Original Paper

# Efficacy and Safety of Darusentan in Patients With Resistant Hypertension: Results From a Randomized, Double-Blind, Placebo-Controlled Dose-Ranging Study

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*In this phase 2, randomized, double-blind, placebo-controlled forced dose-titration study, 115 patients with resistant hypertension, receiving background therapy with ≥3 antihypertensive medications including a diuretic at full doses, were randomized 2:1 to increasing doses of darusentan (10, 50, 100, 150, and 300 mg), a selective endothelin receptor antagonist, or matching placebo once daily for 10 weeks. Darusentan treatment decreased mean systolic and diastolic blood pressure levels in a dose-dependent fashion compared with placebo; the largest reductions were observed at week 10 (300-mg dose) (systolic, –11.5±3.1 mm Hg [P=.015]; diastolic, –6.3±2.0 mm Hg [P=.002]). Darusentan (300 mg) also decreased mean 24-hour, daytime, and nighttime ambulatory blood pressures from baseline to week 10. Darusentan was generally well tolerated; mild to moderate edema and headache were the most common adverse events. This study demonstrates a clinical benefit from a new class of antihypertensive agent in patients classified as resistant by the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure guidelines. (J Clin Hypertens. 2007;9:760–769)* ©2007 Le Jacq

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*Manuscript received May 2, 2007;*
*revised July 26, 2007;*
*accepted July 27, 2007*

www.lejacq.com ID: 7244

Hypertension (HTN) currently affects approximately 1 billion individuals worldwide.[1] Control of HTN is vital because increased blood pressure (BP) levels raise the risk of stroke, coronary artery disease, myocardial infarction, heart failure, kidney disease, and cardiovascular (CV) mortality.[2,3] Treatment guidelines have highlighted the need for aggressive management to reduce morbidity and mortality. Despite enhanced awareness, lifestyle modification, and extensive use of combination antihypertensive therapy, recommended BP goals are not achieved in a substantial number of hypertensive patients, however.

Resistant HTN, as defined by the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7),[4] is the failure to achieve guideline-defined BP goals in patients who are adhering to full doses of an appropriate 3-drug regimen, 1 of which is a diuretic. Although the

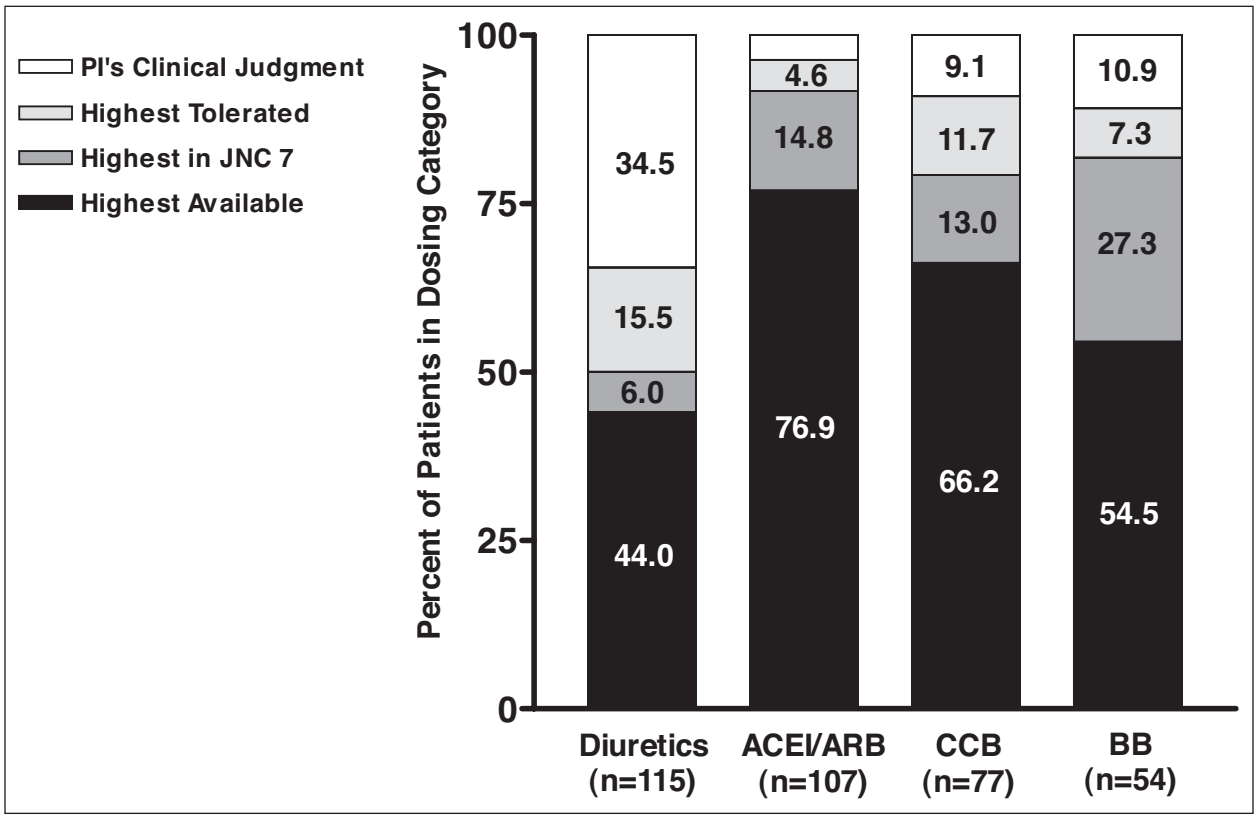


*Figure 1. Full dosing classification of qualifying antihypertensive medications. Justification for full dosing was documented using the following categories: (1) clinical judgment of the principle investigator (PI); (2) highest dose previously tolerated by that patient; (3) highest dose listed in the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7); or (4) highest available dose (ie, listed in the manufacturer's label or Physicians Desk Reference). For patients who qualified for study entry using each class of drugs shown (Table I), percent of patients in each full-dose category are displayed. ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CCB, calcium channel blocker; BB, β-blocker.*

true prevalence of resistant HTN is unknown, it is estimated to affect 2% to 5% of hypertensive patients in general practice, or approximately 3 million individuals in the United States.[5,6] In specialty referral clinics, the prevalence is believed to be substantially higher, potentially approaching 50%.[6–8] Currently, there is no accepted standard of care for the treatment of patients with resistant HTN. In many patients, current approaches fail to achieve goal BP levels, despite treatment with multiple medications. Once the usual initial treatment choices have failed, the only remaining option is to use agents that are associated with an increasing number of adverse effects, thus creating an unmet need for better ways to treat this population.

Endothelin-1 (ET-1) is a potent endothelium-derived vasoconstrictor implicated in the pathogenesis and progression of CV disease, including HTN. Activation of ET-1 signaling pathways via the endothelin type A receptor results in vasoconstriction and vascular smooth muscle cell proliferation.[9,10] In contrast, ET-1 activation of the endothelin type B receptor causes vasodilatation via production of prostacyclin and nitric oxide.[11] Elevated circulating ET-1 concentrations have been previously reported in patients with essential HTN[12] and patients with HTN and diabetes,[13,14] suggesting that direct modulation of the ET-1 pathway may represent a novel approach to reducing BP levels and may provide a new way to achieve BP goals when used with traditional antihypertensive medications.

Endothelin receptor antagonists (ERAs) have previously been evaluated in randomized clinical studies for the treatment of mild to moderate essential HTN.[15,16] Daily treatment with 500 mg of bosentan, a nonselective sulfonamide-class ERA, for 4 weeks was associated with a decrease in systolic BP (SBP) and diastolic BP (DBP) levels of 8.4 and 5.7 mm Hg, respectively, which was comparable to treatment with 20 mg of enalapril.[15] Darusentan, an orally effective, once-daily endothelin type A receptor–selective propanoic acid–class ERA, has been shown to reduce SBP and DBP levels by 11.3 and 8.3 mm Hg, respectively, in essential hypertensive patients after treatment with 100 mg for 6 weeks.[16] Although these drugs successfully

lower BP levels, concerns regarding the adverse event profile of the ERA class of agents, particularly teratogenicity and potential hepatotoxicity, make it unlikely that these drugs would be reasonable options for the treatment of uncomplicated HTN when other effective and well-tolerated treatments are available. Therefore, we hypothesized that treatment with darusentan, which reduces BP levels by a different mechanism than other available agents, may be useful in reducing BP levels in patients with resistant HTN, when used as add-on therapy to existing antihypertensive regimens.

This phase 2, randomized, double-blind dose-ranging study examined the efficacy and safety of darusentan 10 to 300 mg compared with once-daily placebo in patients with resistant HTN, as defined by JNC 7 criteria.

## METHODS

This study was approved by the institutional review boards of participating investigative centers and conducted in accordance with the principles of Good Clinical Practice and the revised Declaration of Helsinki.

### Patients

All patients provided written informed consent before the conduct of any study-related procedures. Eligible patients included men and women aged 35 to 85 years with resistant HTN as defined by the JNC 7 guidelines.[4] Patients were required to have a SBP level above recommended goals and to be receiving treatment with full doses of a diuretic (preferably a thiazide) and 2 or more antihypertensive medications from different drug classes (ie, calcium channel blockers [CCBs], β-blockers, angiotensin-converting enzyme inhibitors [ACEIs]/angiotensin II receptor blockers [ARBs]) at study entry. The study medical monitor reviewed screening data for concomitant antihypertensive medications to ensure that the entry criteria for full dosing, number, and combination of drugs were satisfied before patient randomization. Full disclosure defined as: (1) the principal investigator's best judgment; (2) highest dose tolerated by an individual patient; (3) highest dose listed in the JNC 7 guidelines; or (4) highest available (ie, listed in the manufacturer's label or Physician's Desk Reference). The criteria noted for full dosing of concomitant antihypertensive medications at study entry are presented in Figure 1.

There were no differences between the 2 treatment groups in the drugs selected or reasons for classifying doses as full. No adjustments to concomitant antihypertensive medications were permitted during study participation, per the protocol. SBP entry criteria were ≥140 mm Hg for patients without comorbid diabetes and/or chronic kidney disease (CKD) and ≥130 mm Hg for patients with diabetes and/or CKD. Estimated glomerular filtration rate (eGFR) was calculated for all patients at the time of screening using an abbreviated version of the Modification of Diet in Renal Disease equation.[17] Patients were identified as having diabetes if a preexisting diagnosis (type I or type II) was documented in the medical history, and all patients were assessed for the presence of CKD using laboratory results from the screening visit. CKD was defined, according to JNC 7 guidelines, as either (1) reduced excretory function with an eGFR <60 mL/min/1.73 $m^2$ or (2) the presence of albuminuria (urinary albumin-to-creatinine ratio >200 mg/g). Women of childbearing potential were required to have a negative serum pregnancy test result at the screening visit and a negative urine pregnancy test result at baseline and must have agreed to use contraception throughout participation in the study. Patients with an average sitting SBP level ≥180 mm Hg, DBP level ≥110 mm Hg, eGFR <30 mL/min/1.73 $m^2$, or serum alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >2 times the upper limit of normal (ULN) during screening were excluded from the study. Other exclusion criteria included arrhythmias, unstable angina pectoris, chronic heart failure, valvular heart disease, and significant pulmonary disease; myocardial infarction, unstable angina, or a cerebrovascular accident within 6 months of screening; and hemodialysis, peritoneal dialysis, or a history of renal transplant. Women who were pregnant or nursing were also excluded from participation.

### Study Design and Treatment

This phase 2, randomized, double-blind, placebo-controlled, forced dose-titration study was conducted between July 2004 and July 2005 at 30 investigative centers in the United States. Eligible patients were randomized 2:1 to receive increasing doses of darusentan or matching placebo once daily in the morning for 10 weeks after completing a 2-week single-blind placebo run-in period. Darusentan was initiated at a dosage of 10 mg/d and titrated every 2 weeks at doses of 50, 100, and 150 mg/d until reaching a maximum of 300 mg/d. One blinded dose maintenance or reduction was allowed in patients who did not tolerate up-titration. At the conclusion of the 10-week treatment period, patients discontinued the study drug within 2 weeks. Adjustment of background

**Table I.** Patient Demographics and Baseline Characteristics

| Parameter | Darusentan (n=76) | Placebo (n=39) | Total (N=115) |
|---|---|---|---|
| Age, y | 62±10 | 63±11 | 62±10 |
| Male sex, No. (%) | 43 (57) | 25 (64) | 68 (59) |
| Race, No. (%) | | | |
| White | 53 (70) | 29 (74) | 82 (71) |
| Black | 23 (30) | 9 (23) | 32 (28) |
| American Indian or Alaska Native | 0 | 1 (3) | 1 (1) |
| Weight, kg | 91.2±16.3 | 96.6±17.3 | 93.0±16.7 |
| Body mass index, kg/m$^2$ | 31.2±5.0 | 32.6±4.8 | 31.7±4.9 |
| Estimated GFR, mL/min/1.73 m$^2$ | 74.2±24.3 | 79.3±26.3 | 75.9±25.0 |
| Diabetes and/or chronic kidney disease, No. (%) | 46 (61) | 24 (62) | 70 (61) |
| Diabetes, No. (%) | 36 (47) | 19 (49) | 55 (48) |
| Chronic kidney disease, No. (%) | 20 (26) | 9 (23) | 29 (25) |
| Sitting SBP, mm Hg | 149.6±12.7 | 149.0±13.9 | 149.4±13.1 |
| Sitting DBP, mm Hg | 82.4±12.4 | 79.7±14.1 | 81.5±13.0 |
| Mean 24-hour SBP, mm Hg | 136.0±13.7 | 138.1±15.8 | 136.7±14.4 |
| Mean 24-hour DBP, mm Hg | 77.6±12.1 | 74.7±11.3 | 76.6±11.9 |
| Sitting heart rate, bpm | 66.7±10.6 | 68.7±11.2 | 67.4±10.8 |
| Qualifying concomitant antihypertensives, No. (%) | | | |
| Diuretics | 76 (100) | 39 (100) | 115 (100) |
| Calcium channel blockers | 49 (65) | 28 (72) | 77 (67) |
| β-Blockers | 37 (49) | 17 (44) | 54 (47) |
| ACEIs or ARBs | 71 (93) | 36 (92) | 107 (93) |

Data are presented as mean ± SD unless otherwise indicated. Abbreviations: ACEI, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; bpm, beats per minute; DBP, diastolic blood pressure; GFR, glomerular filtration rate; SBP, systolic blood pressure.

antihypertensive therapy was not allowed during study participation.

### Clinical Assessments

Coprimary efficacy end points were the changes from baseline through weeks 8 and 10 (ie, at doses of 150 and 300 mg, respectively) in trough sitting SBP level. BP was measured at every study visit (baseline and weeks 2, 4, 6, 8, and 10) using standard sphygmomanometry. Secondary end points included 24-hour SBP level as measured by ambulatory BP monitoring (ABPM), percentage of patients who achieved JNC 7 SBP goals,[4] and change from baseline in trough sitting DBP level. ABPM was performed once immediately before randomization and repeated during the 24 hours immediately preceding the week 10 study visit.

Physical examinations, vital sign measurements, clinical chemistry and hematologic laboratory tests, and electrocardiography were performed at the screening visit and periodically throughout the study. Blood samples were obtained at baseline and at weeks 4, 8, and 10 during study drug treatment to monitor liver function. Adverse events were monitored throughout the study.

### Statistical Methods

A sample size of 35 patients in the placebo arm and 70 patients in the darusentan arm was planned to provide at least 85% power to detect a difference from placebo for the darusentan 150- or 300-mg doses, assuming a placebo-corrected reduction from baseline in trough sitting SBP level of 8 mm Hg, a standard deviation of 12 mm Hg, and a correlation between week 8 and week 10 SBP level change of 0.85.

All patients who were randomized to treatment, received at least 1 dose of blinded study drug, and had a postbaseline BP measurement were included in the efficacy analyses. A nonlinear mixed effect model was used for the analysis of change in BP level, with comorbidity status (ie, the presence of diabetes and/or CKD vs the absence of both) as a covariate. This model used all observed BP measurements with no imputation for missing values. Linear contrast statements were used to test the slope through a given time point to assess the effect of the dose administered that week. Estimates of treatment effect were obtained via least square means. An analysis of covariance model including comorbidity, baseline SBP level, and treatment

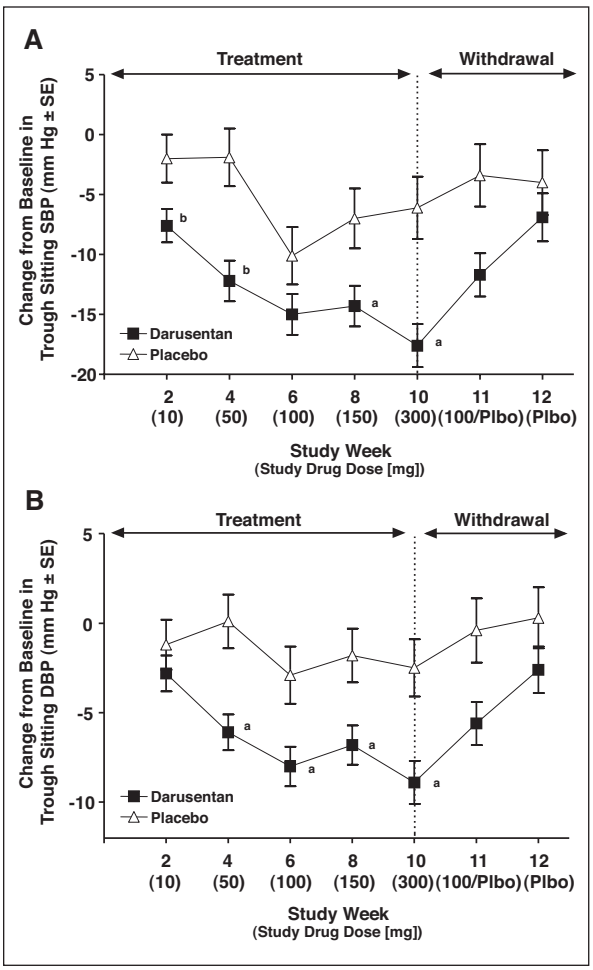


*Figure 2. Improvements in trough sitting systolic (A) and diastolic (B) blood pressure levels were dose-dependent. Data are least squares means ± standard error (SE). SBP indicates systolic blood pressure; Plbo, placebo; DBP, diastolic blood pressure. [a]P<.05 vs placebo. [b]P<.05 vs placebo before adjustment for multiple comparisons.*

group was used for the analysis of ambulatory BP data; missing values were not imputed. Response rates at each scheduled measurement were compared with logistic regression models at each BP measurement with comorbidity status as a covariate; missing values were imputed with last observation carried forward. Safety summaries include all patients who received at least 1 dose of blinded study drug.

Type I error rate for analysis of multiple doses was controlled by using the Hochberg method on the coprimary time points (weeks 8 and 10, corresponding to the 150- and 300-mg doses, respectively).[18] If 1 or more of these were significant, testing would proceed stepwise to week 6, week 4, and week 2 (doses of 100, 50, and 10 mg, respectively) as long as the prior comparison was significant at $\alpha$=0.05. This controlled the type I error rate for each measurement (eg, SBP, DBP, response). Adjusted *P* values were reported unless otherwise noted.

## RESULTS

### Study Demographics

A total of 192 patients were screened and 115 patients were randomized; 76 received darusentan and 39 received placebo. The majority of patients (87%) in each treatment group completed the study. The most common reasons for study discontinuation were adverse events (7 patients), withdrawal of consent (4 patients), and loss to follow-up (3 patients).

Patient demographics and baseline characteristics were generally similar between treatment groups (Table I). Overall, participants were predominantly male (59%) and white (71%), although a relatively high number of black patients were enrolled in the study (28%) compared with the general population. Participants had a mean age of 62 years and a mean weight of 93 kg; the prevalence of obesity (defined as a body mass index >30 kg/m$^2$) was >50% (median body mass index, 31.4; range, 20.0–42.5 kg/m$^2$). The majority of participants (61%) had comorbid diabetes, CKD, or both at baseline. Approximately 75% of the patient population had a reduced eGFR (ie, <90 mL/min/1.73 m$^2$); most participants (50.4%) were in the 60 to 89 mL/min/1.73 m$^2$ range. The use of concomitant antihypertensive medications was similar between treatment groups: all patients received a diuretic and ≥2 other antihypertensive agents at documented full doses, as specified in the protocol. In addition to diuretics, the most common classes of antihypertensive drugs used to qualify for study entry (ie, those that were documented at full dose) were ACEIs/ARBs (93%) and CCBs (67%), followed by β-blockers (47%). The total percentage of patients receiving these classes of drugs at any dose at study entry was slightly higher: 97% for ACEIs/ARBs, 74% for CCBs, and 68% for β-blockers. In addition, approximately 17% of patients were receiving antihypertensive drugs from classes other than those described above.

### Efficacy of Darusentan

The change from baseline SBP and DBP levels over time is shown in Figure 2, with data points corresponding to the scheduled time of dose escalation. Darusentan significantly reduced placebo-corrected mean trough sitting SBP level after 10 weeks of treatment (300-mg dose; –11.5±3.1 mm Hg; *P*=.015; Figure 2A), an effect that was also consistent across predefined subgroups (eg, age,

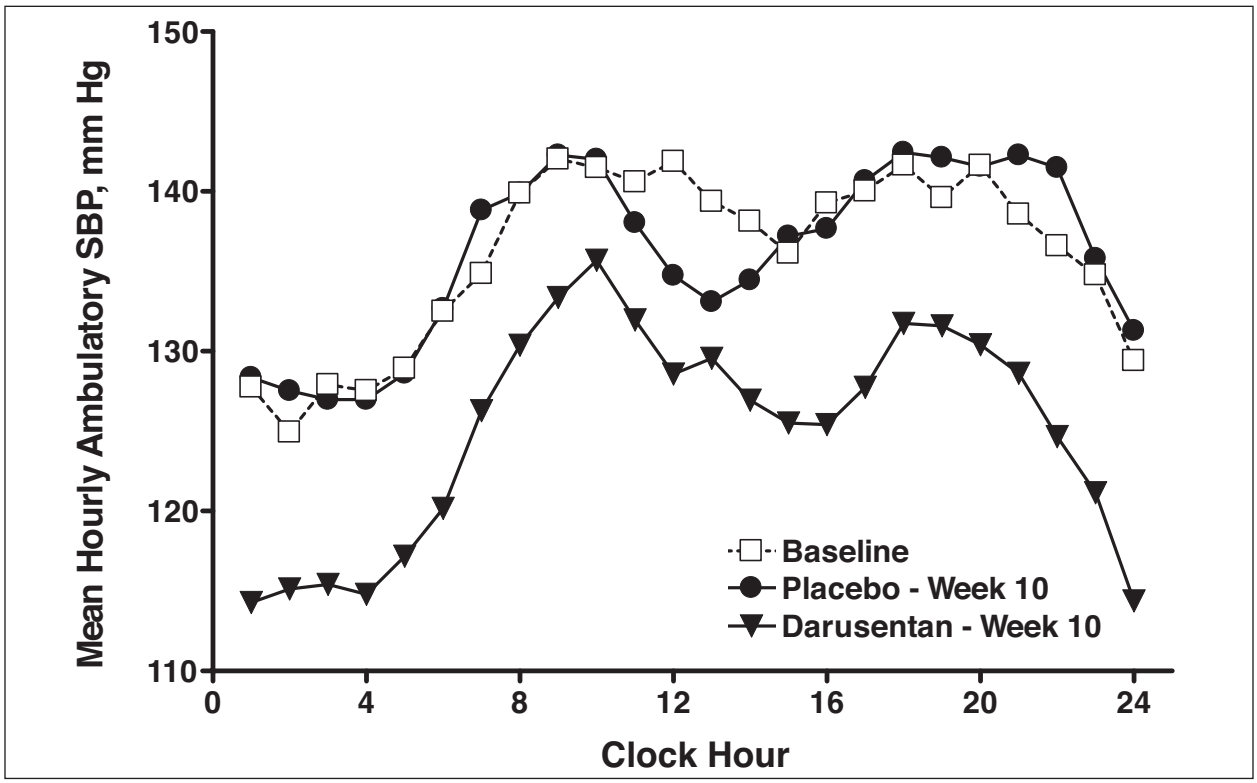


*Figure 3. Blood pressure–lowering effects of darusentan throughout the day. Plot of the circadian variation in mean systolic blood pressure (SBP) level was determined by ambulatory blood pressure monitoring at baseline and after 10 weeks of treatment with darusentan or placebo.*

race, sex, comorbidity status; data not shown). Improvement in the coprimary variable, change from baseline to week 8 in trough sitting SBP level was also significant compared with placebo (150-mg dose; placebo-corrected, –7.4±3.0 mm Hg; *P*=.048). At week 8 (150-mg dose), SBP goal was achieved in 43% of patients taking darusentan and 28% of patients taking placebo (*P*=.054). The percent of patients in whom SBP goal was met increased to 51% with darusentan compared with 33% with placebo (*P*=.054) at week 10 (300-mg dose), although neither of these results achieved statistical significance.

Darusentan significantly reduced placebo-corrected mean trough sitting DBP level after 10 weeks of treatment (–6.3±2.0 mm Hg; *P*=.002; Figure 2B). Significant improvements compared with placebo were evident beginning at week 4 (–6.2 mm Hg; *P*=.004) and were maintained or improved throughout the study. For both trough sitting SBP and DBP levels, improvements were dose-dependent in patients treated with darusentan, although not all changes in SBP level reached statistical significance because of the unusually large placebo response observed at week 6 (100-mg dose). The number of doses of concomitant antihypertensive drugs were not adjusted during the study.

ABPM performed at week 10 revealed significant reductions from baseline in placebo-corrected 24-hour SBP and DBP levels in patients treated with darusentan (–9.2±2.2 and –7.2±1.6 mm Hg, respectively; unadjusted *P*<.001). Reductions in BP level were maintained throughout the 24-hour monitoring period (Figure 3), with an estimated trough-to-peak ratio of 96%. A post hoc analysis demonstrated that darusentan reduced mean daytime and nighttime SBP levels from baseline to week 10 by 10.6±1.4 and 11.9±1.6 mm Hg, respectively (unadjusted *P*<.001; Table II), and daytime-nighttime ratio improved to 9.5% with darusentan as compared with 6.7% with placebo (unadjusted *P*=.057).

**Darusentan Safety and Tolerability**

In 78% of patients treated with darusentan, dosages were successfully escalated to the maximum study drug dosage of 300 mg/d. All patients were adherent to study drug regimen (mean compliance, 98%). Adverse events were generally mild to moderate in intensity. The most common adverse events among patients in the darusentan group were peripheral edema and headache (Table III). Peripheral edema was mild or moderate in intensity; only 1 case of severe edema was reported (with darusentan). On

**Table II.** Change in Daytime and Nighttime Ambulatory SBP Level

| Variable | No. | Darusentan | No. | Placebo |
|---|---|---|---|---|
| Baseline | | | | |
| Mean daytime SBP, mm Hg | 76 | 139.3±1.6 | 39 | 141.3±2.2 |
| Mean nighttime SBP, mm Hg | 75 | 127.6±1.6 | 39 | 131.9±3.2 |
| Mean daytime-nighttime SBP ratio | 75 | 7.8±0.9 | 39 | 6.9±1.2 |
| Week 10 (300-mg dose) | | | | |
| Mean daytime SBP, mm Hg | 64 | 129.5±1.6 | 33 | 139.3±2.3 |
| Mean nighttime SBP, mm Hg | 63 | 117.1±1.8 | 31 | 129.6±2.7 |
| Mean daytime-nighttime SBP ratio | 63 | 9.5±1.0[a] | 31 | 6.7±1.1 |
| Mean change from baseline to week 10 | | | | |
| Daytime SBP, mm Hg | 64 | –10.6±1.4[b] | 33 | –2.2±2.3 |
| Nighttime SBP, mm Hg | 62 | –11.9±1.6[b] | 31 | –3.3±2.6 |

Data are means ± SE. Mean daytime systolic blood pressure (SBP) was defined as the average ambulatory SBP level between 6 PM and 10 PM. Mean nighttime SBP was defined as the average ambulatory SBP level between 10 PM and 6 AM. Daytime-nighttime SBP ratio was calculated as the difference between mean daytime SBP level and mean nighttime SBP level divided by mean daytime SBP level and was expressed as a percentage. [a]*P*=.057 unadjusted for multiple comparisons. [b]*P*<.001 unadjusted for multiple comparisons.

**Table III.** Most Commonly Reported Adverse Events[a]

| | Patients, No. (%) | |
|---|---|---|
| Adverse Event | Darusentan (n=76) | Placebo (n=39) |
| Peripheral edema | 13 (17) | 2 (5) |
| Headache | 8 (11) | 2 (5) |
| Sinusitis | 6 (8) | 0 |
| Dizziness | 5 (7) | 1 (3) |
| Nasopharyngitis | 5 (7) | 1 (3) |
| Upper respiratory tract infection[b] | 4 (5) | 2 (5) |
| Gastroenteritis | 4 (5) | 1 (3) |
| Arthralgia/arthritis | 2 (3) | 6 (15) |
| Diarrhea | 1 (1) | 2 (5) |

[a]Occurred in ≥5% of patients in a treatment group. [b]Included patients with symptoms of an upper respiratory tract infection.

average, patients in the darusentan group gained approximately 0.5±2.4 kg of body weight while on active treatment, while those receiving placebo gained approximately 0.2 to 2.0 kg. Following randomization, 5 serious adverse events were reported in 4 patients in the darusentan group (coronary artery disease, aseptic meningitis, pneumonia, lung squamous cell carcinoma, and pleural effusion), and 1 serious adverse event was reported by a patient in the placebo group (ischemic colitis). Three serious adverse events (pneumonia, pleural effusion, and ischemic colitis) led to study discontinuation. None of these events was considered to be related to the study drug. No important changes in frequency or severity of adverse events over time were observed, and no deaths occurred during the study.

Heart rate was unaffected by treatment with darusentan, with a change from baseline of 0.4±0.9 beats per minute at week 10, which was comparable to the change of 2.3±1.3 beats per minute observed in the placebo group. Modest placebo-adjusted reductions in hemoglobin (Hb) and hematocrit (HCT) levels were observed at weeks 4 (Hb, –1.0 g/dL; HCT, –3.0%; *P*<.001, compared with placebo for both comparisons) and 10 (Hb, –1.3 g/dL; HCT, –3.7%; *P*<.001 vs placebo for both comparisons) in darusentan-treated patients. Decreases in Hb and HCT values were reported as adverse events in 2 patients treated with darusentan; both events were mild in intensity. Liver function test results were comparable between treatment groups; mean concentrations of ALT, AST, and γ-glutamyltransferase decreased slightly from baseline in both groups. No patients experienced elevations in ALT or AST levels >2 times the ULN at any time during the study. There were no other clinically significant changes in laboratory parameters observed.

## DISCUSSION

To our knowledge, this is the first randomized, double-blind, placebo-controlled drug study designed to treat patients with resistant HTN, currently

defined by JNC 7 as a treated hypertensive patient whose BP is above goal on full doses of at least 3 antihypertensive agents, 1 of which is a diuretic. By strictly adhering to the JNC 7 definition of this syndrome, we enrolled a clearly defined patient population and eliminated other factors (eg, nonadherence to therapy, inadequate drug treatment, secondary HTN) that can result in a patient's HTN being considered resistant but which usually do not require additional antihypertensive drugs in order to reach BP goal, a level determined arbitrarily by JNC 7 and other guideline committees. Despite the best efforts of physicians to optimize antihypertensive drug therapy in adherent patients, SBP level remains above guideline-recommended goals in many patients. This phase 2 study investigated the effectiveness and safety of darusentan, a drug with a different mechanism of action than those commonly used, in patients with guideline-defined resistant HTN.

Darusentan force up-titrated from 10 to 300 mg once daily over 10 weeks achieved statistically and clinically meaningful improvements in BP level in patients with resistant HTN. Reductions in SBP and DBP levels were dose-dependent, with the greatest benefit observed after 2 weeks of treatment with darusentan 300 mg/d (week 10). Conclusions about the effect of lower doses of darusentan were complicated by a study design that confounded time and dose; however, there was evidence that a dosage as low as 50 mg/d provided a clinically meaningful decrease in both SBP and DBP levels. Reductions in trough sitting SBP level in patients receiving added darusentan compared with added placebo were statistically significant throughout the study, with the exception of week 6, because of the larger-than-anticipated placebo effect observed at this time point (–10.1 mm Hg). No obvious outliers were found that would explain these placebo results. The magnitude of the placebo effect may be, in part, attributed to the relatively small sample size. However, because a large placebo effect has also been reported in other HTN trials,[19–21] it is possible that this fluctuation is reflective of the inherent variability of sphygmomanometric measurements of SBP, especially in difficult-to-treat patients. It should be noted that DBP measurements in all participants were stable over time. The variability in ambulatory SBP and DBP values was also consistent with past studies.[19] Differences in achievement of goal BP levels at weeks 8 and 10 between the darusentan and placebo groups were not statistically significant, however, potentially because of the small sample size.

The study population was largely composed of patients with diabetes and/or CKD, as would be expected in patients with resistant HTN. It is well recognized that the prevalence of HTN is significantly higher among persons with diabetes than in the general population.[22,23] Likewise, the risk of CV morbidity is also greatly increased among patients with diabetes or CKD,[24,25] and clinical trials have identified diabetics as a subgroup of patients with hypertension in whom BP control is difficult to achieve and particularly beneficial.[26–28] In an effort to reduce CV disease risk and progression of diabetic nephropathy to end-stage renal disease, the target BP goal in JNC 7 was reduced from 140/90 mm Hg to 130/80 mm Hg in persons with diabetes.[4] In a population in which achieving BP goals is particularly difficult, a lower BP target will inevitably result in an increase in the prevalence of resistant HTN within this subgroup. The addition of darusentan was equally effective in reducing SBP and DBP levels in patients with and without comorbidities in this study.

The BP-lowering benefits of darusentan were maintained over 24 hours; mean 24-hour BP levels, as well as daytime and nighttime measurements, were significantly reduced relative to placebo at the end of the study. Maintained efficacy throughout the day is supportive of the once-daily dosing regimen of this medication.

Darusentan was generally safe and well tolerated in this patient population. The majority of adverse events were mild to moderate, with few serious adverse events or patients who withdrew from the study because of adverse events. The severity of peripheral edema was mild to moderate and infrequently resulted in discontinuation. Because of the design of this trial, changes in the diuretic regimen of participants were not allowed; however, in clinical practice, adjustments would likely be made and so the significance of this adverse effect may have been magnified in this trial. Future studies will examine the effectiveness of diuretic dose adjustments to manage the adverse effect of peripheral edema and whether the decrease in Hb and HCT levels may reflect hemodilution due to volume expansion. No evidence of specific bone marrow suppression or another mechanism has been found to account for the reduction in Hb and HCT values. A significant and important reassuring safety finding was the lack of liver function test abnormalities commonly associated with daily treatment with sulfonamide-class ERAs.[29,30] No patients experienced elevations in ALT or AST levels >2 times the ULN at any time during this study.

One of the limitations of the current study was the lack of independent-dose groups. Doses were escalated in patients at 2-week intervals, limiting the ability to assess the efficacy of a single darusentan dosage over time. Long-term studies with discrete dose groups will be necessary to fully evaluate the appropriate dosage for patients with resistant HTN.

## CONCLUSIONS

Darusentan was effective at lowering BP values when used as add-on antihypertensive therapy in patients with guideline-defined resistant HTN with BP that was not at guideline-defined treatment goals. A statistically significant difference in patients achieving SBP goal at weeks 8 and 10 was not observed compared with placebo, however. All participants received ≥3 antihypertensive medications, including a diuretic, at documented full doses at entry and throughout the study. The safety and tolerability profile of darusentan was favorable; most patients tolerated the maximum administered dose and no aminotransferase elevations above 2 times the ULN were observed. Edema, the most common adverse reaction, appears to be due to volume expansion, which is likely to be manageable in clinical practice. Based on the results of this study, phase 3 clinical studies of darusentan in resistant HTN at dosages up to 300 mg/d are warranted and are under way.

*Acknowledgments and disclosure: The authors would like to thank* ***Kenneth Borow, MD***, ***Richard Bittman, PhD***, ***Rebecca Light***, *and* ***Marshelle Warren, MD****, for their assistance. In addition, this manuscript was prepared with editorial assistance from* ***Crystal Murcia, PhD****, and* ***Larry Nelson, PhD****. This study was supported by Gilead Colorado, Inc.*

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