 (8.69)
		Wk8	84.20 (8.41)	75.00 (9.80)	75.00 (6.97)	86.10 (21.92)	76.07 (11.02)	71.42 (7.10)
		CFB	-1.67 (8.09)	-6.07 (9.01)	-5.33 (8.88)	0.20 (16.85)	-9.67 (8.59)	-6.88 (7.81)
Seated SBP Tertile	Low	n	10	5	11	8	12	10
		BL	81.30 (7.04)	77.30 (8.82)	77.64 (9.33)	83.31 (4.92)	83.50 (8.31)	75.95 (9.36)
		Wk8	78.11 (9.06)	78.50 (9.88)	72.40 (9.55)	78.50 (7.48)	81.08 (9.65)	73.86 (11.01)
		CFB	-3.44 (7.02)	-2.25 (7.56)	-6.15 (8.84)	-4.17 (6.69)	-2.42 (8.22)	-0.29 (6.44)
	Middle	n	12	10	11	4	8	9
		BL	85.04 (10.15)	83.50 (7.71)	78.18 (8.42)	76.25 (5.81)	84.63 (4.07)	79.39 (8.71)
		Wk8	84.67 (8.33)	73.88 (9.48)	79.09 (17.89)	79.00 (5.57)	74.00 (10.06)	73.22 (5.97)
		CFB	-0.38 (7.76)	-6.69 (10.60)	0.91 (15.57)	0.83 (5.62)	-10.63 (7.25)	-6.17 (6.64)
	High	n	8	7	8	11	8	11
		BL	83.44 (9.03)	81.79 (6.23)	81.69 (4.91)	83.95 (14.28)	87.19 (4.67)	81.09 (10.64)
		Wk8	79.75 (10.82)	74.86 (11.87)	74.00 (7.39)	84.22 (23.90)	73.25 (8.33)	72.11 (11.78)
		CFB	-3.69 (10.91)	-6.93 (7.79)	-7.36 (5.62)	-1.06 (18.28)	-13.94 (7.82)	-8.78 (8.56)

Category	Sub-group	Visit	Placebo (N=30)	12.5 mg BID (N=22)	25 mg BID (N=30)	12.5 mg QD (N=23)	50 mg QD (N=28)	100 mg QD (N=30)
AHTs	2	n	17	7	14	14	20	14
		BL	84.53 (5.44)	86.00 (5.78)	81.61 (5.93)	84.32 (12.72)	83.43 (6.54)	82.61 (7.68)
		Wk8	81.31 (9.05)	79.67 (11.78)	79.31 (15.91)	80.80 (18.35)	76.40 (10.12)	74.09 (4.66)
		CFB	-3.56 (8.99)	-5.25 (7.78)	-2.12 (15.46)	-4.60 (10.04)	-7.03 (9.50)	-8.09 (8.81)
	≥3	n	13	15	16	9	8	16
		BL	81.85 (11.90)	79.47 (7.58)	76.56 (8.90)	79.39 (5.69)	88.50 (4.38)	75.59 (10.12)
		Wk8	81.23 (10.24)	73.15 (8.93)	72.07 (9.26)	82.25 (16.96)	77.88 (9.58)	72.14 (12.08)
		CFB	-0.62 (7.57)	-6.12 (9.49)	-5.03 (7.45)	1.75 (16.61)	-10.63 (8.12)	-3.39 (6.60)
ACEi/ ARBs	Yes	n	22	17	27	18	20	23
		BL	83.57 (9.59)	82.91 (7.06)	78.91 (8.00)	83.39 (11.47)	85.55 (6.70)	77.74 (8.97)
		Wk8	81.32 (10.11)	74.93 (9.86)	76.24 (13.40)	83.79 (17.89)	76.05 (8.09)	73.40 (9.37)
		CFB	-2.25 (8.51)	-6.33 (9.02)	-2.88 (11.56)	-0.71 (13.94)	-9.50 (8.30)	-4.58 (8.10)
	No	n	8	5	3	5	8	7
		BL	82.81 (6.46)	76.90 (8.23)	79.00 (9.18)	78.80 (6.64)	83.19 (5.47)	82.57 (11.38)
		Wk8	81.14 (7.54)	76.25 (12.37)	68.67 (8.33)	73.25 (13.50)	78.75 (13.72)	71.40 (10.62)
		CFB	-2.21 (8.58)	-4.00 (8.79)	-10.33 (13.25)	-5.50 (11.85)	-4.44 (10.67)	-9.00 (6.21)

[0247] Abbreviations: AA, African American; ARB, angiotensin receptor blocker; ACEi, angiotensin converting enzyme inhibitor; AHT, antihypertensive; BID, twice daily; BL, baseline; BMI, body mass index; CFB change from baseline; kg, kilogram; m, meters; QD, once daily; SBP, systolic blood pressure; SD, standard deviation; Wk8, Week 8; yr, years.

Table 33: Mean (SD) Change from Baseline at Week 8 in Automated Office-Measured Diastolic Blood Pressure, by Subgroup, Part 2 (Full Analysis Set)

Category	Sub-group	Visit	Placebo (N=6)	100 mg QD (N=31)
Sex	Male	n	2	10
		BL	80.75 (7.42)	79.50 (8.18)
		Wk8	74.50 (17.68)	75.00 (6.85)
		CFB	-6.25 (10.25)	-4.50 (9.14)
	Female	n	4	21
		BL	77.00 (8.44)	77.36 (7.48)
		Wk8	77.00 (9.70)	70.75 (8.89)
		CFB	0.00 (7.71)	-6.28 (11.69)
Age (yr)	<65	n	4	8
		BL	82.38 (2.75)	82.88 (4.92)
		Wk8	82.25 (7.09)	72.50 (10.73)
		CFB	-0.13 (7.69)	-10.38 (12.61)
	65-79	n	2	22
		BL	70.00 (7.78)	76.57 (7.90)
		Wk8	64.00 (2.83)	72.38 (7.70)
		CFB	-6.00 (10.61)	-3.83 (10.02)
	≥80	n	0	1
		BL		72.00 (NE)
		Wk8		65.00 (NE)
		CFB		-7.00 (NE)
Race	Black or AA	n	2	6
		BL	80.25 (0.35)	76.67 (7.74)
		Wk8	85.00 (2.83)	72.00 (10.79)
		CFB	4.75 (3.18)	-4.67 (11.45)
	Other	n	4	25
		BL	77.25 (9.58)	78.38 (7.74)
BMI (kg /m ²)	<25	n	1	2
		BL	83.00 (NE)	78.25 (12.37)
		Wk8	72.00 (NE)	77.00 (14.14)
		CFB	-11.00 (NE)	-1.25 (1.77)
	25-30	n	0	15
		BL		76.50 (7.14)
		Wk8		70.40 (10.22)
		CFB		-6.10 (12.04)
	>30	n	5	14
		BL	77.30 (8.07)	79.68 (7.90)
		Wk8	77.00 (12.06)	73.46 (4.70)
		CFB	-0.30 (7.75)	-5.88 (10.38)

Category	Sub-group	Visit	Placebo (N=6)	100 mg QD (N=31)
Seated SBP Tertile	Low	n	4	10
		BL	75.88 (8.20)	79.60 (6.56)
		Wk8	70.75 (9.14)	72.33 (10.76)
		CFB	-5.13 (8.30)	-6.78 (13.35)
	Middle	n	1	10
		BL	86.00 (NE)	78.50 (7.42)
		Wk8	87.00 (NE)	72.10 (4.41)
		CFB	1.00 (NE)	-6.40 (9.59)
	High	n	1	11
		BL	80.00 (NE)	76.23 (8.99)
		Wk8	87.00 (NE)	72.09 (9.71)
		CFB	7.00 (NE)	-4.14 (10.37)
AHTs	2	n	4	20
		BL	75.88 (8.20)	78.10 (7.16)
		Wk8	70.75 (9.14)	71.58 (9.17)
		CFB	-5.13 (8.30)	-6.21 (10.33)
	≥3	n	2	11
		BL	83.00 (4.24)	77.95 (8.82)
		Wk8	87.00 (0.00)	73.18 (7.17)
		CFB	4.00 (4.24)	-4.77 (11.98)
ACEi/ ARBs	Yes	n	5	30
		BL	77.80 (8.39)	77.75 (7.59)
		Wk8	74.80 (11.69)	71.66 (8.05)
		CFB	-3.00 (8.81)	-5.88 (10.92)
	No	n	1	1
		BL	80.50 (NE)	87.00 (NE)
		Wk8	83.00 (NE)	87.00 (NE)
		CFB	2.50 (NE)	0.00 (NE)
PRA	1-5 ng/mL/ hr	n	5	14
		BL	78.80 (8.34)	74.07 (5.74)
		Wk8	79.00 (9.51)	71.93 (6.65)
		CFB	0.20 (6.70)	-2.14 (8.23)
	>5 ng/mL/ hr	n	1	8
		BL	75.50 (NE)	83.19 (5.06)
		Wk8	62.00 (NE)	71.29 (11.40)
		CFB	-13.50 (NE)	-11.79 (12.93)

[0248] Abbreviations: AA, African American; ARB, angiotensin receptor blocker; ACEi, angiotensin converting enzyme inhibitor; AHT, antihypertensive; BL, baseline; BMI, body mass index; CFB change from baseline; hr, hour; kg, kilogram; m, meters; mL, milliliter; ng, nanograms; PRA, plasma renin activity; QD, once daily; SBP, systolic blood pressure; SD, standard deviation; Wk8, Week 8; yr, years.

[0249] A modest increase in the AHT effect of lorundrostat was apparent with concomitant use of thiazide diuretics in Part 1 (Table 34), but this was not present in Part 2 (Table 35). In Part 1, a statistically significant placebo-adjusted reduction in AOBP DBP was achieved at Week 8 in

patients with thiazide diuretic use at baseline for the 50 mg QD cohort (-7.7 mmHg, $p=0.0291$), but not for any of the dose cohorts in patients not on thiazide diuretics at baseline.

Table 34: Mean (SD) Change from Baseline at Week 8 in Automated Office-Measured Diastolic Blood Pressure, by Thiazide Diuretic Use at Baseline, Part 1 (Full Analysis Set)

Sub-group	Visit	Placebo (N=30)	12.5 mg BID (N=22)	25 mg BID (N=30)	12.5 mg QD (N=23)	50 mg QD (N=28)	100 mg QD (N=30)
Yes	n	16	13	18	12	16	17
	BL	82.31 (10.80)	78.73 (5.57)	78.56 (8.71)	78.92 (5.86)	86.50 (4.60)	80.50 (9.51)
	Week 8	80.69 (9.82)	72.67 (9.15)	76.12 (15.60)	74.78 (8.58)	75.94 (11.89)	73.40 (8.98)
	CFB	-1.63 (8.57)	-7.33 (8.79)	-2.12 (13.83)	-5.11 (6.26)	-10.56 (9.49)	-6.43 (8.79)
No	n	14	9	12	11	12	13
	BL	84.57 (5.81)	85.61 (8.54)	79.46 (6.99)	86.18 (13.47)	82.71 (7.86)	76.73 (9.65)
	Week 8	82.00 (9.25)	79.57 (10.75)	74.36 (8.31)	88.11 (21.40)	78.00 (6.42)	72.40 (10.54)
	CFB	-3.00 (8.39)	-3.29 (8.80)	-6.09 (7.34)	1.56 (17.70)	-4.71 (7.77)	-4.00 (6.33)

Table 35: Mean (SD) Change from Baseline at Week 8 in Automated Office-Measured Diastolic Blood Pressure, by Thiazide Diuretic Use at Baseline, Part 2 (Full Analysis Set)

Sub-group	Visit	Placebo (N=6)	100 mg QD (N=31)
Yes	n	5	19
	BL	78.80 (8.34)	79.00 (7.73)
	Week 8	79.00 (9.51)	74.67 (7.39)
	CFB	0.20 (6.70)	-4.06 (10.70)
No	n	1	12
	BL	75.50 (NE)	76.54 (7.58)
	Week 8	62.00 (NE)	68.42 (8.71)
	CFB	-13.50 (NE)	-8.13 (10.89)

Pharmacokinetic Response

[0250] Systemic exposure to lorundrostat, expressed as C_{max} or AUC increased with increasing dose, although there was moderately high inter-subject variability. For the dose of 100 mg QD in Cohort 1 and Cohort 2, steady-state (Day 28) C_{max} was 1620 ng/mL and 1360 ng/mL, respectively (mean approximately 1490 ng/mL) and AUC_{0-24} was 14900 ng*h/mL and 7480 ng*h/mL, respectively (mean approximately 11190 ng*h/mL). Other key parameters are summarized in Table 36. Values of trough plasma concentrations are shown in Table 37.

Table 36: Summary of Key Steady-State Pharmacokinetic Parameters Following Administration of Lorundrostat

Parameter (Unit)	Statistics (Day 28)	12.5 mg BID (N=22)	25 mg BID (N=30)	12.5 mg QD (N=23)	50 mg QD (N=28)	100 mg QD Part 1 (N=30)	100 mg QD Part 2 (N=31)
AUC_{0-24} (hr*ng/mL)	n (missing)	3 (19)	7 (23)	5 (18)	3 (25)	4 (26)	11 (20)
	Mean (SD)	992 (398)	1760 (774)	1020 (1090)	3390 (1260)	14900 (11200)	7480 (3070)
	%CV	40.1	43.9	107	37.3	75.3	41.1

	Geo Mean	940	1640	726	3230	10400	6920
	Geo CV (%)	42.1	41.8	102	40.3	164	44.5
	Median	922	1670	498	3320	15000	7090
	Min ; Max	634 ; 1420	931 ; 3330	397 ; 2940	2160 ; 4680	2140 ; 27600	2870 ; 14700
C _{max} (ng/mL)	n (missing)	7 (15)	16 (14)	9 (14)	6 (22)	8 (22)	17 (14)
	Mean (SD)	142 (28.3)	361 (175)	153 (129)	518 (223)	1620 (867)	1360 (913)
	%CV	19.8	48.6	84.6	43.1	53.5	67.2
	Geo Mean	140	325	120	477	1370	1000
	Geo CV (%)	21	50.9	78.2	47.8	78.9	124
	Median	137	335	94.9	488	1590	1250
	Min ; Max	99.8 ; 176	112 ; 862	56.1 ; 459	266 ; 790	331 ; 2890	66.7 ; 3260
T _{max} (hr)	n (missing)	7 (15)	16 (14)	9 (14)	6 (22)	8 (22)	17 (14)
	Median	2	2	1.08	2.01	1.02	1
	Min ; Max	1.00 ; 3.00	1.00 ; 4.02	1.00 ; 3.00	1.00 ; 4.05	1.00 ; 2.08	1.00 ; 4.00

[0251] Abbreviations: AUC, area under the curve; BID, twice daily; CV, coefficient of variation; geo, geometric; hr, hours; mg, milligrams; mL, milliliters; N, number of subjects; n, number of observations; ng, nanograms; QD, once daily.

Table 37: Summary of Trough Plasma Concentrations (ng/mL) Following Administration of Lorundrostat

Visit	Statistic	12.5 mg BID (N=22)	25 mg BID (N=30)	12.5 mg QD (N=23)	50 mg QD (N=28)	100 mg QD Part 1 (N=30)	100 mg QD Part 2 (N=31)
Day 7	n (missing)	20 (2)	27 (3)	22 (1)	26 (2)	23 (7)	30 (1)
	Mean (SD)	52.3 (83.3)	94.2 (137)	11.6 (18.2)	93.1 (216)	299 (571)	151 (346)
	%CV	159	146	156	233	191	228
	Geo Mean	20.4	49.6	6.55	16.6	53.4	35.1
	Geo CV (%)	573	364	306	2680	2080	625
	Median	26.1	52	5.52	12.1	28.2	29.8
	Min ; Max	0.00 ; 366	0.00 ; 603	0.00 ; 61.2	0.00 ; 909	0.00 ; 2060	0.00 ; 1370
Day 28	n (missing)	16 (6)	23 (7)	17 (6)	22 (6)	22 (8)	23 (8)
	Mean (SD)	33.4 (37.5)	109 (161)	7.91 (10.9)	87.4 (184)	303 (603)	26.4 (29.2)
	%CV	112	148	138	210	199	110
	Geo Mean	10.7	62.1	5.77	46.8	50.7	12.9
	Geo CV (%)	1300	310	297	219	3510	377
	Median	27.3	56.3	4.1	20.9	38.6	19.9
	Min ; Max	0.143 ; 150	0.00 ; 787	0.00 ; 37.9	0.00 ; 675	0.00 ; 1980	0.00 ; 127
Day 56	n (missing)	13 (9)	21 (9)	12 (11)	25 (3)	19 (11)	26 (5)
	Mean (SD)	40.4 (58.9)	104 (167)	39.9 (61.3)	155 (314)	258 (487)	23.2 (24.6)
	%CV	146	160	154	203	189	106
	Geometric Mean	18.5	46	22.1	38.1	72.1	20.3
	Geometric CV (%)	732	447	540	698	1060	178
	Median	21.6	32.3	7.6	18	30.4	20
	Min ; Max	0.00 ; 201	0.00 ; 720	0.00 ; 186	0.00 ; 1290	0.00 ; 1900	0.00 ; 110

[0252] Concentrations are in units of ng/mL. Abbreviations: BID, twice daily; CV, coefficient of variation; geo, geometric; mg, milligrams; mL, milliliters; N, number of subjects; n, number of observations; ng, nanograms; QD, once daily.

Pharmacodynamic Response

[0253] At baseline in Part 1, active arm mean serum cortisol levels ranged between 9.443 µg/dL and 11.272 µg/dL, compared with 10.507 µg/dL for placebo (Table 38). No consistent substantial changes in serum cortisol levels were observed over the course of treatment and follow-up relative to baseline values with percent change from baseline values of 3.8% to 19.2% (active) vs -0.8% (placebo) at Week 4, 20.6% to 51.4% (active) vs 37.7% (placebo) at Week 8, and -1.2% to 22.7% (active) vs 17.1% (placebo) at Week 12. A similar pattern was observed in Part 2, with active arm serum cortisol baseline levels of 11.118 µg/dL in the 100 mg QD dose group and no substantial changes observed over the course of treatment and subsequent follow-up. Percent change from baseline was 20.1% at Week 4, 153.4% at Week 8, and 1.5% at Week 12 (Table 39).

[0254] Transient increases in 11-deoxycorticosterone and 11-deoxycortisol were seen in Part 1 in the active treatment arms at Week 4 compared with placebo, albeit with large variation within each individual dose cohort. Values returned to a similar range as placebo at Week 12 (Table 38). In Part 2, 11-deoxycorticosterone and 11-deoxycortisol were similar to baseline in subjects treated with lorundrostat 100 mg QD at Week 4 and Week 10 (Table 39).

[0255] In Part 1, aldosterone levels generally decreased at Week 4 relative to baseline in lorundrostat-treated subjects (-40.1% to 7.4%) compared with those who received placebo (3.6%), and remained lower relative to placebo at Week 12 (-26.6% to 15.9% vs 38.1%, respectively; Table 38). In Part 2, aldosterone levels remained consistent although lower than baseline through Week 4 and Week 10 in subjects receiving lorundrostat. (Table 39).

[0256] Renin activity, expressed as a percent change from baseline, increased in all subjects treated with lorundrostat, irrespective of dose and baseline PRA values, reaching highest levels at Week 4 and remaining elevated compared with baseline at Week 12 (Part 1) and Week 10 (Part 2) (Table 38 and Table 39, respectively). Placebo values in Part 1 remained relatively consistent with baseline.

Table 38: Mean (SD) Observed and Mean (SD) Percent Change from Baseline in Pharmacodynamic Parameters, Part 1 (PK/PD Analysis Set)

Parameter	Visit	Placebo (N=30)	12.5 mg BID (N=22)	25 mg BID (N=30)	12.5 mg QD (N=23)	50 mg QD (N=28)	100 mg QD (N=30)
Cortisol (µg/dL)	BL	10.507 (3.444)	10.195 (2.979)	10.577 (2.506)	9.443 (4.111)	10.807 (2.733)	11.272 (3.548)
	Wk4	10.248 (3.673)	10.895 (3.859)	12.311 (5.180)	9.305 (4.164)	10.875 (3.368)	11.842 (4.350)
	%CFB	-0.81 (31.53)	10.26 (45.03)	19.20 (49.39)	7.47 (37.82)	3.83 (32.48)	3.91 (32.33)
	Wk 8	14.190 (8.589)	12.316 (7.649)	15.525 (8.258)	12.511 (8.784)	15.650 (7.102)	16.680 (9.083)
	%CFB	37.72 (89.31)	20.56 (73.01)	49.57 (77.17)	41.84 (90.37)	51.35 (78.86)	47.29 (92.65)
	Wk12	11.800 (4.620)	9.978 (2.742)	12.559 (4.287)	9.317 (3.294)	11.262 (3.590)	12.680 (5.659)
	%CFB	17.13 (39.18)	-1.22 (21.10)	22.65 (41.94)	18.06 (48.59)	6.91 (35.36)	8.40 (30.09)
11-Deoxy cortico- sterone (ng/dL)	BL	8.1 (0.7)	8.0 (0.0)	8.0 (0.0)	8.3 (1.5)	8.3 (1.2)	8.4 (2.0)
	Wk4	8.0 (0.0)	9.0 (3.0)	13.7 (13.9)	11.1 (5.5)	8.0 (0.0)	9.5 (5.2)
	%CFB	-1.15 (6.18)	12.50 (37.50)	71.63 (173.69)	31.41 (60.95)	-2.66 (9.61)	16.18 (66.37)
	Wk12	8.0 (0.0)	8.0 (0.0)	8.0 (0.0)	9.2 (4.9)	8.5 (2.4)	8.4 (2.0)
11-Deoxy cortisol (ng/dL)	BL	26.24 (16.08)	28.36 (17.85)	25.87 (11.45)	29.07 (26.29)	31.14 (20.96)	29.97 (20.53)
	Wk4	28.41 (28.72)	24.89 (18.99)	35.23 (33.00)	24.21 (19.92)	27.15 (13.97)	29.29 (23.99)
	%CFB	-0.23 (48.42)	22.56 (118.56)	40.12 (118.32)	10.07 (76.22)	10.80 (61.95)	9.43 (60.26)
	Wk12	31.03 (18.04)	20.94 (10.27)	31.55 (26.82)	31.56 (29.77)	26.15 (18.89)	31.17 (25.98)
Aldo- sterone (ng/dL)	BL	6.475 (3.419)	6.636 (3.357)	6.558 (4.454)	7.065 (3.728)	6.205 (3.777)	6.533 (3.298)
	Wk4	6.768 (4.779)	4.447 (3.681)	3.192 (3.274)	6.132 (4.606)	3.923 (5.283)	4.000 (4.252)
	%CFB	3.58 (52.63)	-37.86 (35.66)	1.66 (233.60)	7.39 (91.87)	-40.06 (70.25)	-32.18 (75.13)
	Wk12	7.914 (5.943)	6.765 (4.085)	4.983 (3.432)	6.833 (4.743)	5.385 (4.087)	4.563 (2.868)
Renin Activity (µg/L/hr)	BL	0.536 (0.437)	1.299 (1.898)	1.104 (2.239)	0.950 (1.067)	1.258 (3.008)	0.956 (2.120)
	Wk4	0.687 (0.973)	5.989 (11.272)	2.860 (4.219)	1.804 (3.565)	3.940 (9.162)	3.870 (6.308)
	%CFB	24.53 (87.34)	838.89 (2411.4)	344.07 (480.75)	85.09 (291.65)	359.69 (888.86)	489.18 (974.60)
	Wk12	0.615 (1.033)	5.118 (11.751)	2.898 (8.323)	2.429 (5.048)	3.374 (7.008)	1.653 (2.830)
Renin Activity (µg/L/hr)	BL	0.536 (0.437)	1.299 (1.898)	1.104 (2.239)	0.950 (1.067)	1.258 (3.008)	0.956 (2.120)
	Wk4	0.687 (0.973)	5.989 (11.272)	2.860 (4.219)	1.804 (3.565)	3.940 (9.162)	3.870 (6.308)
	%CFB	24.53 (87.34)	838.89 (2411.4)	344.07 (480.75)	85.09 (291.65)	359.69 (888.86)	489.18 (974.60)
	Wk12	0.615 (1.033)	5.118 (11.751)	2.898 (8.323)	2.429 (5.048)	3.374 (7.008)	1.653 (2.830)

Table 39: Mean Observed (SD) and Mean (SD) Percent Change from Baseline in Pharmacodynamic Parameters, Part 2 (PK/PD Analysis Set)

Parameter	Visit	Placebo (N=6)	100 mg QD (N=31)
Cortisol (ug/dL)	BL	10.508 (2.655)	11.118 (3.465)
	Wk 4	12.217 (3.898)	13.464 (5.061)
	%CFB	20.42 (39.75)	20.10 (37.25)
	Wk 8	28.050 (5.400)	25.393 (6.743)
	%CFB	190.53 (122.33)	153.35 (106.59)
	Wk 10	11.917 (2.934)	10.763 (4.677)
	%CFB	14.93 (16.92)	1.45 (37.30)
11-Deoxycortico- sterone (ng/dL)	BL	8.00 (0.00)	10.71 (8.25)
	Wk 4	9.33 (3.27)	10.28 (4.28)
	%CFB	16.67 (40.82)	6.02 (40.58)
	Wk 10	8.00 (0.00)	8.00 (0.00)
	%CFB	0.00 (0.00)	-8.78 (23.71)
11-Deoxycortisol (ng/dL)	BL	14.17 (6.82)	40.79 (55.80)
	Wk 4	21.83 (14.92)	35.96 (29.50)
	%CFB	65.30 (110.59)	22.95 (81.16)
	Wk 10	16.17 (10.96)	27.60 (25.66)
	%CFB	22.20 (62.92)	-2.13 (71.17)
Aldosterone (ng/dL)	BL	5.917 (1.800)	6.435 (3.397)
	Wk 4	6.000 (3.225)	5.060 (4.835)
	%CFB	11.78 (77.75)	-6.05 (93.64)
	Wk 10	5.667 (2.875)	4.929 (3.319)
	%CFB	1.35 (56.01)	-4.06 (74.89)
Renin Activity (ug/L/hr)	BL	5.531 (8.663)	5.417 (7.052)
	Wk 4	4.097 (2.492)	12.642 (12.078)
	%CFB	44.08 (77.01)	811.54 (2089.82)
	Wk 10	5.628 (8.593)	7.602 (7.419)
	%CFB	9.73 (63.97)	192.62 (376.08)

[0257] Subjects dosed with lorundrostat in Part 1, irrespective of dose, exhibited greater declines in eGFR relative to placebo as early as 1 week after the initiation of treatment that persisted at a consistent level until Week 8 (Table 40). The greatest reductions relative to baseline were seen in the 100 mg QD dose group, reaching a mean maximum decline of 10.91 mL/min/1.73m² at Week 2 (range: -6.80 mL/min/1.73m² to -10.91 mL/min/1.73m² over 8 weeks of treatment). In contrast, mean eGFR for the Placebo group was relatively stable throughout treatment, reaching a mean maximal reduction of -2.80 mL/min/1.73m² at Week 2 (range: -0.83 mL/min/1.73m² to -2.80 mL/min/1.73m²). Estimated glomerular filtration rate was estimated using the CKD-EPI equation.

[0258] Similar trends were seen with mean eGFR for the 100 mg QD treatment group in Part 2, with a rapid initial decline following a lesser reduction persisting out to Week 8 (Table 41).

Table 40: Mean (SD) Observed and Mean (SD) Change from Baseline in Estimated Glomerular Filtration Rate (mL/min/1.73m²), Part 1 (Safety Analysis Set)

Visit	Placebo (N=30)	12.5 mg BID (N=22)	25 mg BID (N=30)	12.5 mg QD (N=23)	50 mg QD (N=28)	100 mg QD (N=30)
BL	81.63 (17.31)	81.70 (16.28)	80.85 (12.37)	77.87 (18.69)	77.18 (14.05)	77.35 (13.95)
Week 1	80.80 (16.35)	79.45 (15.19)	74.00 (13.13)	73.57 (20.33)	74.21 (16.88)	70.81 (17.66)
CFB	-0.83 (7.62)	-2.25 (8.42)	-6.85 (8.88)	-4.30 (7.14)	-2.96 (8.52)	-6.80 (10.03)
Week 2	79.61 (16.07)	78.86 (18.56)	75.43 (15.32)	73.00 (20.81)	72.86 (16.55)	65.56 (17.66)
CFB	-2.80 (10.11)	-3.69 (6.46)	-5.42 (10.01)	-4.87 (5.03)	-4.32 (9.06)	-10.91 (8.57)
Week 3	79.79 (17.85)	77.38 (16.68)	75.07 (11.95)	77.21 (20.38)	74.81 (15.62)	67.22 (19.24)
CFB	-1.34 (6.34)	-5.17 (8.54)	-5.90 (8.63)	-2.05 (6.43)	-2.35 (8.51)	-9.24 (10.99)
Week 4	79.43 (18.62)	76.30 (18.28)	73.48 (15.26)	73.40 (19.29)	73.63 (16.75)	67.23 (19.70)
CFB	-2.79 (5.94)	-6.58 (9.17)	-6.69 (8.97)	-5.45 (6.37)	-3.61 (9.24)	-9.46 (12.53)
Week 5	80.55 (17.44)	73.84 (20.78)	73.25 (14.75)	75.25 (19.58)	70.58 (13.23)	66.19 (19.58)
CFB	-2.33 (7.69)	-7.58 (8.00)	-7.41 (9.65)	-3.60 (5.70)	-4.10 (9.61)	-10.50 (10.94)
Week 6	81.70 (16.92)	74.70 (16.86)	72.64 (15.33)	73.39 (20.48)	74.63 (16.59)	66.19 (21.44)
CFB	-1.72 (6.75)	-6.45 (8.05)	-8.02 (9.17)	-6.28 (6.77)	-2.83 (8.61)	-9.94 (12.91)
Week 7	81.75 (17.43)	75.85 (21.29)	72.22 (13.89)	72.50 (22.45)	69.68 (12.23)	66.96 (21.02)
CFB	-1.77 (7.67)	-7.03 (8.98)	-7.85 (9.47)	-7.17 (8.80)	-5.46 (10.42)	-9.50 (12.17)
Week 8	83.83 (17.32)	76.32 (19.63)	75.11 (14.81)	76.00 (21.00)	72.54 (16.89)	68.42 (20.14)
CFB	0.95 (7.06)	-6.66 (7.92)	-5.55 (9.22)	-3.67 (8.10)	-4.64 (9.87)	-7.83 (11.62)

Table 41: Mean (SD) Observed and Mean (SD) Change from Baseline in Estimated Glomerular Filtration Rate (mL/min/1.73m²), Part 2 (Safety Analysis Set)

Visit	Placebo (N=6)	100 mg QD (N=31)
BL	83.92 (18.59)	79.90 (13.10)
Week 1	78.67 (22.40)	70.73 (20.11)
CFB	-5.25 (4.78)	-9.65 (10.96)
Week 2	81.17 (17.78)	72.07 (17.16)
CFB	-2.75 (5.24)	-8.05 (6.72)
Week 3	78.17 (14.74)	72.69 (16.83)
CFB	-5.75 (7.83)	-7.33 (8.39)
Week 4	82.83 (11.30)	72.92 (15.44)
CFB	-1.08 (8.55)	-7.20 (7.02)
Week 5	84.00 (17.92)	71.23 (18.13)
CFB	0.08 (8.23)	-8.69 (10.16)
Week 6	74.80 (12.68)	68.04 (15.17)
CFB	-2.90 (2.68)	-10.87 (8.39)
Week 7	80.17 (17.14)	72.82 (13.35)
CFB	-3.75 (3.39)	-7.34 (9.07)
Week 8	79.83 (15.78)	72.43 (16.32)
CFB	-4.08 (3.94)	-7.95 (9.13)

Safety

[0259] At least one on-treatment TEAE was reported by 83 subjects in Part 1 (73 [54.9%] treated with lorundrostat and 10 [33.3%] treated with placebo) and by 20 subjects in Part 2 (19 [61.3%] treated with lorundrostat and 1 [16.7%] treated with placebo). Of these subjects, 30 (27 [20.3%] treated with active drug and 3 [10%] treated with placebo) from Part 1 and 9 (29.0% with lorundrostat only) from Part 2 experienced TEAEs that were considered at least possibly related to study drug.

[0260] Two (1.5%) subjects in Part 1 and one (3.2%) subject in Part 2 reported an SAE, one of which (a worsening of pre-existing hyponatremia) was considered possibly related to study drug. All events occurred in lorundrostat treated subjects.

[0261] Thirty-six subjects in Part 1 (35 [26.3%] treated with lorundrostat and 1 (3.3) treated with placebo) and four (12.9%) subjects treated with active drug in Part 2 reported at least one AESI.

[0262] Ten subjects in Part 1 and two subjects in Part 2, all in active treatment cohorts, experienced a TEAE that resulted in permanent discontinuation of study drug and 24 in Part 1 and 7 in Part 2 experienced a TEAE that resulted in dose modification.

[0263] No deaths were reported in either Part 1 or Part 2.

[0264] The most frequently reported events by PT were hyperkalemia (1 [3.3%] subject in the Part 1 Placebo cohort, 31 [23.3%] subjects in the Part 1 active treatment cohorts, and 8 [25.8%] subjects in the Part 2 100 mg QD cohort), eGFR decreased (1 [3.3%] subject in the Part 1 Placebo cohort, and 9 [6.8%] subjects in the Part 1 active treatment cohorts), and urinary tract infection (7 [5.3%] subjects in Part 1 active treatment cohorts, and 2 [6.5%] subjects in Part 2 100 mg QD cohort). Muscle spasms were reported by 3 (9.7%) subjects in the Part 2 100 mg QD cohort.

[0265] There was no apparent association between dose of study drug and frequency of on-treatment TEAEs, on-treatment TEAEs of at least moderate severity, or on-treatment TEAEs considered at least possible related to study drug by the Investigator.

[0266] Serum potassium levels and serum creatinine levels increased in the active treatment cohorts compared with placebo in both Parts 1 and 2 while serum sodium levels decreased. These changes are consistent with the mechanism of action of lorundrostat.

[0267] Seven subjects experienced transient elevated serum potassium (greater than 6.0 mmol/L), none of which were considered an SAE, and all rapidly resolved after intervention (study drug discontinuation or dose adjustment).

[0268] There were no notable findings in terms of vital signs, physical examination, or ECG parameters.

Treatment-emergent Adverse Events (TEAEs)

[0269] Overall, 28 subjects in Part 1 experienced on-treatment TEAEs of moderate intensity (3 [10.0%] subjects in the placebo cohort and 25 [18.8%] subjects in the active treatment cohorts) and one subject (0.8%) in the 12.5 mg QD cohort experienced a severe on-treatment TEAE (Table 42). The only on-treatment TEAEs of moderate severity reported in ≥ 2 subjects in any dose group by PT were hyperkalemia (4 [3.0%] subjects) and hypertension (3 [2.3%] subjects), all of which were reported in subjects in the active treatment cohorts. The one severe on-treatment TEAE was a case of hyperkalemia.

[0270] In Part 2, there were 12 (38.7%) subjects who experienced ≥ 1 moderate on-treatment TEAE, and one (3.2%) subject who experienced ≥ 1 severe on-treatment TEAE, all of whom were in the 100 mg QD cohort (Table 43). The only on-treatment TEAEs of moderate severity reported in ≥ 2 subjects were hyperkalemia (5 [16.1%] subjects) and muscle spasms (2 [6.5%] subjects). The one severe on-treatment TEAE was a case of hyponatremia.

Table 42: Severity of On-Treatment Treatment-Emergent Adverse Events by System Organ Class and Preferred Term Reported by ≥2 Subjects in Any Treatment Group, Part 1 (Safety Analysis Set)

System Organ Class Preferred Term Severity	Placebo (N=30) n (%)	Active (N=133) n (%)	12.5 mg BID (N=22) n (%)	25 mg BID (N=30) n (%)	12.5 mg QD (N=23) n (%)	50 mg QD (N=28) n (%)	100 mg QD (N=30) n (%)
Subjects with any On-treatment TEAEs							
Mild	7 (23.3)	47 (35.3)	8 (36.4)	14 (46.7)	12 (52.2)	4 (14.3)	9 (30.0)
Moderate	3 (10.0)	25 (18.8)	5 (22.7)	4 (13.3)	3 (13.0)	6 (21.4)	7 (23.3)
Severe	0	1 (0.8)	0	0	1 (4.3)	0	0
Blood and lymphatic system disorders							
Mild	0	2 (1.5)	0	2 (6.7)	0	0	0
Cardiac disorders							
Mild	0	2 (1.5)	0	2 (6.7)	0	0	0
Cardiac disorders							
Mild	0	4 (3.0)	1 (4.5)	0	2 (8.7)	1 (3.6)	0
Gastrointestinal disorders							
Mild	2 (6.7)	6 (4.5)	0	1 (3.3)	2 (8.7)	1 (3.6)	2 (6.7)
Mild	1 (3.3)	5 (3.8)	0	1 (3.3)	1 (4.3)	1 (3.6)	2 (6.7)
General disorders and administration site conditions							
Mild	2 (6.7)	5 (3.8)	2 (9.1)	0	1 (4.3)	2 (7.1)	0
Mild	2 (6.7)	2 (1.5)	1 (4.5)	0	0	1 (3.6)	0
Infections and infestations							
Mild	1 (3.3)	11 (8.3)	1 (4.5)	3 (10.0)	3 (13.0)	2 (7.1)	2 (6.7)
Mild	0	5 (3.8)	0	2 (6.7)	3 (13.0)	0	0
Moderate	1 (3.3)	6 (4.5)	1 (4.5)	1 (3.3)	0	2 (7.1)	2 (6.7)
Urinary tract infection	0	7 (5.3)	0	3 (10.0)	1 (4.3)	2 (7.1)	1 (3.3)
Mild	0	4 (3.0)	0	2 (6.7)	1 (4.3)	1 (3.6)	0
Investigations							
Mild	4 (13.3)	21 (15.8)	6 (27.3)	3 (10.0)	3 (13.0)	1 (3.6)	8 (26.7)
Mild	4 (13.3)	17 (12.8)	5 (22.7)	2 (6.7)	3 (13.0)	1 (3.6)	6 (20.0)
Moderate	0	4 (3.0)	1 (4.5)	1 (3.3)	0	0	2 (6.7)
Blood creatinine increased							
Mild	0	3 (2.3)	0	0	0	0	3 (10.0)
Mild	0	3 (2.3)	0	0	0	0	3 (10.0)
Cortisol decreased							
Mild	1 (3.3)	3 (2.3)	2 (9.1)	1 (3.3)	0	0	0
Mild	1 (3.3)	3 (2.3)	2 (9.1)	1 (3.3)	0	0	0
Glomerular filtration rate decreased							
Mild	1 (3.3)	9 (6.8)	3 (13.6)	0	1 (4.3)	0	5 (16.7)
Mild	1 (3.3)	8 (6.0)	3 (13.6)	0	1 (4.3)	0	4 (13.3)
Metabolism and nutrition disorders							
Mild	2 (6.7)	34 (25.6)	5 (22.7)	10 (33.3)	6 (26.1)	5 (17.9)	8 (26.7)
Mild	2 (6.7)	29 (21.8)	4 (18.2)	8 (26.7)	4 (17.4)	5 (17.9)	8 (26.7)
Moderate	0	4 (3.0)	1 (4.5)	2 (6.7)	1 (4.3)	0	0
Hyperkalaemia							
Mild	1 (3.3)	31 (23.3)	5 (22.7)	9 (30.0)	6 (26.1)	3 (10.7)	8 (26.7)
Mild	1 (3.3)	26 (19.5)	4 (18.2)	7 (23.3)	4 (17.4)	3 (10.7)	8 (26.7)
Moderate	0	4 (3.0)	1 (4.5)	2 (6.7)	1 (4.3)	0	0
Severe	0	1 (0.8)	0	0	1 (4.3)	0	0

System Organ Class Preferred Term Severity	Placebo (N=30) n (%)	Active (N=133) n (%)	12.5 mg BID (N=22) n (%)	25 mg BID (N=30) n (%)	12.5 mg QD (N=23) n (%)	50 mg QD (N=28) n (%)	100 mg QD (N=30) n (%)
Nervous system disorders	0	8 (6.0)	1 (4.5)	3 (10.0)	2 (8.7)	2 (7.1)	0
Mild	0	6 (4.5)	1 (4.5)	2 (6.7)	2 (8.7)	1 (3.6)	0
Dizziness	0	3 (2.3)	0	0	1 (4.3)	2 (7.1)	0
Headache	0	3 (2.3)	0	2 (6.7)	0	1 (3.6)	0
Mild	0	3 (2.3)	0	2 (6.7)	0	1 (3.6)	0
Psychiatric disorders	0	3 (2.3)	1 (4.5)	0	0	0	2 (6.7)
Moderate	0	3 (2.3)	1 (4.5)	0	0	0	2 (6.7)
Vascular disorders	1 (3.3)	9 (6.8)	2 (9.1)	1 (3.3)	3 (13.0)	2 (7.1)	1 (3.3)
Mild	1 (3.3)	5 (3.8)	2 (9.1)	1 (3.3)	2 (8.7)	0	0
Moderate	0	4 (3.0)	0	0	1 (4.3)	2 (7.1)	1 (3.3)
Hypertension	0	5 (3.8)	0	1 (3.3)	2 (8.7)	2 (7.1)	0
Moderate	0	3 (2.3)	0	0	1 (4.3)	2 (7.1)	0
Orthostatic hypotension	0	3 (2.3)	1 (4.5)	0	2 (8.7)	0	0
Mild	0	3 (2.3)	1 (4.5)	0	2 (8.7)	0	0

[0271] Adverse events occurring in at least two subjects in any dose group by SOC and/or PT and/or severity are presented. SOC with no PT and/or severity with at least two subjects are presented by SOC only. PTs with no severity with at least two subjects are presented by SOC and PT only.

Table 43: Severity of On-Treatment Treatment-Emergent Adverse Events by System Organ Class and Preferred Term Reported by ≥2 Subjects in Any Treatment Group, Part 1 (Safety Analysis Set)

System Organ Class Preferred Term Severity	Placebo (N=6) n (%)	100 mg QD (N=31) n (%)
Subjects with any On-treatment TEAEs		
Mild	1 (16.7)	6 (19.4)
Moderate	0	12 (38.7)
Severe	0	1 (3.2)
Gastrointestinal disorders	0	5 (16.1)
Mild	0	3 (9.7)
Moderate	0	2 (6.5)
Diarrhoea	0	2 (6.5)
Mild	0	2 (6.5)
Nausea	0	2 (6.5)
Mild	0	2 (6.5)
Infections and infestations	0	5 (16.1)
Mild	0	2 (6.5)
Moderate	0	3 (9.7)
COVID-19	0	2 (6.5)
Urinary tract infection	0	2 (6.5)
Investigations	1 (16.7)	2 (6.5)

System Organ Class Preferred Term Severity	Placebo (N=6) n (%)	100 mg QD (N=31) n (%)
Metabolism and nutrition disorders	1 (16.7)	10 (32.3)
Mild	1 (16.7)	2 (6.5)
Moderate	0	7 (22.6)
Hyperkalaemia	0	8 (25.8)
Mild	0	3 (9.7)
Moderate	0	5 (16.1)
Hyponatraemia	0	2 (6.5)
Musculoskeletal and connective tissue disorders	0	5 (16.1)
Mild	0	2 (6.5)
Moderate	0	3 (9.7)
Muscle spasms	0	3 (9.7)
Moderate	0	2 (6.5)
Nervous system disorders	0	2 (6.5)
Mild	0	2 (6.5)
Dizziness	0	2 (6.5)
Mild	0	2 (6.5)
Renal and urinary disorders	0	2 (6.5)
Mild	0	2 (6.5)
Chronic kidney disease	0	2 (6.5)
Mild	0	2 (6.5)

[0272] Adverse events occurring in at least two subjects in any dose group by SOC and/or PT and/or severity are presented. SOC with no PT and/or severity with at least two subjects are presented by SOC only. PTs with no severity with at least two subjects are presented by SOC and PT only.

[0273] Ten (7.5%) subjects in Part 1, all in active treatment cohorts, experienced on-treatment TEAEs that resulted in permanent discontinuation of study drug (Table 44); hyperkalemia (5 [3.8%] subjects) was the only such event that was reported in ≥ 2 subjects.

[0274] In Part 2, there were 2 (6.5%) subjects who experienced an on-treatment TEAEs that resulted in permanent discontinuation of study drug, both of whom were in the 100 mg QD cohort (). No such events occurred in both subjects.

Table 44: On-Treatment Treatment-Emergent Adverse Events Leading to Permanent Discontinuation from Study Drug by System Organ Class and Preferred Term, Part 1 (Safety Analysis Set)

System Organ Class Preferred Term	Placebo (N=30) n (%)	Active (N=133) n (%)	12.5 mg BID (N=22) n (%)	25 mg BID (N=30) n (%)	12.5 mg QD (N=23) n (%)	50 mg QD (N=28) n (%)	100 mg QD (N=30) n (%)
Subjects with any On-treatment TEAEs leading to withdrawal from study drug	0	10 (7.5)	1 (4.5)	1 (3.3)	4 (17.4)	0	4 (13.3)
Cardiac disorders	0	1 (0.8)	0	0	1 (4.3)	0	0
Coronary artery disease	0	1 (0.8)	0	0	1 (4.3)	0	0
Investigations	0	1 (0.8)	0	0	0	0	1 (3.3)
Activated partial thromboplastin time prolonged	0	1 (0.8)	0	0	0	0	1 (3.3)
Metabolism and nutrition disorders	0	5 (3.8)	0	1 (3.3)	2 (8.7)	0	2 (6.7)
Hyperkalaemia	0	5 (3.8)	0	1 (3.3)	2 (8.7)	0	2 (6.7)
Nervous system disorders	0	1 (0.8)	0	0	1 (4.3)	0	0
Dizziness	0	1 (0.8)	0	0	1 (4.3)	0	0
Vascular disorders	0	3 (2.3)	1 (4.5)	1 (3.3)	0	0	1 (3.3)
Hypertension	0	1 (0.8)	0	1 (3.3)	0	0	0
Hypotension	0	1 (0.8)	0	0	0	0	1 (3.3)
Orthostatic hypotension	0	1 (0.8)	1 (4.5)	0	0	0	0

Table 45: On-Treatment Treatment-Emergent Adverse Events Leading to Permanent Withdrawal from Study Drug by System Organ Class and Preferred Term, Part 2 (Safety Analysis Set)

System Organ Class Preferred Term	Placebo (N=6) n (%)	100 mg QD (N=31) n (%)
Subjects with any On-treatment TEAEs leading to withdrawal from study drug	0	2 (6.5)
Investigations	0	1 (3.2)
Glomerular filtration rate decreased	0	1 (3.2)
Metabolism and nutrition disorders	0	1 (3.2)
Hyponatraemia	0	1 (3.2)
Musculoskeletal and connective tissue disorders	0	1 (3.2)
Muscle spasms	0	1 (3.2)

Change in estimated glomerular filtration rate (eGFR)

[0275] A dose-dependent and reversible reduction in eGFR was observed. This phenomenon has been reported with ACE/ARB and more recently SGLT2 inhibition due to reduced intra-glomerular pressure and felt to attenuate progression of hypertensive nephropathy. A graph showing the change in estimated glomerular filtration rate (eGFR) in different dosing cohorts is provided in **Figure 8**.

Clinical Laboratory Evaluations

[0276] There were no meaningful changes from baseline to Week 8 in bicarbonate, calcium, glucose, magnesium, phosphate, alanine aminotransferase (ALT), aspartate aminotransferase (AST), lactate dehydrogenase (LDH), alanine phosphatase (ALP), total or indirect bilirubin, albumin, protein, urate or urea nitrogen in Part 1 or Part 2. There were no meaningful changes from baseline to Week 8 in hematology and coagulation parameters in Part 1 or Part 2, or in urinalysis and spot/24-hour urine parameters.

Serum potassium

[0277] Serum potassium levels increased in the active treatment cohorts compared with the placebo cohort in both Parts 1 and 2, with the greatest increases seen in the 100 mg QD cohorts in Parts 1 and 2, and the two BID cohorts in Part 1 (**Figure 20**, **Figure 21**, and **Figure 22**).

[0278] Change in group mean serum potassium (K⁺) is summarized in the table below.

Table 46

	Part 1	Part 2	Pooled
Mean (mMol/L)	+0.50	+0.23	+0.35
SD	0.96	0.51	0.75
N	26*	31	57
SEM	0.19	0.09	0.10

[0279] Number of individuals with verified or multiple increased serum potassium above normal range during treatment is shown in the table below.

Table 47

Serum K⁺	Mean Change from Baseline to Wk 8	Mild 5.6-6.0mMol/L	Moderate 6.1-6.5mMol/L	Severe >6.5mMol/L
50 mg QD (n=28)	+0.25 mmol/L	1 (10.7%)	0	1* (3.6%)
100 mg QD (n=61)	+0.29 mmol/L	8 (13.1%)	1 (1.6%)	1 (1.6%)
All Active (n=163)		16 (9.8%)	4 (2.5%)	2*
Placebo (n=36)		1 (2.8%)	0	0

[0280] 6/163 (3.6%) of subjects with one or more observed episodes of serum K⁺>6.0mmol/L. 5 of 6 judged not related to study medication.

[0281] *Measure in 1 subject was an isolated incident not verified by repeat measurement with study drug discontinuation (protocol deviation).

Serum Sodium

[0282] Serum sodium concentration decreased in the active treatment arms (**Figure 23, Figure 24, and Figure 25**).

Discussion

[0283] This example describes a multicenter, prospective, randomized, placebo-controlled, double-blind, dose ranging study among adults with uncontrolled hypertension despite treatment with at least 2 background AHT medications. The results of this study demonstrate that aldosterone synthase inhibition with lorundrostat as an add-on therapy to a stable regimen of AHT medications was well tolerated, and induced a reduction in AOBP that was both clinically meaningful and statistically significant following treatment for 8 weeks.

[0284] Overall, 42 clinical trial sites across the USA participated in the trial, with 163 subjects randomized into Part 1 (of which 141 [86.5%] completed the trial on study drug) and 37 subjects randomized into Part 2 (of which 33 [89.2%] completed the trial on study drug). Baseline demographic, lifestyle and cardiovascular history characteristics were similar across all doses and study parts, with a relatively even distribution by sex, relevant race and ethnicity minority groups. As anticipated, the study population was primarily an older, overweight/obese group with a large minority of subjects being treated for Type II diabetes mellitus. Approximately 36% of participants were Black or African American. Furthermore, approximately half of the enrolled subjects had been prescribed a 2-drug AHT regimen, with most subjects (>77%) being treated with an ACEi or ARB, and a large majority (58%) being treated with a thiazide diuretic.

[0285] Analysis of the primary efficacy endpoint demonstrated that the majority of BP reductions achieved were within 4 weeks of starting therapy and were generally well-maintained for the remainder of the 8-week treatment period. Clinically meaningful placebo-adjusted reductions in AOBP SBP were seen across all doses tested, with statistically significant reductions of 9.58 mmHg ($p=0.0114$) and 7.81 mmHg ($p=0.0422$) seen in the 50 mg and 100 mg QD cohorts, respectively, in Part 1. Such reductions in SBP are salient to the effective treatment of subjects suffering with uncontrolled hypertension. In a recent meta-analysis of 147 randomized trials, 10 mmHg reductions in SBP were shown to reduce the risk of stroke by 41% and coronary heart disease by 22% . (Law, Morris, and Wald 2009) Furthermore, the reductions in AOBP SBP were validated by comparable reductions in 24-hour ABPM SBP, and confirmed with the associated benefit of lorundrostat reducing both central and nighttime ABPM SBP, two indicators of elevated cardiovascular event risk (Hermida et al. 2014; Mousa et al. 2004).

[0286] Beneficial effects were seen despite non-standardized background therapy, supporting the generalizability of effect across all subjects with uncontrolled hypertension. Moreover, the identification of sub-groups with statistically significant and clinically meaningful changes in AOBP SBP (i.e., subjects with a BMI ≥ 30 kg/m² and subjects with concomitant thiazide diuretic use) suggest the full efficacy of lorundrostat after 8 weeks of treatment may still be underestimated. Further studies exploring the effects of standardized background regimens and/or current prescribing paradigms with add-on lorundrostat therapy, or within specific sub-populations are warranted.

[0287] Suppressed renin is common among patients with hypertension and in theory, these patients should benefit most from drugs that decrease aldosterone production. Interestingly, subjects enrolled in Part 2 (i.e., subjects with non-suppressed renin levels) treated with lorundrostat demonstrated similar BP lowering efficacy to subjects with suppressed plasma renin levels (i.e., subjects enrolled in Part 1). While the PATHWAY-2 trial demonstrated other MRAs (such as spironolactone) are effective at lowering BP across a wide range of plasma renin levels, further study of lorundrostat in a population not selected for baseline PRA will be important to confirm the effect seen here.

[0288] Pharmacodynamic responses demonstrated dose-dependent reduction in serum aldosterone levels and a commensurate increase in plasma renin activity, in line with the mechanism of action of lorundrostat. No substantial decreases in serum cortisol levels were observed over the course of treatment and follow-up relative to placebo with percent change from baseline values of 20.6% to 51.4% (active) vs 37.7% (placebo) at Week 8, and -1.2 to 22.6% (active) vs 17.1% (placebo) at Week 12. A similar pattern was observed in Part 2, with active arm serum cortisol baseline levels of 11.1 µg/dL in the 100 mg QD dose group and no substantial changes observed over the course of treatment and subsequent follow-up. Most importantly, no adrenocortical insufficiency occurred during the trial.

[0289] Overall, lorundrostat was safe and well tolerated. Two (1.5%) subjects in Part 1 and one (3.2%) subject in Part 2 reported a treatment emergent SAE, of which the worsening of pre-existing hyponatremia was considered possibly related to study drug. No treatment emergent SAEs occurred in a subject treated with placebo. No deaths were reported in either Part 1 or Part 2.

[0290] At least one on-treatment TEAE was reported by 83 subjects in Part 1 (73 [54.9%] treated with lorundrostat versus 10 [33.3%] treated with placebo) and by 20 subjects in Part 2 (19 [61.3%] treated with lorundrostat versus 1 [16.7%] treated with placebo). Of the subjects treated with lorundrostat, 27 (20.3%) and 9 (29.0%) from Part 1 and Part 2, respectively, experienced TEAEs that were considered at least possibly related to study drug. The most commonly reported AE by PT was hyperkalemia and a decreased eGFR. All active doses saw modest increases in potassium levels at Week 8 relative to baseline ranging from 0.208 mmol/L (100 mg QD Part 2) to 0.341 mmol/L (25 mg BID Part 1). While seven subjects experienced transient elevated serum potassium greater than 6.0 mmol/L, none were considered an SAE and all rapidly resolved after

discontinuation or dose adjustment, consistent with the short half-life of lorundrostat. It should be noted that one of these events was assessed as erroneous due to incorrect sample processing. In a manner similar to ACE inhibitors and ARBs, the BP lowering effect of lorundrostat led to a beneficial, reversible dose-dependent reduction in eGFR.

[0291] Hypotension related to treatment was seen in three subjects and was reversible with treatment cessation and expected based on lorundrostat's mechanism of action. Two of these subjects were randomized to the 100 mg QD cohorts (1 in both Part 1 and Part 2), and one to 12.5 mg BID. In addition, three subjects developed orthostatic hypotension, defined as a fall of 20 mmHg in SBP or 10 mmHg in DBP when going from sitting to standing. In each case, the episode resolved and did not recur for the remainder of the treatment period. Ongoing observation for symptoms of hypotension, even if minimal and reversible, is warranted for future clinical studies.

[0292] In conclusion, the primary objective of the study was to characterize the safety and efficacy of lorundrostat on blood pressure at 5 dosing levels and 2 dosing regimens versus placebo when administered orally for the treatment of uncontrolled hypertension as add-on therapy to stable background treatment. The results of this study indicate:

- (a) Lorundrostat was effective at lowering BP in individuals with inadequately treated or treatment resistant hypertension;
- (b) There was a dose- and exposure-response relationship, with mean placebo-adjusted reduction in SBP of 9.58 mmHg and 7.81 mmHg seen at doses of 50 mg QD and 100 mg QD, respectively;
- (c) 24-hour ABPM, central BP and nighttime SBP values confirmed the reduction in SBP seen with AOBP, most prominently in the 100 mg QD dose cohort; and
- (d) The safety dataset lorundrostat was safe and well tolerated, with no effects on serum cortisol and an expected modest increase in serum potassium with relatively few episodes of clinically meaningful hyperkalemia.

[0293] Future studies evaluating the long-term efficacy and safety of lorundrostat in patients with uncontrolled hypertension are warranted.

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CLAIMS

What is claimed is:

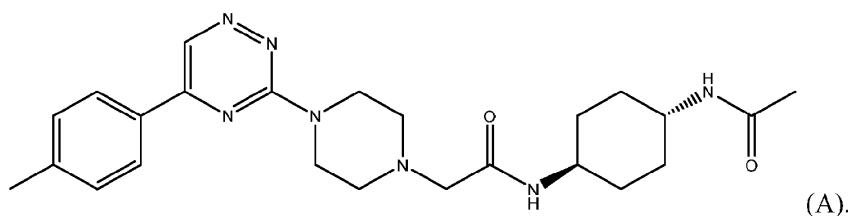
1. A method of treating hypertension in a hypertensive subject having a body mass index of at least 30, the method comprising administering to the subject a CYP 11 β 2 beta hydroxylase inhibitor once or twice per day in an amount sufficient to treat hypertension in the hypertensive subject.
2. A method of treating hypertension in a male hypertensive subject having a waist-hip ratio above 0.90, or in a female hypertensive subject having a waist-hip ratio above 0.85, the method comprising administering to the subject a CYP 11 β 2 beta hydroxylase inhibitor once or twice per day in an amount sufficient to treat hypertension in the hypertensive subject.
3. A method of treating hypertension in a hypertensive subject having a body mass index of more than 30, preferably 30-50, more preferably 30-40, the method comprising administering to the subject a CYP 11 β 2 beta hydroxylase inhibitor once or twice per day in an amount sufficient to treat hypertension in the hypertensive subject.
4. A method of treating hypertension in a hypertensive subject having a serum leptin concentration of at least 30 ng/dL, preferably at least 35 ng/dL, more preferably at least 40 ng/dL, or more preferably 30-50 ng/dL, 30-45 ng/dL, or 35-50 ng/dL, the method comprising administering to the subject a CYP 11 β 2 beta hydroxylase inhibitor once or twice per day in an amount sufficient to treat hypertension in the hypertensive subject.
5. The method of any one of claims 1 to 4, wherein the hypertensive subject has:
 - a) a plasma aldosterone concentration of greater than or equal to 6 ng/dL by immunoassay in said subject; and/or
 - b) a plasma aldosterone concentration of greater than or equal to 1 ng/dL by LC-MS in said subject.
6. A method of treating hypertension in a hypertensive subject in need thereof, the method comprising
 - a) measuring

- i) a systolic blood pressure of greater than 130 mmHg in said subject;
 - ii) a diastolic BP of greater than 80 mmHg in said subject; and
 - iii) a body mass index (BMI) of at least 30, preferably 30-50, more preferably 30-40, in said subject, or a waist-hip ratio above 0.90 in said subject if the hypertensive subject is male, or a waist-hip ratio above 0.85 in said subject if the hypertensive subject is female; and
 - b) administering to said subject an effective amount of a CYP 11 β 2 beta hydroxylase inhibitor.
7. A method of treating hypertension in a hypertensive subject in need thereof, the method comprising
- a) measuring in said hypertensive subject
 - i) a systolic blood pressure of greater than 130 mmHg;
 - ii) a diastolic BP of greater than 80 mmHg; and
 - iii) one or more or all of the following:
 - (1) a body mass index (BMI) of at least 30, preferably more than 30, preferably 30-50, more preferably 30-40;
 - (2) a waist-hip ratio above 0.90 if the hypertensive subject is male or a waist-hip ratio above 0.85 if the hypertensive subject is female; and
 - (3) a serum leptin of at least 30 ng/dL, preferably at least 35 ng/dL, more preferably at least 40 ng/dL, or more preferably 30-50 ng/dL, 30-45 ng/dL, or 35-50 ng/dL; and
 - b) administering to said subject an effective amount of a CYP 11 β 2 beta hydroxylase inhibitor.
8. A method of treating hypertension in a hypertensive subject in need thereof, the method comprising
- a) receiving an identification of the hypertensive subject as having
 - i) a systolic blood pressure of greater than 130 mmHg;
 - ii) a diastolic BP of greater than 80 mmHg; and
 - iii) one or more or all of the following:

- (1) a body mass index (BMI) of at least 30, preferably more than 30, preferably 30-50, more preferably 30-40,;
 - (2) a waist-hip ratio above 0.90 if the hypertensive subject is male or a waist-hip ratio above 0.85 if the hypertensive subject is female; and
 - (3) a serum leptin of at least 30 ng/dL, preferably at least 35 ng/dL, more preferably at least 40 ng/dL, or more preferably 30-50 ng/dL, 30-45 ng/dL, or 35-50 ng/dL; and
 - b) administering to said subject an effective amount of a CYP 11 β 2 beta hydroxylase inhibitor.
9. The method of any one of claims 6 to 8, wherein step a) further comprises:
- a) measuring a plasma aldosterone concentration of greater than or equal to 6 ng/dL in said subject by immunoassay; or
 - b) measuring a plasma aldosterone concentration of greater than or equal to 1 ng/dL in said subject by LC-MS.
10. The method of any one of claims 6 to 8, wherein step a) further comprises receiving an identification of the hypertensive subject as having:
- a) a plasma aldosterone concentration of greater than or equal to 6 ng/dL as measured by immunoassay; or
 - b) a plasma aldosterone concentration of greater than or equal to 1 ng/dL as measured by LC-MS.
11. The method of any one of claims 1 to 10, wherein the hypertensive subject is taking or has taken a hypertension medication selected from a diuretic, an ACE inhibitor, an angiotensin receptor blocker, a calcium channel blocker, or a combination of two or more thereof.
12. The method of claim 11, wherein the hypertensive subject is taking or has taken at least two of said hypertension medications.
13. The method of any one of claims 1 to 12, wherein the CYP 11 β 2 beta hydroxylase inhibitor is administered to the subject once per day.

14. The method of any one of claims 1 to 13, wherein the CYP 11 β 2 beta hydroxylase inhibitor is administered in the morning.
15. The method of any one of claims 1 to 12, wherein the CYP 11 β 2 beta hydroxylase inhibitor is administered to the subject twice per day.
16. The method of any one of claims 1 to 15, wherein the CYP 11 β 2 beta hydroxylase inhibitor:
 - a) is administered daily for at least one week;
 - b) is administered daily for at least two weeks;
 - c) is administered daily for at least four weeks; or
 - d) is administered daily for at least eight weeks.
17. The method of any one of claims 1 to 16, wherein the hypertensive subject's ambulatory systolic blood pressure is reduced by at least 10 mmHg, by 10-55 mmHg, by 10-50 mmHg, by 10-45 mmHg, by 10-40 mmHg, by 10-35 mmHg, by 10-30 mmHg, by 10-25 mmHg, by 10-20 mmHg, or by 10-15 mmHg, relative to the hypertensive subject's ambulatory systolic blood pressure prior to administration of the CYP 11 β 2 beta hydroxylase inhibitor for a period of at least eight weeks.
18. The method of any one of claims 1 to 17, wherein the hypertensive subject's ambulatory diastolic blood pressure is reduced by at least 5 mmHg, by 5-25 mmHg, by 5-20 mmHg, or by 5-15 mmHg relative to the hypertensive subject's ambulatory diastolic blood pressure prior to administration of the CYP 11 β 2 beta hydroxylase inhibitor for a period of at least eight weeks.
19. The method of any one of claims 1 to 18, wherein the hypertensive subject's aldosterone level follows a substantially normal circadian rhythm.
20. The method of any one of claims 1 to 19, wherein the hypertensive subject's average systolic blood pressure during sleep is reduced (a) relative to the hypertensive subject's average systolic blood pressure during sleep prior to receiving the CYP 11 β 2 beta hydroxylase inhibitor, and/or (b) relative to the hypertensive subject's average daytime systolic blood pressure.

21. The method of any one of claims 1 to 20, wherein the hypertensive subject's average systolic blood pressure during sleep is reduced:
- by at least 10%, by between 10% and 40%, by between 10% and 30%, or by between 10% and 20% relative to the hypertensive subject's average daytime systolic blood pressure; and/or
 - by at least 8 mmHg, by at least 10mmHg, by between 8 and 55 mmHg, by between 10 and 45 mmHg, or by between 10 and 25 mmHg, relative to the hypertensive subject's average systolic blood pressure during sleep prior to receiving the CYP 11 β 2 beta hydroxylase inhibitor.
22. The method of any one of claims 1 to 21, wherein said CYP 11 β 2 beta hydroxylase inhibitor is selective for inhibition of CYP 11 β 2 beta hydroxylase activity relative to inhibition of CYP 11 β 1 beta hydroxylase activity, preferably wherein the inhibition constant (K_i) for CYP 11 β 1 beta hydroxylase divided by the K_i for CYP 11 β 2 beta hydroxylase is greater than 100.
23. The method of any one of claims 1 to 22, wherein said CYP 11 β 2 beta hydroxylase inhibitor is a compound of Formula (A) or a pharmaceutically acceptable salt thereof:



24. The method of claim 23, wherein the compound is in the form of an HBr salt of the compound of Formula (A).
25. The method of any one of claims 23 to 24, wherein:
- between 5 mg and 50 mg of the CYP 11 β 2 beta hydroxylase inhibitor is administered orally twice a day, 12 hours apart;
 - between 10 mg and 30 mg of the CYP 11 β 2 beta hydroxylase inhibitor is administered orally twice a day, 12 hours apart;

- c) between 30 mg and 120 mg of the CYP 11 β 2 beta hydroxylase inhibitor is administered orally once a day; or
 - d) between 40 mg and 110 mg of the CYP 11 β 2 beta hydroxylase inhibitor is administered orally once a day.
26. The method of any one of claims 1 to 25, wherein the hypertensive subject does not have primary aldosteronism, preferably wherein the hypertensive subject has primary hypertension.
27. A method of identifying a subject for hypertension treatment with a CYP 11 β 2 beta hydroxylase inhibitor, the method comprising:
- a) measuring a systolic blood pressure of greater than 130 mmHg in said subject;
 - b) measuring a diastolic BP of greater than 80 mmHg in said subject; and
 - c) measuring a body mass index (BMI) of at least 30, preferably 30-50, more preferably 30-40, in said subject, or measuring a waist-hip ratio above 0.90 in said subject if the subject is male, or measuring a waist-hip ratio above 0.85 in said subject if the subject is female;
- thereby identifying said subject for hypertension treatment with a CYP 11 β 2 beta hydroxylase inhibitor.
28. A method of identifying a subject for hypertension treatment with a CYP 11 β 2 beta hydroxylase inhibitor, the method comprising:
- a) measuring a systolic blood pressure of greater than 130 mmHg in said subject;
 - b) measuring a diastolic BP of greater than 80 mmHg in said subject; and
 - c) measuring one or more or all of the following in said subject:
 - i) a body mass index (BMI) of at least 30, preferably 30-50, more preferably 30-40;
 - ii) a waist-hip ratio above 0.90 if the subject is male or a waist-hip ratio above 0.85 if the subject is female; and
 - iii) a serum leptin concentration of at least 30 ng/dL, preferably at least 35 ng/dL, more preferably at least 40 ng/dL, or more preferably 30-50 ng/dL, 30-45 ng/dL, or 35-50 ng/dL;

thereby identifying said subject for hypertension treatment with a CYP 11 β 2 beta hydroxylase inhibitor.

29. The method of claim 27 or 28, the method further comprising:
- a) measuring a plasma aldosterone concentration of greater than or equal to 6 ng/dL by immunoassay in said subject; or
 - b) measuring a plasma aldosterone concentration of greater than or equal to 1 ng/dL by LC-MS in said subject.