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Effects of the oral testosterone undecanoate Kyzatrex™ on ambulatory blood pressure in hypogonadal men

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Abstract

Testosterone replacement therapies have been shown to increase blood pressure (BP) in hypogonadal men. We studied the effects of a new formulation of testosterone undecanoate (Kyzatrex™) on ambulatory blood pressure (ABP) and heart rate, in 155 men with hypogonadism (mean age, 50.5 years, 76.8% white, 36.1% on antihypertensive therapy). The ABP, heart rate and clinical assessments were obtained at baseline and following 120 and 180 days of therapy. Mean changes from baseline in 24-h ambulatory systolic BP of 1.7 mmHg (95% CI, 0.3, 3.1) at day 120 and 1.8 mmHg (95% CI, 0.3, 3.2) at day 180 were observed post-treatment. For those men on antihypertensive drug therapy, increases in mean 24-h systolic BP were greater than those not taking antihypertensive drugs (3.4 *vs* 0.7 mmHg at day 120 and 3.1 *vs* 1.0 mmHg at day 180, respectively). Changes from baseline in 24-h diastolic BP and heart rate at day 120 were smaller (<1 mmHg and <1 beat/min, respectively). There were no relationships observed between testosterone concentration or hemoglobin levels with ABP. Multivariable analyses showed that baseline ambulatory BP and antihypertensive therapy were significantly correlated with BP changes. These data demonstrate small increases in ambulatory BP following 120 days on this oral testosterone undecanoate with no further changes at 180 days. Changes in ambulatory BP were minimal in patients not taking antihypertensive therapy.

1 | INTRODUCTION

Testosterone replacement therapy for male hypogonadism or androgen deficiency has been administered by intramuscular and subcutaneous injections, transdermal gels and lotions, dermal patches, intranasal gels, and oral delivery.[1] Testosterone itself has limited oral bioavailability. Long-chain fatty acid esterification of testosterone to create testosterone undecanoate allows for absorption via the intestinal lymphatic system and bypasses first pass metabolism in the liver.[2] Testosterone is then liberated from testosterone undecanoate by endogenous non-specific esterases. Oral formulations of testosterone undecanoate have been developed to provide average serum testosterone levels in the eugonadal range (typically 300–1000 ng/dl) and avoid peak concentrations above 1500 ng/dl. During recent studies with both injectable and oral testosterone formulations, increases in both clinic and ambulatory blood pressure (BP) have been observed[3,4] but the mechanism of these increases have not been elucidated

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nor has there been clarity regarding clinical predictors associated with BP increases. In the present BP safety study, we evaluated a new oral testosterone undecanoate therapy using ambulatory BP monitoring performed at baseline and following 120 and 180 days of daily therapy along with standard clinical and laboratory safety parameters.

2 | METHODS

The study, which followed guidance by the US Food and Drug Administration (FDA), was an open-label, multicenter, single arm study with an untreated screening period, a baseline visit to assess BP and heart rate via 24-h ambulatory BP monitoring (ABPM) prior to administration of study medication, and two visits at 120 days and 180 days after initiating oral testosterone undecanoate. The trial was conducted between September 2018 and October 2019. In addition, seated clinic BP measurements were performed at all study visits. All study participants initially received oral testosterone undecanoate at a dose of 200 mg twice daily with breakfast and dinner meals. Based on thresholds of morning plasma testosterone between 3-5 h post morning dose (<400 ng/dl to titrate upwards or >900 ng/dl to titrate downwards), dose decreases to (100 mg twice daily or increases to 300 mg twice daily) took place at day 28. A further potential titration of dose (decrease to a minimum of 100 mg daily or increase to a maximum of 400 mg twice daily) occurred at day 56 to achieve therapeutic levels of plasma testosterone; the day 56 dose was maintained until end of treatment (withdrawal or 180 days).

2.1 | Study participants

All participants were men between 18 and 65 years of age, inclusive, with documented hypogonadism as defined by a below normal serum testosterone and at least one sign or symptom of testosterone deficiency. The total serum testosterone level was required to be ≤281 ng/dl on 2 consecutive blood samples obtained between 7 and 10 AM on separate days, at least 3 days apart either in individuals naïve to androgen replacement or following at least 8 weeks of washout of current androgen therapy (washout periods of 6 months were required for testosterone implants). Also required was that there was no change in medications, including antihypertensive agents, within the 3 months prior to enrollment. Subjects with uncontrolled hypertension (clinic BP >140/90 mmHg) were excluded from participation based on FDA guidance. Other key exclusion criteria were the use of any medications or clinical conditions that could affect absorption or levels of testosterone undecanoate; hemoglobin A1c > 8%; hemoglobin <11.0 g/dl or >16.0 g/dl; serum transaminases >2 times the upper limits of normal; estimated glomerular filtration rate of <60 ml/min/1.73 m, or prostatic specific antigen (PSA) > 2.5 ng/ml and/or an abnormal prostate gland on palpation. Additionally, exclusionary criteria due to the ambulatory BP monitoring procedures were an upper-arm circumference >45 cm; long-distance driving or a planned trip of >60 min while wearing the monitor and cardiac arrhythmias (eg, atrial fibrillation) that might interfere with the ability of the ambulatory BP recorder to obtain reliable measurements.

The trial was conducted in accordance with Good Clinical Practice requirements, as described in the current revision of International Conference on Harmonization of Technical Requirements of Pharmaceuticals for Human Use (ICH) guidelines and the Declaration of Helsinki. The study protocol and informed consent forms were reviewed and approved by the Copernicus Group Institutional Review Board (Cary, NC, USA). Before any study procedures could occur, a written informed consent was obtained from each study participant.

2.2 | Safety assessments

Clinical evaluation and vital signs were assessed at baseline and after 14, 42, 90, 119 and 179days. At each clinic visit following the screening visit, all study participants were queried about adverse events and a symptom-directed physical examination was performed as indicated clinically. Laboratory tests were assessed at baseline and after 90 and 180 days.

2.3 | Blood pressure monitoring

Blood pressure was monitored manually in the clinic at the baseline and post-treatment study visits. The clinic measurements were made in the seated position in triplicate after 10 min of rest and using appropriately sized cuff and bladder with a digital recorder. Any study participant with a baseline clinic average BP >140/90 mmHg was withdrawn from participation in the trial. For ambulatory BP measurements, study participants were fitted with a recorder that was initiated to measure the BP at 30-min intervals during the day (7:00 AM to 11:00 PM) and night (11:00 PM to 7:00 AM) (Spacelabs Medical Model 90207; Redmond, WA). The ABPM data were evaluated both manually and programmatically by standardized, computerized methods, for validity and required that no more than 4 consecutive timepoints were missing, no more than 10 of the possible 48 timepoints over 24 h were missing, and at least 22 of 24 h had valid data. If these quality control criteria were not met, the study could be repeated within 48 h of the failed ambulatory BP procedure.

2.4 | Statistical analyses

The 24-h, daytime and nighttime average systolic and diastolic BPs were summarized with means and 95% confidence intervals (CIs), and cumulative distribution curves. Using a mixed model repeated measures (MMRM) analysis with study participant as a random effect (all participants with non-missing post-baseline results), and visit, baseline diabetes status and baseline antihypertensive treatment status

as fixed effects; direct comparisons of visits were performed. The least squares mean at each visit and the least squares mean for the difference between 120 days and baseline with the associated 95% CIs were calculated. Cumulative distribution function curves of change from baseline to Day 120 and Day 180 were also performed. The primary end point in this BP safety study was the change from baseline to day 120 for the average 24-h systolic BP. A key secondary end point was the change from baseline to day 180 for the average 24-h systolic BP. Comparisons were also made for the ambulatory BP changes at 180 versus 120 days. Other assessments included changes from baseline in the awake (daytime) and sleep (nighttime) systolic BP, the 24-h, awake, and sleep diastolic BPs and the 24-h, awake and sleep heart rates. Additionally, the BP and heart rate changes were evaluated in subgroups of study participants with and without antihypertensive therapy at baseline and with and without a baseline history of diabetes mellitus. The incidence of adverse events was tabulated in all participants who received at least one dose of study drug (safety population).

The change of 24-h BP from baseline was calculated using the time-weighted average BP obtained over 24 h divided by the time duration. Changes in hourly average BPs were calculated by taking the difference between the corresponding hourly BP at the end of the treatment visits and the baseline visit for a given post-dosing hour. Post-hoc analyses were also performed to assess relationships among changes from baseline in ambulatory systolic and diastolic BP with changes in body weight, heart rate, testosterone concentration and hemoglobin.

2.4.1 | Sample size calculation

A sample size of 135 subjects would yield a two-sided 90% confidence interval with a distance from the difference in means to the limits that was equal to 1.4 mmHg when the estimated standard deviation of the differences for 120 days versus baseline for the 24-h mean systolic BP was 10 mmHg. In addition, a sample size of 119 study participants achieved 90% power to detect non-inferiority (versus baseline) using a one-sided one-sample t test when the non-inferiority margin was 3.0 mmHg, the actual mean was 0, and the significance level (α) of the test was 0.025. Assuming a 10% drop-out or non-evaluable ambulatory BP monitoring rate, 133 study participants would be required for enrollment to achieve 119 evaluable study participants.

3 | RESULTS

3.1 | Subject disposition and baseline characteristics

A total of 155 study participants were enrolled who received at least 1 dose of study drug and of these 155 participants, 153 also had an evaluable ambulatory BP study at baseline and 2 were discontinued from further participation in the study. One hundred thirty-six (89%) participants completed the 120-day visit and 125 (82%) completed the 180-day visit and had valid baseline and successful on-treatment ABPM studies. The primary reasons for early termination were withdrawal by the subject (5.6%), adverse events (1.3%), lost to follow-up (6%) and other (2.6% and includes withdrawal of subject by site, non-return to an appointment, adverse events). The demographic and baseline characteristics of the study participants are shown in Table 1. The mean age at baseline was 51.2 years (52% older than 50 years), 77% were white and 19% were black. Thirty-seven percent (56 of 155) of the study participants were taking antihypertensive therapy. There were no dose increases in antihypertensive medications however, 5 (3.2%) were started on new antihypertensive agents during the 180-day study. Twenty-two percent (34 of 155) of the study cohort had a history of diabetes mellitus. A greater percentage of study participants taking antihypertensive therapy had diabetes (44.6%) than those not taking antihypertensive therapy (9.1%). A high percentage (96%) of study participants with both diabetes and who were taking

TABLE 1 Characteristics of the patient population at baseline (*n* = 155)

Characteristic	Value
Age (years)	
Mean	51.2 (9.4)
Race, *N* (%)	
Asian	4 (2.6)
Black	29 (18.7)
White	119 (76.8)
Other	3 (1.9)
Body mass index (BMI) (kg/m^2)	
Mean (SD)	34.0 (7.3)
Medical history, *N* (%)	
On antihypertensive therapy	56 (36.1)
Type 2 diabetes	34 (21.9)
On statin therapy	38 (24.5)
Cardiovascular disease	17 (12.3)
Blood pressure (mmHg)	
Clinic, mean (SD)	
Systolic	126.1 (9.8)
Diastolic	78.7 (6.7)
Ambulatory, mean (95% CI)	
24-h systolic	128.9 (126.8, 131.0)
24-h diastolic	76.2 (74.6, 77.9)
Daytime systolic	132.7 (130.5, 134.8)
Daytime diastolic	79.2 (77.5, 80.9)
Nighttime systolic	121.0 (118.7, 123.3)
Nighttime diastolic	70.0 (68.2, 71.8)
Heart rate	
Clinic, mean (SD)	71.9 (9.5)
24-h, mean (95% CI)	76.3 (74.4, 78.3)

TABLE 2 Changes from baseline in blood pressure and heart rate following oral testosterone undecanoate

Parameter	Mean (SE)	Change from baseline (95% CI)[b]	*p*-value[2]
24-h ambulatory systolic BP (mmHg)			
Baseline (*n* = 153)	128.9 (1.1)		
Day 120 (*n* = 136)	130.6 (1.1)	1.7 (0.3, 3.1)	.018
Day 180 (*n* = 125)	130.7 (1.1)	1.8 (0.3, 3.2)	.016
24-h ambulatory diastolic BP (mmHg)			
Baseline	76.2 (0.8)		
Day 120	76.9 (0.8)	0.6 (−0.3, 1.6)	.193
Day 180	76.9 (0.8)	0.6 (−0.4, 1.6)	.210
24-h ambulatory heart rate (beats/minute)			
Baseline	76.3 (1.0)		
Day 120	77.0 (1.0)	0.7 (−0.5, 1.9)	.261
Day 180	78.2 (1.0)	1.9 (0.6, 3.1)	.004
Parameter	**Mean (SD)**	**Change from baseline (95% CI)**	***p*-value [1]**
Clinic systolic BP (mmHg)[a]			
Baseline (*n* = 152)	126.1 (9.8)		
Day 120 (*n* = 141)	128.5 (10.9)	2.7 (0.9, 4.5)	.003
Day 180 (*n* = 132)	128.1 (10.0)	2.4 (0.6, 4.2)	.010
Clinic diastolic BP (mmHg)[a]			
Baseline	78.7 (6.7)		
Day 120	80.0 (7.7)	1.5 (0.3, 2.6)	.017
Day 180	80.1 (7.6)	1.7 (0.5, 2.9)	.006
Clinic heart rate (beats/min)[a]			
Baseline	71.9 (9.5)		
Day 120	72.9 (9.4)	1.1 (−0.4, 2.6)	.152
Day 180	74.3 (10.3)	2.6 (1.0, 4.2)	.002

[a]Clinic BPs were assessed prior to the start of corresponding ambulatory BP assessment.

[b]Least square mean changes for ambulatory BP and heart rate.

[1]*p*-values based on paired *t* test.

[2]Based on mixed model repeated measures analysis with visit, prior randomized treatment, baseline antihypertensive treatment status, and baseline diabetes status as fixed effects and subject as a random effect.

antihypertensive therapy were obese (body mass index ≥30 kg/m^2) whereas for those participants without these comorbidities, 56% were obese. The percentage of study participants achieving a normal testosterone (plasma collected in NaF/EDTA tubes) after 90 days of treatment was 96.1% (plasma $C_{avg0-24}$ = 393.3 ng/dl); quantitation was by liquid chromatography-mass spectrometry.[5,6] A single pre-treatment (Day 1) pre-dose sample for total testosterone had a mean value of 231.5 ng/dl.

3.2 | Blood pressure and heart rate

Change from baseline in the 24-h ambulatory systolic BP on oral testosterone undecanoate following 120 days of treatment was 1.7 mmHg, p = .018 (Table 2). Lesser effects were seen for the ambulatory diastolic BP and were not statistically significant (Table 2). Results following 180 days of oral testosterone undecanoate therapy were comparable to the 120-day results (Table 2). The nocturnal decline in systolic BP (daytime-nighttime/daytime BP × 100 [%]) was unchanged by the oral testosterone undecanoate therapy (8.8% at baseline versus 8.9%) at day 120 of the study. Small increases in the 24-h ambulatory heart rate were observed following 120 and 180 days of therapy (0.7 and 1.9 beats/minute, respectively) (Table 2).

Ambulatory systolic and diastolic BPs over 24 hours at baseline and at the end of the 120- and 180-day treatment periods are shown in Figure 1. The BP over 24 h was higher following 120 and 180 days of treatment with oral testosterone undecanoate primarily between the hours 13–16 after initiation of the ambulatory BP monitoring. The effects on diastolic BP over 24 h were less than for the systolic BP, particularly toward the end of the dosing periods. Cumulative distribution function (CDF) curves for the 24-h ambulatory systolic and diastolic BPs are shown in Figure 2. For systolic BP, there was separation of the CDF curves at days 120

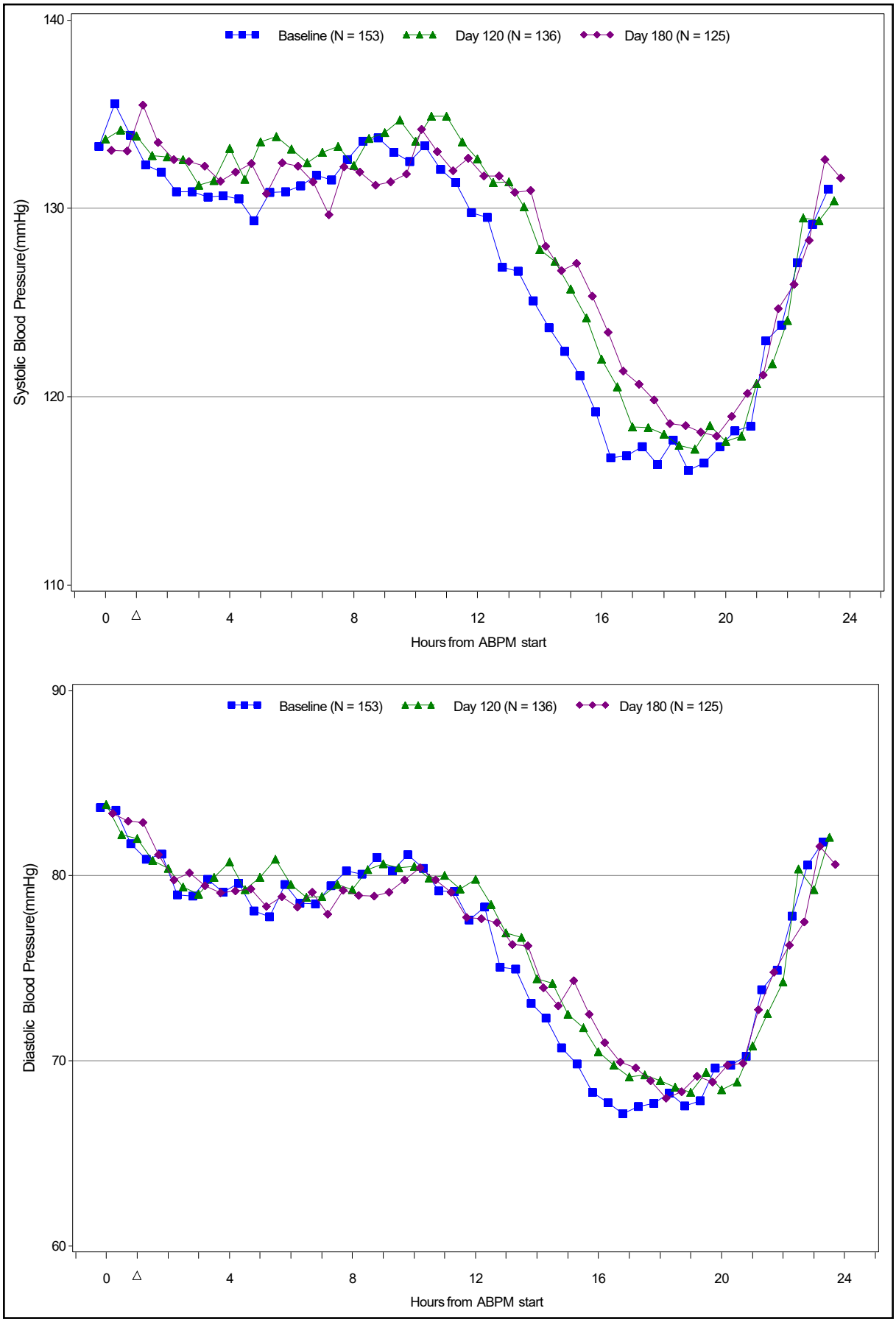

FIGURE 1 Hourly ambulatory blood pressure (BP) results at baseline and 120 and 180 days after initiating oral testosterone undecanoate therapy. The upper panel depicts the ambulatory systolic BP; the lower panel shows the ambulatory diastolic BP

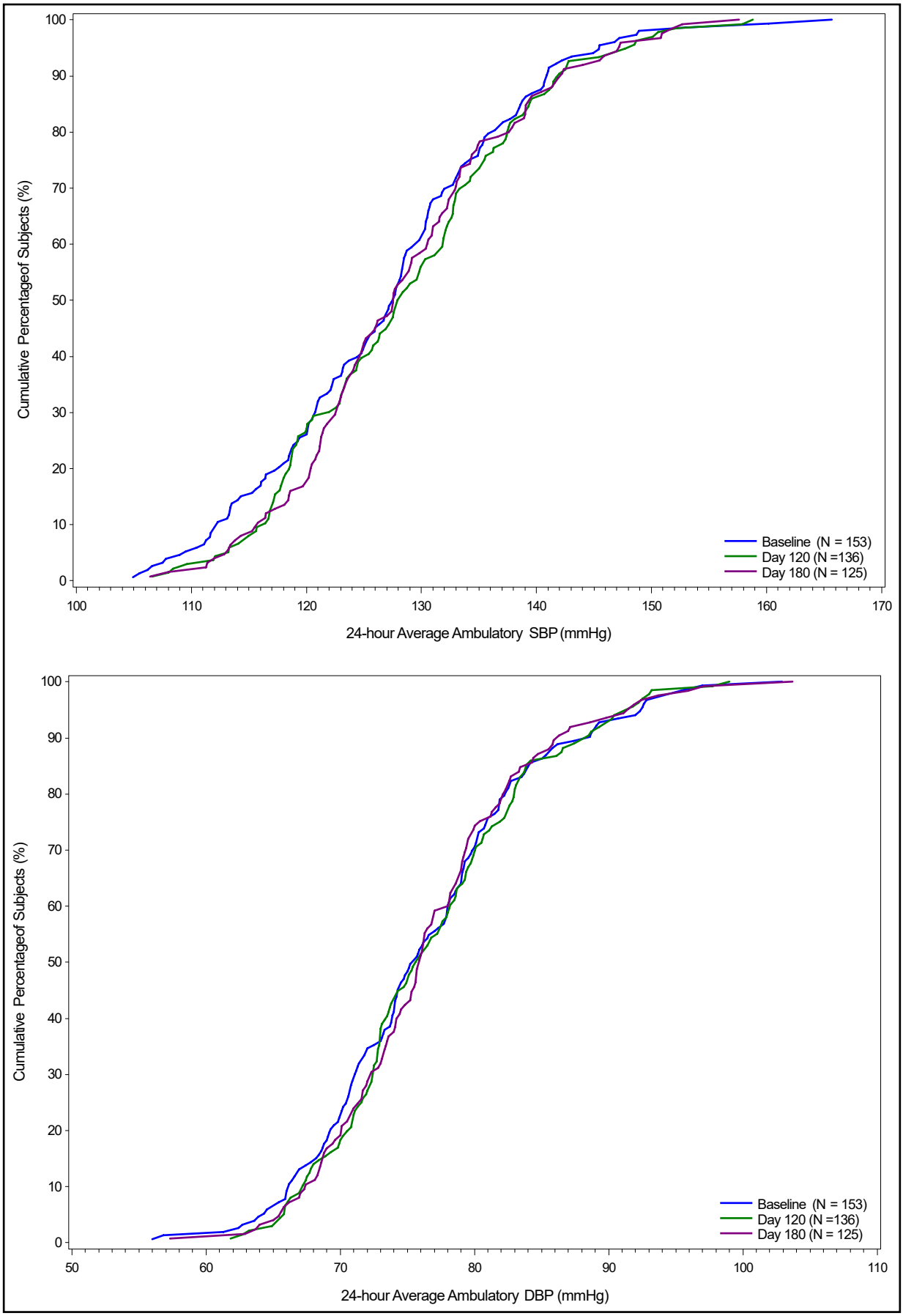

FIGURE 2 Cumulative distribution functions of percentage change from baseline to days 120 and 180 in ambulatory blood pressure. The upper panel depicts the ambulatory systolic BP; the lower panel shows the ambulatory diastolic BP

TABLE 3 Changes from baseline at Day 120 in 24-h blood pressure and heart rate in study participants with and without antihypertensive therapy and with and without diabetes mellitus following treatment with oral testosterone undecanoate

	Systolic BP (mmHg)		Diastolic BP (mmHg)		Heart Rate (beats/minute)	
Subgroup	Baseline	Change from baseline at day 120 (95% CI)	Baseline	Change from baseline at day 120 (95% CI)	Baseline	Change from baseline at day 120 (95% CI)
With antihypertensive therapy (n = 49)	131.3 (127.8, 134.8)	3.4 (1.0, 5.9)**	75.9 (73.3, 78.6)	1.8 (0.2, 3.5)*	75.8 (72.6, 79.3)	1.3 (−0.9, 3.5)
Without antihypertensive therapy (n = 90)	127.9 (124.9, 130.9)	0.7 (−1.0, 2.4)	78.2 (75.8, 80.5)	0.0 (−1.2, 1.2)	76.9 (73.9, 79.8)	0.4 (−1.1, 1.9)
With diabetes mellitus (n = 29)	130.8 (125.9, 135.6)	3.0 (−0.2, 6.2)	76.3 (73.1, 79.6)	1.7 (−0.3, 3.7)	77.7 (73.7, 81.7)	1.9 (−1.1, 4.9)
Without diabetes mellitus (n = 110)	127.9 (125.8, 130.1)	1.3 (−0.2, 2.9)	76.9 (75.2, 78.6)	0.4 (−0.8, 1.5)	74.5 (72.4, 76.6)	0.4 (−1.0, 1.7)

Note: Values are least square mean based on a mixed model repeated measures analysis with visit, prior treatment, baseline antihypertensive treatment status or baseline diabetes status as fixed effects and study participant as a random effect.

*p < .05.; **p < .01.

TABLE 4 Change in 24- h average ambulatory SBP as a function of baseline SBP, dose, age, weight, diabetes and baseline hypertensive treatment status by visit

Visit covariate	Estimate 95% CI	p-value
Day 120		
Intercept	49.523 (32.352, 66.694)	<.0001
Systolic blood pressure at baseline	−0.433 (−0.556, −0.310)	<.0001
Age	0.053 (−0.100, 0.207)	.493
Weight at baseline	0.005 (−0.059, 0.068)	.889
Dose (600 mg)	3.020 (−0.123, 6.163)	.060
Dose (800 mg)	4.201 (0.469, 7.934)	.028
Diabetic status (with diabetes mellitus)	0.387 (−3.280, 4.054)	.835
Hypertension treatment status (with antihypertensive therapy at baseline)	4.330 (1.230, 7.431)	.007
Day 180		
Intercept	48.474 (33.205, 63.742)	<.0001
Systolic blood pressure at baseline	−0.402 (−0.510, −0.295)	<.0001
Age	0.021 (−0.118, 0.160)	.765
Weight at baseline	0.007 (−0.048, 0.062)	.809
Dose (600 mg)	1.091 (−1.697, 3.880)	.440
Dose (800 mg)	2.962 (−0.539, 6.464)	.097
Diabetic status (with diabetes mellitus)	1.798 (−1.478, 5.075)	.279
Hypertension treatment status (with antihypertensive therapy at baseline)	2.905 (0.102, 5.708)	.042

Note: Intercept includes the effect of doses below 600 mg.

Abbreviation: SBP, systolic blood pressure.

and 180 versus the baseline period observed primarily when the 24-h systolic BP values were <125 mmHg. Changes in 24-h diastolic BP were negligible (Figure 2).

The clinic blood pressure increased by 2.7/1.5 mmHg following 120 days of treatment with oral testosterone undecanoate and 1.7/1.7 mmHg following 180 days of treatment with oral testosterone undecanoate (Table 2). The clinic pulse rate increased by 1.1 and 2.6 beats/minute, respectively at days 120 and 180 (Table 2).

3.3 | Blood pressure changes in subgroups on antihypertensive therapy or with type 2 diabetes

Changes from baseline in 24-h blood pressure and heart rate at 120 days in study participants with and without antihypertensive therapy and with and without type 2 diabetes are shown in Table 3. Changes from baseline in 24-h systolic and diastolic BP and heart rate were greater in patients taking antihypertensive drugs versus those without antihypertensive therapy.

There were 33 study participants with diabetes mellitus and 120 study participants without diabetes mellitus at baseline who had evaluable ambulatory BP data. Changes from baseline in 24-h systolic and diastolic BP at Day 120 were numerically, but not significantly greater in patients with type 2 diabetes versus those without type 2 diabetes. Similarly, changes in ambulatory heart rate were nominally greater in patients with diabetes versus those without diabetes.

Of note, for the study participants with type 2 diabetes, 25 (74%) were on antihypertensive therapy, thus there is substantial overlap of diabetic and antihypertensive therapy participants. There were 90 subjects in the study without antihypertensive medications at baseline, of whom only 9 had diabetes mellitus. For the subgroup not on antihypertensive therapy, the change from baseline in 24-h systolic and diastolic BP at 120 days was 0.8 mmHg and 0.0 mmHg, respectively and were not statistically significant.

3.4 | Blood pressure findings as a function of clinical characteristics

Changes in the primary end point as a function of baseline ambulatory systolic BP, age, dose of oral testosterone undecanoate, body weight, and antihypertensive treatment status are shown in Table 4. At both days 120 and 180, baseline blood pressure and hypertension treatment status were significantly related to the changes in 24-hour systolic BP. Other clinical characteristics had no significant relationship with the primary end point at either of days 120 and 180.

The serum hemoglobin was 14.7 ± 1.1 g/dl at baseline, 15.1 ± 1.5 g/dl at day 90 and 15.2 ± 1.5 g/dl at day 180 (hemoglobin values were not obtained at day 120). The levels of hemoglobin at day 90 of the study had a weak, but significant relationship with 24-h ambulatory systolic BP at days 120 and 180 (R^2 = .052, p = .0002 for day 120 and R^2 = .049, p = .0005 for day 180) (Figure 3). However, the change from baseline in serum hemoglobin was not a predictor of changes in 24-h ambulatory systolic BP in the study. Regression analyses of change from baseline in 24-h systolic BP after 120 days versus 24-h testosterone average concentration (after 90 days) showed no relationship (R^2 = .009, p = .3109), (Figure 4). The testosterone undecanoate dose was constant in this study after 56 days until the end of treatment, nominally 180 days.

4 | DISCUSSION

The results of our dedicated BP safety study demonstrated that the oral testosterone undecanoate formulation Kyzatrex™ was associated with small increases in clinic and ambulatory systolic BP following approximately 120 and 180 days of replacement therapy in hypogonadal men. No differences were observed between visits at 120 and 180 days suggesting that the impact of the drug on BP had reached a plateau by 120 days. The increases were larger for the systolic BP than for the diastolic BP, both when measured in the clinical setting as well as with 24-h ambulatory BP monitoring. There were also small increases in the clinic and ambulatory heart rates observed on this oral testosterone undecanoate. The increases in ambulatory systolic BP were inversely related to baseline levels of ambulatory BP (likely related in part to regression to the mean) as well as antihypertensive treatment status but were not related to ambulatory heart rate, body weight,

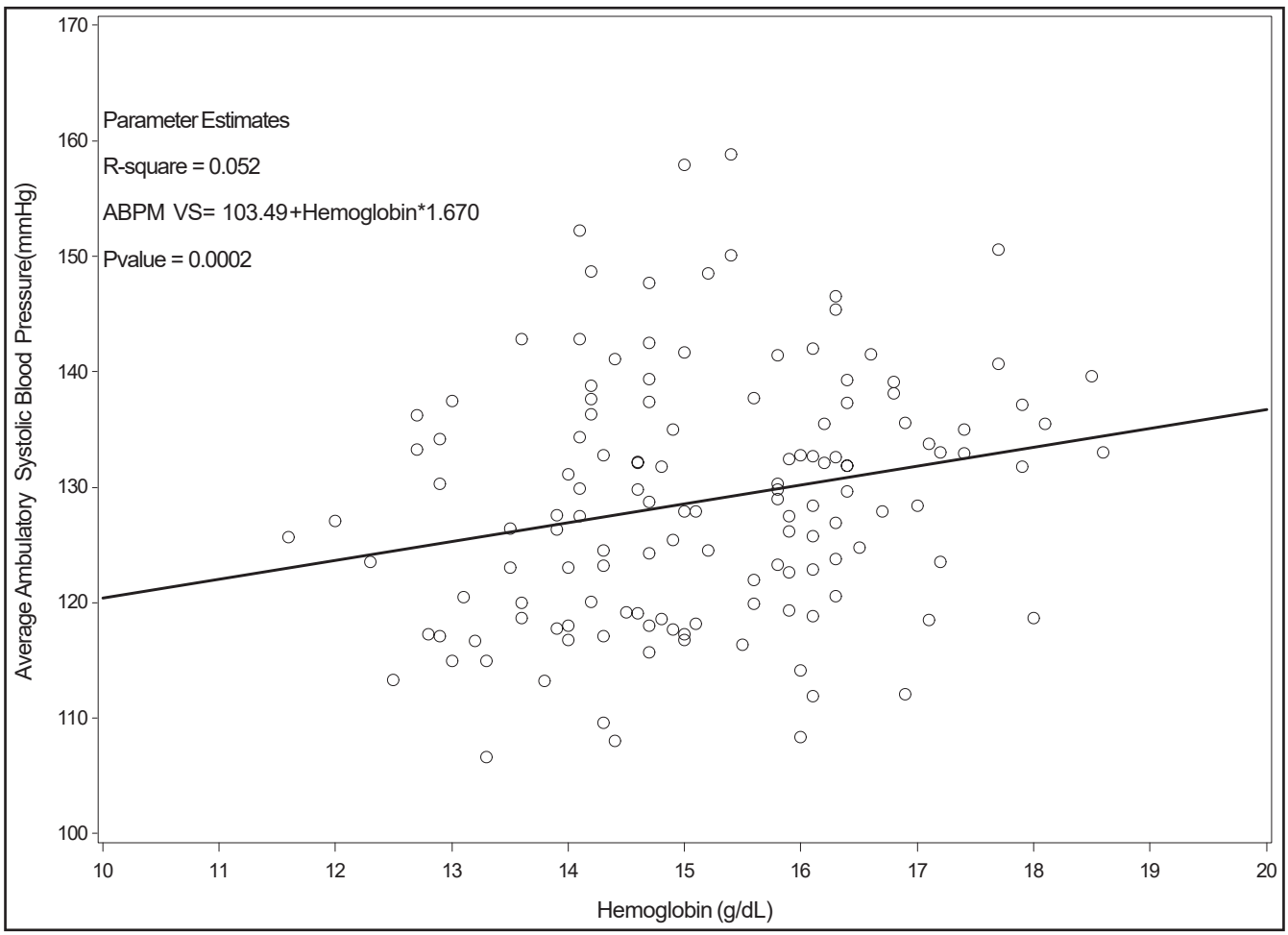

FIGURE 3 Relationship between serum hemoglobin (g/L) at day 90 of treatment and ambulatory systolic BP at day 120 of treatment. A weak, significant, positive relationship was observed

diabetes mellitus or changes in hemoglobin or testosterone levels. These findings are meaningful since a relation to heart rate might have suggested increases in sympathetic nervous system activity and relations with changes in body weight or hemoglobin in men treated with oral testosterone undecanoate might have supported an increase in plasma volume as one possible mechanism for the small increases in BP.

The study was designed to evaluate changes in the 24-h ABP as the primary outcome measure in this study rather than changes in the clinic BP. Of note, the US Food and Drug Administration has advocated for use of ABP measurements in drug safety research[6,7] since these devices have the potential to detect smaller changes in BP with improved reproducibility compared to clinical BP measurements and have virtually no placebo effects.[7–9] As a result of the objectivity of ABP measurements, a placebo treatment arm for studies such as ours have not been a requirement to provide evidence for a small BP effect. The frequent readings obtained over a 24-h period also improves the precision of a BP safety study with statistical power to exclude 3–4 mmHg shifts in BP.[7,8] It is also noteworthy that changes in clinic BP were slightly greater than the changes in 24-h ambulatory BP in this study. This phenomenon is not uncommon and may be associated with a 'white-coat' effect seen with clinical readings that are abolished by ambulatory BP measurements.

We observed larger changes from baseline in ambulatory BP in those men taking antihypertensive drug therapy and in those with type 2 diabetes, a finding that has been previously reported with testosterone replacement therapies.[3] The average change in ambulatory BP in those men on antihypertensive therapy was about 3.4/1.8 mmHg whereas those not taking antihypertensive therapy had a substantially smaller and insignificant change of 0.7/0.0 mmHg. Similar findings were observed for those patients with and without diabetes although a high proportion of the study participants with diabetes were also taking antihypertensive therapy and are not truly separate sub-populations. The mechanisms for the BP differences observed following testosterone replacement therapy when administered to those men with treated hypertension versus those with normotension are not established. However, data from animal models have shown that testosterone will result in some upregulation of norepinephrine synthesis, angiotensin II expression, endothelin-1 action and attenuation of vasodilator action (eg adenosine).[10] These influences may be more

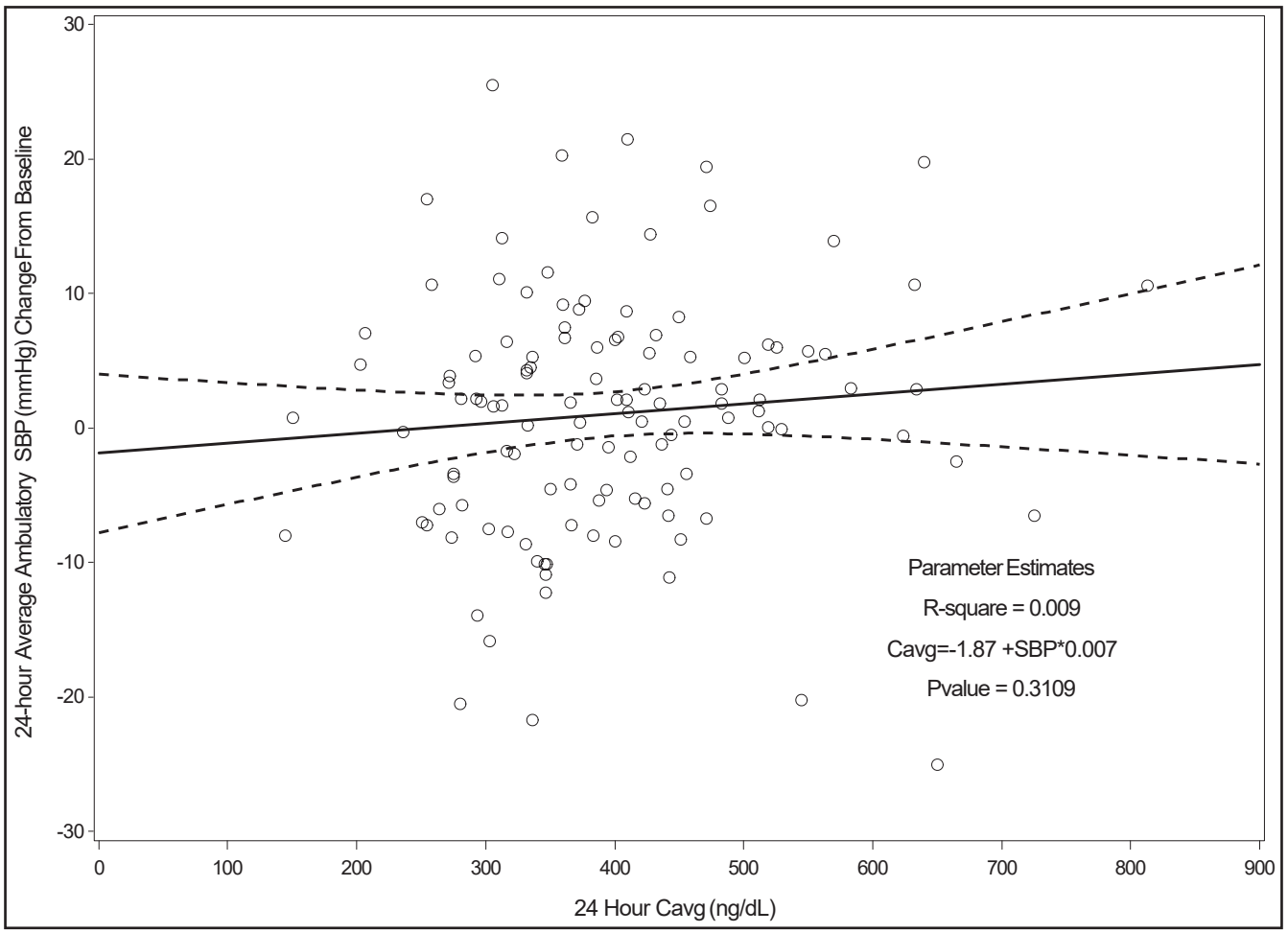

FIGURE 4 Concentration of the serum testosterone versus the changes in ambulatory systolic BP at day 120 of treatment. No relationship was observed

prominent in men with underlying hypertension than those without hypertension. Furthermore, Dalmasso C et al[11] have reported that there are differential effects of testosterone on BP in the spontaneously hypertensive rat (SHR) depending on the age of the SHR – an effect that may be mediated in part by the renin-angiotensin system.

The increases in 24-h ambulatory BP on treatment in our study were modest (SBP 1.7 mmHg, with 95% CI 0.3, 3.1) and lower than with previous testosterone studies that employed both clinic and ambulatory BP measurements.[3,4] These previous studies used testosterone undecanoate (oral) and testosterone enanthate (subcutaneous) routes of administration and reported increases in ambulatory SBP of 4.9 and 3.7 mmHg, respectively. For the previously reported study of another oral testosterone undecanoate formulation,[3] the increase in ambulatory systolic BP for subjects receiving antihypertensive medication was 5.5 mmHg. In both our study and in the previous study of a different oral testosterone undecanoate formulation,[3] no correlations were observed between testosterone exposure and ambulatory systolic BP. The total testosterone (NaF/EDTA plasma $C_{avg\ 0-24}$) observed after 90 days of treatment in the previous study[3] and in the present study were also comparable (402.5 ± 127.7 and 393.3 ± 113.6 ng/dl, respectively).

Increases in clinic systolic BP of 3–5 mmHg in prospective studies of large populations have been shown to have strong relationships with adverse cardiovascular events, particularly heart failure and stroke.[12] However, the clinical importance of the small increases in BP in hypogonadal men observed in our study is less clear since men with testosterone deficiencies have increases in cardiovascular risk[13] and there are data that suggest that normalizing testosterone levels in hypogonadal men may be associated with lower rates of cardiovascular morbidity than men who stay at low testosterone levels.[14] Nevertheless, in hypogonadal men who require testosterone replacement, particularly those with a history of hypertension, careful clinical assessment for possible increases in BP remains important in clinical practice.

5 | CONCLUSIONS

In conclusion, this new oral formulation of testosterone undecanoate dosed between 100 mg once daily and 400 mg twice daily induced small increases in clinic and ambulatory BP. There were minimal increases in ambulatory heart rate that were not related to ambulatory BP changes. Study participants with a history of hypertension taking antihypertensive therapy and those with type 2 diabetes had larger increases in both ambulatory BP and heart rate following chronic oral testosterone undecanoate therapy than those without these 2 comorbidities. Hypogonadal men who were not receiving antihypertensive medication had negligible changes in ambulatory BP and heart rate.

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CONFLICT OF INTEREST

Dr White has received consulting fees from Marius Pharmaceuticals, Inc; Drs. Bernstein, and Dhingra are employees of Marius Pharmaceuticals, Inc; Dr Rittmaster is a former consultant to Marius Pharmaceuticals, Inc There was no remuneration for the drafting, review or editing of the manuscript.

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