

# A selective endothelin-receptor antagonist to reduce blood pressure in patients with treatment-resistant hypertension: a randomised, double-blind, placebo-controlled trial



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## Summary

**Background** Hypertension cannot always be adequately controlled with available drugs. We investigated the blood-pressure-lowering effects of the new vasodilatory, selective endothelin type A antagonist, darusentan, in patients with treatment-resistant hypertension.

**Methods** This randomised, double-blind study was undertaken in 117 sites in North and South America, Europe, New Zealand, and Australia. 379 patients with systolic blood pressure of 140 mm Hg or more ( $\geq 130$  mm Hg if patient had diabetes or chronic kidney disease) who were receiving at least three blood-pressure-lowering drugs, including a diuretic, at full or maximum tolerated doses were randomly assigned to 14 weeks' treatment with placebo (n=132) or darusentan 50 mg (n=81), 100 mg (n=81), or 300 mg (n=85) taken once daily. Randomisation was made centrally via an automated telephone system, and patients and all investigators were masked to treatment assignments. The primary endpoints were changes in sitting systolic and diastolic blood pressures. Analysis was by intention to treat. The study is registered with ClinicalTrials.gov, number NCT00330369.

**Findings** All randomly assigned participants were analysed. The mean reductions in clinic systolic and diastolic blood pressures were 9/5 mm Hg (SD 14/8) with placebo, 17/10 mm Hg (15/9) with darusentan 50 mg, 18/10 mm Hg (16/9) with darusentan 100 mg, and 18/11 mm Hg (18/10) with darusentan 300 mg ( $p < 0.0001$  for all effects). The main adverse effects were related to fluid accumulation. Oedema or fluid retention occurred in 67 (27%) patients given darusentan compared with 19 (14%) given placebo. One patient in the placebo group died (sudden cardiac death), and five patients in the three darusentan dose groups combined had cardiac-related serious adverse events.

**Interpretation** Darusentan provides additional reduction in blood pressure in patients who have not attained their treatment goals with three or more antihypertensive drugs. As with other vasodilatory drugs, fluid management with effective diuretic therapy might be needed.

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## Introduction

Contemporary guidelines for treatment of hypertension have recommended target blood pressures of less than 140/90 mm Hg (<130/80 mm Hg if the patient has diabetes or chronic kidney disease), with the aim of improving protection against cardiovascular and renal events.<sup>1,2</sup> Most patients with hypertension can achieve these targets when only one or two antihypertensive drugs are administered in addition to appropriate lifestyle changes; however, other patients do not meet these targets, even with regimens of three or four drugs. Sometimes this treatment failure can be resolved by rectifying underlying reasons for inadequate control, including poor treatment compliance by the patient, inexpertly selected treatment regimens, or the conflicting effects of concomitant drugs for other reasons. Despite these approaches, some patients with hypertension do not achieve satisfactory blood pressures.

Treatment-resistant hypertension has been defined as failure to reach blood-pressure targets despite the use of at least three drugs, one of which should be a diuretic, at

the full doses recommended by hypertension guidelines, with approved drug labels, and tolerated by the patient.<sup>1</sup> Patients with this disorder are most likely at increased cardiovascular risk resulting from a history of longstanding, severe hypertension, typically in association with other cardiovascular risks such as obesity, diabetes, and chronic kidney disease.<sup>3</sup> Thus, for patients whose blood pressures cannot be controlled by three or more drugs, innovative agents that might provide additional efficacy need to be assessed. Few prospective clinical trials have assessed treatment strategies in patients with treatment-resistant hypertension, and most have been largely empirical.<sup>3</sup>

One new approach is the use of endothelin-receptor antagonists. Raised circulating concentrations of endothelin 1 have been reported in patients with hypertension and diabetes,<sup>4-6</sup> indicating the potential value of the endothelin-receptor blockade. This approach might be of particular relevance in patients with treatment-resistant hypertension who are already receiving standard antihypertensive therapies, such as

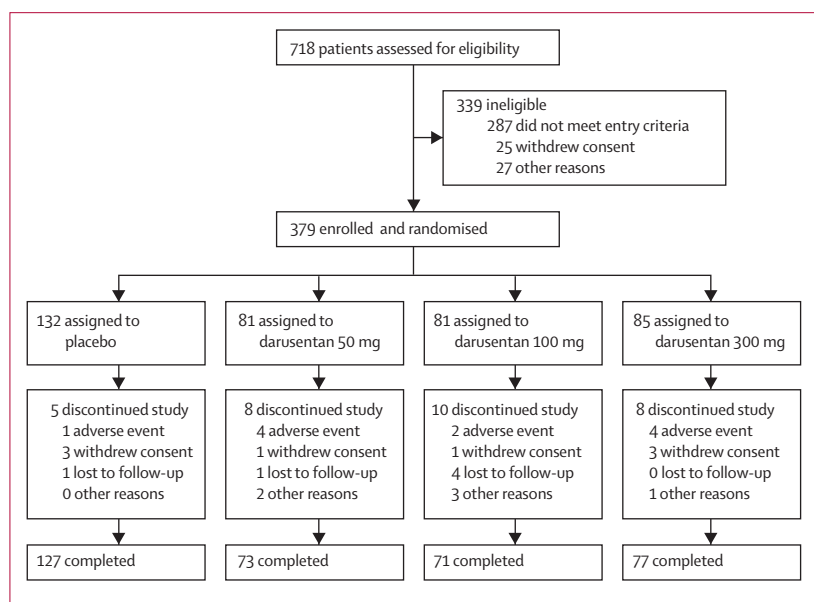
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**Figure 1: Trial profile**

An additional 13 patients discontinued study drug prematurely, mainly due to adverse event, but completed study procedures through week 14.

blockers of the renin-angiotensin system, diuretic drugs, and calcium-channel blockers, since there is no evidence that the vasoconstrictor effects of endothelin at its type A receptor are successfully inhibited by these agents.

Treatment with the non-selective, sulphonamide-type endothelin-receptor antagonist bosentan produced significant reductions in systolic and diastolic blood pressures, similar to those detected with an angiotensin-converting-enzyme (ACE) inhibitor during 4 weeks of treatment in patients with hypertension.<sup>7</sup> Darusentan is a propanoic acid-based endothelin type A selective-receptor antagonist of the propanoic acid class. When used as a single agent in patients with stage 1 or 2 hypertension, darusentan at a dose of 100 mg once daily decreased blood pressure by about 11/8 mm Hg, corrected for the placebo response, after 6 weeks of treatment.<sup>8</sup> However, because of the potential risks associated with the use of endothelin-receptor antagonists, including the potential for teratogenicity, these agents should be used in specific patients, such as those with treatment-resistant hypertension. In a previous study of such patients, sequentially increasing doses of darusentan from 10 mg to 300 mg once daily reduced blood pressure significantly more than did placebo.<sup>9</sup>

We undertook a randomised, double-blind trial comparing differing doses of darusentan with placebo in patients with treatment-resistant hypertension as previously defined.<sup>1</sup> To reflect clinical practice, in which treatment-resistant hypertension is often associated with serious concomitant disorders, we included patients with diabetes, heart disease, and chronic kidney disease in this study.

## Methods

### Patients

Patients were recruited from 117 sites in North and South America, Europe, New Zealand, and Australia. Patients were eligible to participate if they had treatment-resistant hypertension defined as systolic blood pressures of 140 mm Hg or greater ( $\geq 130$  mm Hg if they had diabetes or chronic kidney disease) despite treatment with three or more antihypertensive drugs, including a diuretic, at full doses. The doses of antihypertensive drugs that each patient was receiving were characterised at study entry to ensure that background therapy was sufficient to describe patients as treatment resistant. A minimum dose of 25 mg per day of hydrochlorothiazide (or its equivalent for other thiazide diuretic drugs) was needed. Doses of other baseline antihypertensive drugs were considered to be at full dose when they were at the highest labelled dose, highest usual dose in the local practice, highest tolerated dose, or highest appropriate dose according to the investigator's best clinical judgment. Apart from the blood pressure and background drug criteria, patients were also required to have a body-mass index between 20 kg/m<sup>2</sup> and 43 kg/m<sup>2</sup>, and estimated glomerular filtration rates (GFR) of 30 mL/min/1.73 m<sup>2</sup> or more. Female patients were required to be of non-childbearing potential.

We excluded patients with sitting systolic blood pressure of 180 mm Hg or more or diastolic blood pressure of 110 mm Hg or more. Patients with heart failure, poorly controlled diabetes, anaemia, or liver dysfunction were also excluded, as were those with coronary, arrhythmic, or stroke events within the past 6 months. All patients provided written informed consent. The protocol was approved by the ethics committees or institutional review boards of all participating sites. The trial was undertaken in compliance with Good Clinical Practice guidelines and the ethics principles set out in the Declaration of Helsinki.

### Randomisation and masking

After screening for eligibility, all patients underwent a single-blind, placebo run-in for 2 weeks to ensure that blood pressure remained stable and continued to meet entry criteria. Eligible patients were randomly assigned in a ratio of 7:7:7:11 to darusentan 50 mg, 100 mg, or 300 mg or to placebo orally, once daily in the morning. Patients were stratified by comorbidity status (presence of diabetes or chronic kidney disease *vs* absence of both) and race (black *vs* non-black). The randomisation schedule was generated by a group external to the study sponsor, and all individuals involved in the conduct of the trial were masked to treatment assignments for the duration of the study. Randomisation assignments were made centrally via an automated telephone system. The pregenerated randomisation schedule was programmed via algorithm into the telephone system. Investigational

sites were required to call directly into the telephone system to randomly assign eligible patients (which occurred at the appropriate visit on the basis of demographic data entered into the system by the site) and to receive assignments of masked study drug at each visit (packaged in blister packs identically for each treatment group) according to the randomisation algorithm.

### Procedures

Patients assigned to higher doses of darusentan were titrated to their final doses in 2-week intervals. In the event of study drug intolerance, one blinded dose reduction was allowed. Changes to background antihypertensive therapy were not allowed during the study; however, investigators could increase the use of diuretic drugs to address oedema or other fluid-related side-effects.

The prespecified primary endpoints were the change from baseline to week 14 in sitting systolic and diastolic blood pressures. Secondary endpoints included changes from baseline to final measurement in mean 24-h systolic and diastolic blood pressures, the percentage of patients who reached goal for systolic blood pressure after 14 weeks of treatment, and change from baseline in estimated GFR. We also assessed the safety and tolerability of darusentan.

Clinic blood pressures were measured at lowest study drug concentration in the seated position by standard sphygmomanometry. Ambulatory blood-pressure monitoring was done for all patients at randomisation and at the end of the study. Automated readings were obtained every 20 min throughout the 24-h observations. Laboratory tests were done at baseline, after 2 weeks, and every 4 weeks thereafter.

### Statistical analysis

With the assumption of a difference in placebo-adjusted change from baseline of 8 mm Hg in lowest systolic blood pressure for each darusentan dose and an SD of 15 mm Hg, 121 patients randomly assigned to placebo and 77 randomly assigned to each dose of darusentan were needed to detect a difference between placebo and at least one dose of darusentan with 95% power. The power was estimated with PASS software, and verified for the prespecified endpoint analysis with simulations in SAS (version 8.2).

All data analysis was done according to a pre-established statistical analysis plan. For change from baseline in systolic and diastolic blood pressures, we compared patients randomly assigned to receive each dose of darusentan (50 mg, 100 mg, and 300 mg) with those randomly assigned to receive placebo. ANCOVA was used, with treatment group, baseline comorbidity status, and race (stratification factors for randomisation) and baseline value as explanatory variables in the model, and change in systolic blood pressure from baseline to week 14 as the outcome variable. Patients without week 14

	Placebo (n=132)	Darusentan 50 mg (n=81)	Darusentan 100 mg (n=81)	Darusentan 300 mg (n=85)	All patients (N=379)
Age (years)	62 (9)	62 (8)	62 (9)	61 (10)	62 (9)
Women	72 (55%)	38 (47%)	40 (49%)	41 (48%)	191 (50%)
Black	27 (21%)	16 (20%)	14 (17%)	18 (21%)	75 (20%)
Body-mass index (kg/m <sup>2</sup> )	32 (6)	33 (5)	31 (6)	31 (5)	32 (5)
eGFR (mL/min/1.73 m <sup>2</sup> )	80 (23)	81 (21)	76 (20)	78 (20)	79 (21)
History of heart disease	38 (29%)	20 (25%)	24 (30%)	21 (25%)	103 (27%)
Type 2 diabetes mellitus	55 (42%)	32 (40%)	33 (41%)	33 (39%)	153 (40%)
Chronic kidney disease	34 (26%)	17 (21%)	21 (26%)	24 (28%)	96 (25%)
Albuminuria*	51 (42%)	24 (30%)	35 (44%)	30 (38%)	140 (39%)
≥Four antihypertensive drugs	75 (57%)	50 (62%)	50 (62%)	45 (53%)	220 (58%)
Diuretic drugs	131 (99%)	81 (100%)	81 (100%)	84 (99%)	377 (99%)
ACEI or ARB	127 (96%)	78 (96%)	78 (96%)	84 (99%)	367 (97%)
Calcium-channel blocker	96 (73%)	64 (79%)	56 (69%)	65 (77%)	281 (74%)
β blocker	85 (64%)	51 (63%)	56 (69%)	58 (68%)	250 (66%)
Other antihypertensive drugs	25 (19%)	16 (20%)	23 (28%)	15 (18%)	79 (21%)
SBP (mm Hg)	151 (11)	150 (11)	152 (10)	152 (11)	151 (11)
DBP (mm Hg)	87 (11)	87 (10)	86 (11)	86 (11)	86 (11)
Heart rate (beats per min)	67 (11)	66 (10)	65 (8)	68 (11)	67 (10)
24-h SBP (mm Hg)†	135 (13)	136 (11)	136 (13)	134 (15)	135 (13)
24-h DBP (mm Hg)†	78 (10)	81 (10)	79 (12)	77 (10)	78 (11)

Data are mean (SD) or number of patients (%). eGFR=estimated glomerular filtration rate. ACEI=angiotensin-converting-enzyme inhibitor. ARB=angiotensin-receptor blocker. SBP=systolic blood pressure. DBP=diastolic blood pressure. \*Albuminuria was defined as urinary albumin-to-creatinine ratio 30 mg or more albumin/g creatinine at baseline. †Only patients with a baseline record for ambulatory blood-pressure monitoring that met prespecified quality-control criteria were summarised.

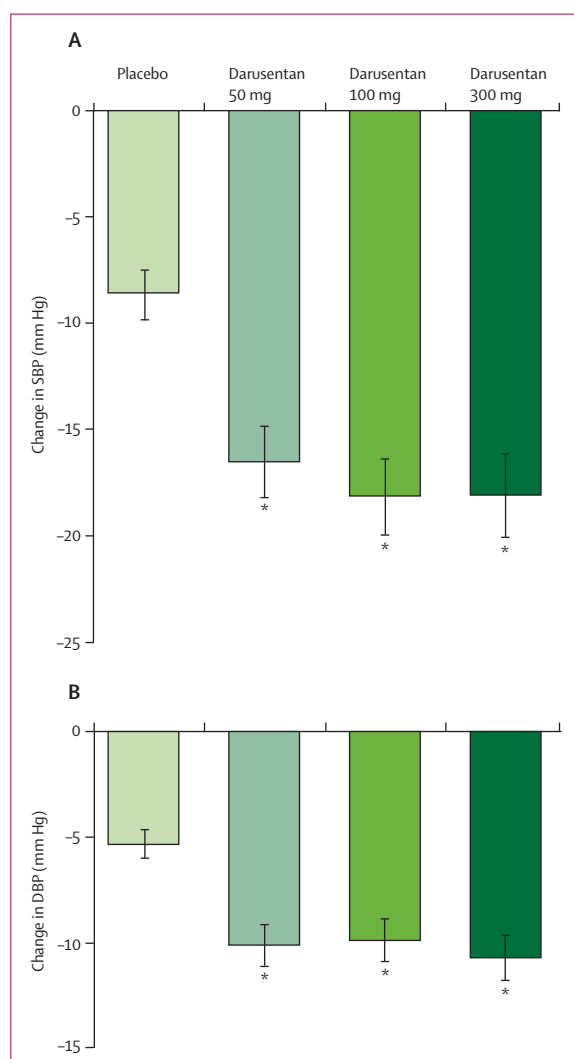
**Table 1: Baseline patient characteristics**

assessments were included with the last available observation. To address the potential effect of protocol-allowed changes to diuretic drugs on the efficacy endpoints, we also analysed changes from baseline in systolic and diastolic blood pressures with the last available observation obtained before a diuretic change (addition or increase in dose). The proportion of patients attaining the goal blood pressure was tested with logistic regression with the same covariates. Mean 24-h data for ambulatory blood-pressure monitoring and estimated GFR data were analysed analogously to the primary efficacy endpoint. Only records for ambulatory blood-pressure monitoring that met prespecified quality control criteria were included in the mean 24-h endpoint analyses. Type-I error rate was controlled for all prespecified primary and secondary efficacy analysis comparisons with the fallback method.<sup>10,11</sup> Laboratory and safety data were assessed as available with no imputation. Analyses were done on an intention-to-treat basis.

The study is registered with ClinicalTrials.gov, number NCT00330369.

### Role of the funding source

This study was designed collaboratively by the academic authors and the sponsor. The sponsor was responsible for gathering data from investigational sites to create the clinical database. On the basis of an analysis plan



**Figure 2: Changes from baseline in clinic seated blood pressure after 14 weeks of treatment**  
(A) Change in systolic blood pressure (SBP). (B) Change in diastolic blood pressure (DBP). Error bars show SE. \* $p < 0.0001$ .

developed in collaboration with the academic authors, who also took responsibility for interpretation of the data and for submitting this paper for publication, the sponsor did the data analysis. All authors had full access to study results after unmasking of data.

## Results

Figure 1 shows the trial profile. 718 patients were screened for this study of treatment-resistant hypertension; 339 patients were ineligible (mainly for not meeting the blood-pressure criteria required for study entry) and 31 withdrew during the study (11 for adverse events). An additional 13 patients prematurely discontinued study drug treatment (two in placebo group, two in darusentan 50 mg group, four in darusentan 100 mg group, five in darusentan 300 mg group), but completed all study

procedures, resulting in 348 patients completing the full 14-week treatment period (335 on study drug). All 379 randomly assigned patients were included in the primary analyses (intention to treat). Baseline characteristics were similar across the four study groups (table 1).

Almost all patients were receiving a blocker of the renin-angiotensin system (table 1). Calcium-channel blockers were used in about three-quarters of patients and roughly two-thirds were taking a  $\beta$  blocker (table 1). About 99% of patients were receiving full doses of the above drugs, according to the criteria in the study protocol. Consistent with entry criteria, almost all patients were receiving a diuretic drug at baseline (table 1). 343 (91%) were receiving thiazide-type diuretics, 315 (83%) of whom were on hydrochlorothiazide specifically (median dose 25 mg per day; range 12.5–150). 43 (11%) patients were on a loop diuretic at baseline. 159 (42%) patients were receiving exactly three antihypertensive drugs at baseline and 220 (58%) were receiving four or more. Additionally, 173 (46%) were receiving a statin, 149 (39%) aspirin, and 135 (36%) one or more antidiabetic drugs (including insulin).

Figure 2 shows the baseline values and treatment-induced changes in clinic seated systolic and diastolic blood pressures for the four treatment groups. Compared with placebo, all three darusentan doses produced significant reductions in both systolic and diastolic blood pressures ( $p < 0.0001$  for all effects; figure 2). We noted no significant differences between darusentan dose groups. These changes resulted in the following mean systolic and diastolic blood pressure values at the end of the study: 143/81 mm Hg (SD 15/12) with placebo, 134/77 mm Hg (16/10) with darusentan 50 mg, 134/76 mm Hg (17/11) with darusentan 100 mg, and 134/76 mm Hg (17/11) with 300 mg.

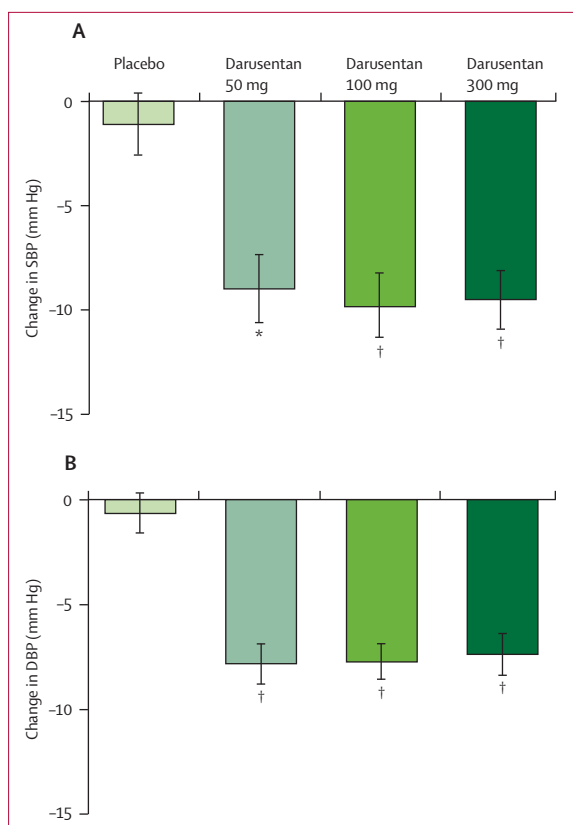
We recorded similar decreases in systolic blood pressure between men and women, between those older and younger than 65 years, and those with or without diabetes or chronic kidney disease; however, not all responses were significant compared with placebo (table 2). For patients who entered the trial on three background antihypertensive agents ( $n=159$ ) compared with those on four or more ( $n=220$ ), the mean decreases in systolic and diastolic blood pressures were 9/6 (SD 12/7) versus 8/5 mm Hg (16/8) for placebo; 15/10 (15/8) versus 17/10 mm Hg (16/9) for darusentan 50 mg; 20/12 (17/9) versus 17/9 mm Hg (16/9) for darusentan 100 mg; and 18/10 (19/11) mm Hg for darusentan 300 mg. Treatment effects between the patients taking three drugs and those taking four or more did not differ significantly.

On the basis of the clinic seated blood pressures for the entire study cohort, the goal for systolic blood pressure ( $<140$  mm Hg or  $<130$  mm Hg if the patient had diabetes or chronic kidney disease) was achieved by 36 (27%) patients in the placebo group, 43 (53%) in darusentan 50 mg group ( $p=0.0002$ ), 43 (53%) in darusentan 100 mg

	Placebo (n=132)	Darusentan 50 mg (n=81)	Darusentan 100 mg (n=81)	Darusentan 300 mg (n=85)
<b>Age (years)</b>				
<65 (n=233)	-8.8 (1.5)	-16.4 (2.3); p=0.0020	-17.2 (2.4); p=0.0014	-19.5 (2.4); p<0.0001
≥65 (n=146)	-8.3 (2.1)	-16.8 (2.3); p=0.0091	-19.4 (2.9); p=0.0038	-15.8 (3.4); p=0.0554
<b>Sex</b>				
Women (n=191)	-9.9 (1.8)	-19.9 (2.4); p=0.0002	-18.3 (2.9); p=0.0035	-20.2 (2.8); p=0.0009
Men (n=188)	-7.1 (1.7)	-13.5 (2.3); p=0.0222	-18.0 (2.3); p=0.0003	-16.1 (2.7); p=0.0036
<b>Comorbidity status</b>				
Diabetes (n=153)	-7.2 (1.9)	-13.7 (2.3); p=0.0104	-18.4 (3.1); p=0.0013	-13.4 (3.0); p=0.0724
CKD (n=96)	-7.6 (2.4)	-11.1 (4.1); p=0.2722	-17.5 (4.0); p=0.0292	-16.0 (4.3); p=0.0514
Neither diabetes nor CKD (n=176)	-10.1 (1.9)	-18.9 (2.6); p=0.0051	-17.8 (2.3); p=0.0114	-22.2 (2.8); p=0.0003
<b>Number of background antihypertensive drugs</b>				
Exactly three (n=159)	-8.7 (1.6)	-15.1 (2.6); p=0.0136	-19.8 (3.1); p=0.0007	-18.3 (2.7); p=0.0009
≥Four (n=220)	-8.5 (1.8)	-17.4 (2.2); p=0.0017	-17.1 (2.3); p=0.0040	-17.9 (2.8); p=0.0070

Data are mean (SE). p values indicate changes from baseline compared with placebo. CKD=chronic kidney disease.

**Table 2: Changes from baseline in systolic blood pressure for selected subgroups**



**Figure 3: Changes from baseline in mean 24-h ambulatory blood pressure after 14 weeks**

(A) Change in systolic blood pressure (SBP). (B) Change in diastolic blood pressure (DBP). Error bars show SE. \*p=0.0002. †p<0.0001.

group (p<0.0001), and 41 (48%) in darusentan 300 mg group (p=0.0007). In patients with diabetes, nine (16%) achieved a systolic blood pressure of less than 130 mm Hg at week 14 in the placebo group, 11 (34%) in darusentan 50 mg group, 15 (45%) in darusentan 100 mg group, and 10 (30%) in darusentan 300 mg group.

Figure 3 shows the changes from baseline in systolic and diastolic blood pressures measured by 24-h ambulatory blood-pressure monitoring for all four treatment groups. This analysis includes 210 randomly assigned patients who had records for ambulatory blood-pressure monitoring at baseline and at least one additional measurement after baseline that met prespecified criteria for quality. The effects of each of the darusentan treatment groups on both systolic and diastolic blood pressures differed significantly from those with placebo (figure 3). We also noted that each of the darusentan dose groups produced sustained blood-pressure reductions across the 24-h dosing interval compared with placebo, which had only a small effect on blood pressure when measured by this technique (data not shown). Figure 4 shows the end-of-study ambulatory values for mean systolic blood pressure over the 24-h recording period.

During the trial, diuretic therapy could be intensified at the discretion of the investigators to manage fluid retention (apart from within 2 weeks of the primary endpoint assessment at week 14). Six patients in the placebo group had diuretic agents added (or altered to increased doses) by investigators to address fluid-related adverse events, nine in darusentan 50 mg group, ten in darusentan 100 mg group, and eight in darusentan 300 mg group. For the three darusentan groups combined, 27 patients with adverse events of oedema or fluid retention received diuretic agents. In 19 (70%) of these cases, the investigators subsequently reported that the clinical findings (eg, oedema) prompting this additional diuretic therapy had resolved. Because of the potential effect of these diuretic changes on the primary efficacy results, mean changes in systolic and diastolic blood pressures were also measured with only the last available blood pressures before implementation of the changes to diuretic drugs. Mean decreases from baseline in systolic and diastolic blood pressures were 8/5 mm Hg

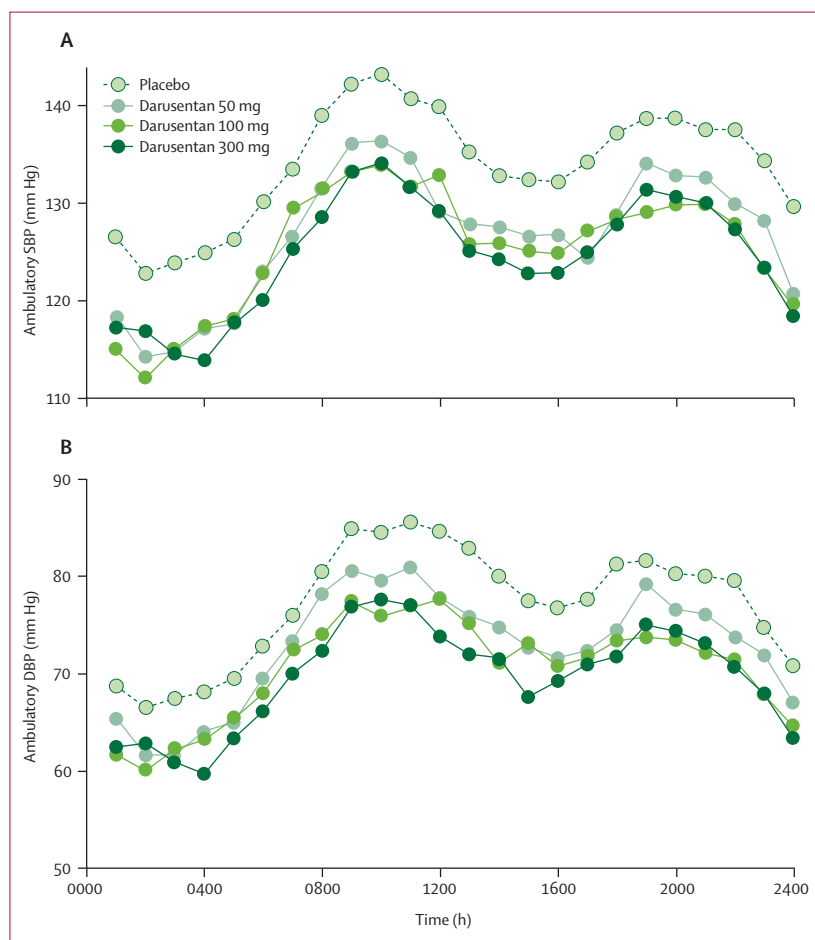


Figure 4: Ambulatory blood pressure (expressed as hourly means for each treatment group) over 24 h, measured at end of trial

(A) Systolic blood pressure (SBP). (B) Diastolic blood pressure (DBP).

(SD 14/8) in placebo group, 16/10 mm Hg (15/8) in darusentan 50 mg group, 15/9 mm Hg (16/9) in darusentan 100 mg group, and 17/10 mm Hg (17/10) in darusentan 300 mg. These results were consistent with the primary endpoint data presented in table 2.

Table 3 shows changes in serum creatinine, estimated GFR, and urinary albumin excretion. We detected no changes in renal function in the placebo group, but noted modest increases in serum creatinine (ranging from 5 to 8  $\mu\text{mol/L}$ ) and decreases in estimated GFR (ranging from 3 to 6  $\text{mL/min/1.73 m}^2$ ) in the two higher darusentan treatment groups (table 3). However, urinary albumin excretion in patients who had albuminuria at baseline was reduced in the combined darusentan groups by about 60% (data not shown;  $p=0.0087$ ).

Table 4 shows the most frequent adverse events reported in the study. Most of these findings are related to fluid retention. One patient (randomly assigned to darusentan 300 mg, but occurred during up-titration at 50 mg) had an investigator-reported non-serious adverse event of heart failure that was of mild intensity, and resolved with

diuresis. Liver transaminase values of more than three times the upper limit of normal occurred in one patient receiving placebo, one patient receiving darusentan 100 mg, and one receiving darusentan 300 mg. Blood haemoglobin concentrations were reduced in all groups, but to a greater extent in patients receiving darusentan (table 3). We also recorded reductions in blood total protein concentrations (data not shown). We noted a correlation between the detected decreases in haemoglobin and total protein after 2 weeks of treatment on 50 mg darusentan ( $r=0.58$ , 95% CI 0.48–0.66;  $p<0.0001$ ), suggestive of a haemodilution mechanism. White blood cell count and platelet concentrations were unchanged (data not shown), consistent with an absence of drug effect on bone marrow production. Reticulocyte counts and bilirubin concentrations were also unchanged (data not shown), suggesting an absence of haemolysis.

Most reports of oedema or other signs of fluid retention during the study occurred during the first 6 weeks after start of treatment. Overall, four (2%) patients in the combined darusentan treatment groups discontinued study participation or study drug because of fluid retention or peripheral oedema. Mean change in bodyweight was 0.2 kg (SD 2.0) in the placebo group, 0.3 kg (2.1) in darusentan 50 mg group,  $-0.2$  kg (2.5) in darusentan 100 mg group, and  $-0.1$  kg (2.5) in darusentan 300 mg group at week 14. Changes in clinic mean heart rates were 0.7 (7.9), 1.2 (7.5),  $-0.2$  (6.9), and  $-1.9$  (9.0) beats per min, respectively. None of these changes was significant.

Six patients had cardiac events during the trial that were reported as serious adverse events. There was one sudden death in a patient in the placebo group. Two patients had non-ST segment elevation myocardial infarctions: one in the darusentan 50 mg group and the other in the darusentan 100 mg group (but while receiving 50 mg during dose titration). Both these events occurred in patients with previous coronary heart disease, and were associated with fluid retention and heart failure. One patient had atrial fibrillation associated with symptoms of heart failure; this patient was receiving 100 mg and had previous left ventricular dysfunction, an exclusion criterion for the trial, and thus was discontinued from further therapy. Lastly, we recorded two instances of fluid retention and heart failure, both in patients randomly assigned to the darusentan 300 mg group (one patient had two episodes: one on 100 mg and one on 300 mg). All episodes of fluid retention and heart failure responded promptly to diuretic therapy and with the exception of the patient with previous heart failure, the other four patients had left ventricular hypertrophy and left ventricular ejection fractions greater than 0.60.

## Discussion

On the basis of conventional readings or ambulatory blood-pressure monitoring, findings from our study have shown that darusentan significantly reduced systolic and diastolic blood pressures in patients with treatment-

resistant hypertension—a patient population believed to be at increased risk for cardiovascular events.<sup>3</sup> Compared with placebo, this selective endothelin-receptor antagonist reduced systolic blood pressures in the clinical setting by almost an additional 10 mm Hg, despite continued antihypertensive therapy with several well selected drugs in recommended full doses. Moreover, this study cohort was typical of patients with treatment-resistant hypertension, with good representations of patients with chronic kidney disease, coronary disease, and diabetes. Results from ambulatory blood-pressure monitoring, with which there is little or no placebo effect,<sup>12</sup> accord with this finding. Furthermore, darusentan treatment was significantly more likely than was placebo to achieve the goal for systolic blood pressure (<140 mm Hg or <130 mm Hg if the patient had diabetes or chronic kidney disease) in these patients. Control of systolic hypertension has been emphasised as the principal target of treatment in middle-aged or older patients.<sup>13</sup>

In consideration of darusentan's effects, however, we should acknowledge limitations and strengths of the study. The definition of treatment resistance used in selection of patients—based on US national hypertension guidelines<sup>1</sup>—was failure to achieve blood-pressure control despite the use of at least three antihypertensive drugs in full doses. There can be some disagreement in definition of maximum doses; therefore we relied on doses specified in drug labels approved by the relevant regulatory agencies or by standards of local practice, or the highest doses that patients could tolerate. Almost all patients satisfied these criteria for the non-diuretic agents. For diuretic drugs, mainly hydrochlorothiazide in this trial, for which potential doses are higher than are those prescribed in clinical practice, we used the doses typically recommended by hypertension guideline committees.<sup>1,2</sup> However, higher doses or the use of more powerful types of diuretics could be appropriate for at least some patients with treatment-resistant hypertension. Apart from any blood-pressure effects, this strategy could also reduce the incidence of fluid retention.

Further clinical experience is needed to clarify fully the place of darusentan in management of treatment-resistant hypertension. Enhanced diuretic treatment in some patients might obviate the need for additional therapies. Moreover, other types of agents, including spironolactone, might be effective when added to the treatment regimens of these patients, although large-scale placebo-controlled trials with these agents should be undertaken to establish their place in therapy.<sup>14–16</sup>

Typically, addition of a second drug to an initial agent to improve antihypertensive efficacy—such as addition of a thiazide diuretic or a calcium-channel blocker to an ACE inhibitor or angiotensin-receptor blocker—produces reductions in blood pressures similar in magnitude to those reported here with darusentan.<sup>17,18</sup> Since the patients

	Placebo	Darusentan 50 mg	Darusentan 100 mg	Darusentan 300 mg
<b>All patients</b>				
n	132	81	81	85
Baseline serum sodium (mmol/L)	140 (2)	139 (3)	139 (2)	140 (3)
Change in serum sodium (mmol/L)	0 (2)	0 (2)	1 (2)	0 (2)
Baseline serum potassium (mmol/L)	4.1 (0.5)	4.0 (0.4)	4.1 (0.6)	4.0 (0.5)
Change in serum potassium (mmol/L)	-0.1 (0.4)	0.1 (0.4)	0.1 (0.4)	0.1 (0.4)
Baseline serum BUN (mmol/L)	6.6 (2.4)	6.7 (2.3)	6.8 (2.4)	6.8 (2.3)
Change in serum BUN (mmol/L)	0.1 (2.5)	0.3 (1.6)	0.7 (2.2)	0.3 (1.6)
Baseline serum creatinine (μmol/L)	88 (30)	87 (22)	92 (31)	92 (32)
Change in serum creatinine (μmol/L)	0 (16)	1 (11)	5 (15)	8 (16)
Baseline eGFR (mL/min/1.73 m <sup>2</sup> )	80 (23)	81 (21)	76 (20)	78 (20)
Change in eGFR (mL/min/1.73 m <sup>2</sup> )	0 (16)	-2 (14)	-3 (11)*	-6 (13)†
Baseline blood haemoglobin concentration (g/L)	140 (14)	140 (13)	141 (12)	142 (12)
Change in blood haemoglobin concentration (g/L)	-2 (10)	-9 (10)	-10 (8)	-11 (9)
<b>Patients with albuminuria at baseline‡</b>				
n	51	24	35	30
Baseline UACR (mg/g creatinine)	127 (4)	136 (4)	132 (3)	119 (3)
End of study UACR (mg/g creatinine)	91 (4)	88 (5)	45 (4)§	49 (6)¶

Data are mean (SD) unless otherwise stated. BUN=blood urea nitrogen. eGFR=estimated glomerular filtration rate. UACR=urinary albumin-to-creatinine ratio. (Data shown for patients who had albuminuria at baseline). \*p=0.0068. †p=0.0003. ‡Albuminuria was defined as UACR 30 mg or more albumin/g creatinine at baseline. §p=0.0014. ¶p=0.0248.

**Table 3: Baseline and changes in laboratory and renal parameters**

	Placebo (n=132)	Darusentan 50 mg (n=81)	Darusentan 100 mg (n=81)	Darusentan 300 mg (n=85)
Any adverse event	65 (49%)	58 (72%)	63 (78%)	65 (77%)
Oedema and/or fluid retention	19 (14%)	20 (25%)	26 (32%)	21 (25%)
Dizziness	7 (5%)	3 (4%)	4 (5%)	4 (5%)
Headache	5 (4%)	2 (3%)	3 (4%)	5 (6%)
Fatigue	2 (2%)	6 (7%)	4 (5%)	3 (4%)
Flushing	0	4 (5%)	3 (4%)	1 (1%)
Cardiac events requiring admission	0	1 (1%)	2 (3%)	2 (2%)
Deaths	1 (1%)	0	0	0

Data are number of patients (%).

**Table 4: Adverse events for all randomly assigned patients**

in this trial were already receiving well constructed multidrug antihypertensive regimens—with at least three drugs, more often four or more—almost invariably including blockers of the renin-angiotensin system and diuretic drugs, these data confirm the complementary benefits of selective endothelin antagonism in this clinical setting. Although caution must be used in interpretation of findings in subgroups, patients with diabetes or chronic kidney disease seemed to have blood-pressure reductions similar to those in other patients. The patients with diabetes receiving darusentan achieved higher control rates (systolic pressure <130 mm Hg) than did those receiving placebo.

We noted no evidence of a dose-response relation for darusentan over the 50–300 mg dose range used in this

study. In a previous trial in similar patients, forced titration of darusentan every 2 weeks across the range of 10–300 mg suggested that 50 mg was more effective than was 10 mg; doses of 100 or 150 mg were similar to 50 mg, but 300 mg seemed to be slightly more efficacious.<sup>9</sup> The result of this earlier study, however, might have reflected a time effect, since in our study, which used parallel treatment groups, the 50, 100, and 300 mg doses produced similar blood-pressure effects. If confirmed by additional data, we could conclude that use of the highest doses does not add clinical benefit, and that a dose lower than 50 mg could be effective in some patients.

We recorded small changes in renal function in patients given darusentan; serum creatinine concentrations rose slightly and we detected corresponding small decreases in estimated GFR. These changes, as with those noted with blockers of the renin-angiotensin system,<sup>19</sup> were most likely an indication of the effects of the drug-induced reductions in blood pressure on intraglomerular haemodynamics. We also noted evidence that darusentan reduced the excretion rate of urinary albumin in patients who entered the trial with evidence for albuminuria. This finding is of interest because it occurred in patients already receiving adequate doses of ACE inhibitors or angiotensin-receptor blockers, suggesting that the effect of darusentan might be mediated by a mechanism separate from that of blockade of the renin-angiotensin system. Additionally, the blood-pressure-lowering action of darusentan could contribute to this effect. This finding deserves further study in patients with nephropathy.

As with other vasodilatory drugs, some fluid retention is an expected effect of endothelin antagonists. Apart from such clinical findings as oedema, evidence of fluid retention was provided by laboratory findings of haemodilution; we recorded decreases in haemoglobin and blood total protein concentrations in patients receiving darusentan, and noted a clear correlation between these changes in haemoglobin and total protein. Investigators in the study could increase or add diuretic therapy at their discretion to deal with clinical findings of fluid retention. Across the darusentan treatment groups, this strategy seemed to be effective in reducing the signs of fluid retention. Almost all reports of clinical fluid retention occurred during the first 6 weeks of treatment, suggesting that a strategy of monitoring patients for such findings during the early phases of treatment with this drug should guide adjunctive diuretic therapy. Patients with treatment-resistant hypertension might need to use higher diuretic doses than are used at present, or consider using agents such as chlorthalidone or loop diuretics that are more powerful than are commonly prescribed drugs such as hydrochlorothiazide.<sup>20</sup>

There were six serious cardiovascular events during this study. Three were coronary events: there was one cardiac death in the placebo group and two non-ST segment elevation myocardial infarctions in patients

given darusentan. All the coronary events occurred in patients with previous histories of coronary heart disease. Five cases of fluid-related cardiac events occurred (including the two patients with myocardial infarctions) in patients receiving darusentan. One of the cases was recurrent heart failure in a patient with previous heart failure (this patient was erroneously allowed into the study). The other cases were all diagnosed as heart failure with preserved left ventricular systolic function. In view of the pathophysiology of this disorder, the reported clinical findings in these patients were probably provoked by fluid retention rather than by any other effect of the treatment. This type of failure in patients with hypertension has been documented previously with other vasodilating agents,<sup>21,22</sup> and potentially could be prevented by early or prophylactic treatment of fluid retention.

In summary, darusentan provided meaningful lowering of systolic and diastolic blood pressures in patients with treatment-resistant hypertension already receiving many well chosen antihypertensive drugs. Generally, darusentan was well tolerated, the main adverse effects being related to fluid retention. The use of this drug accompanied by effective diuretic therapy seems to represent a new and effective strategy for dealing with treatment-resistant hypertension.

#### Contributors

The academic authors (MAW, HB, GB, HK, SL, RW, and LH) all actively contributed to the design of the study, including its analysis plan, and were involved in monitoring the progress of the research throughout the trial. The sponsor authors (JVL, BLW, and MSW) also actively contributed to the design of the trial and were responsible, on a day-to-day basis, for its conduct. All authors participated in the interpretation of the data. MAW wrote the first draft of the report, but all authors then contributed substantively to editing and preparing the report for submission.

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#### Conflicts of interest

MAW received consulting and lecturing fees from Gilead Sciences, Boehringer Ingelheim, Daiichi Sankyo, Forest, GlaxoSmithKline, Eli Lilly, and Nicox. HB has consulted for Intercure, Novartis, MSD, Daiichi Sankyo, Xoma, Ligand, Boehringer Ingelheim, and BioSante, in addition to Gilead Sciences. GB has received grant and research support from Juvenile Diabetes Research Foundation (JDRF), GlaxoSmithKline, Forest, and CVRx; has served as a consultant for GlaxoSmithKline, Merck, Novartis, Boehringer-Ingelheim, Takeda, Abbott, Walgreen's, Bristol-Myers Squibb/Sanofi-Aventis, and Forest, in addition to Gilead Sciences; and has been on speakers bureau for Novartis and GlaxoSmithKline. HK has consulted for Merck kGA, Pfizer, Novartis, Roche, Nicox, CSL, and Schering Plough, in addition to Gilead Sciences. SL has been a speaker for Novartis and Merck, and a consultant for AstraZeneca in addition to Gilead Sciences. RW provides consulting services to Gilead Sciences. LHL has been an adviser to Gilead Sciences on this project. JVL, BLW, and MSW are current or former employees of Gilead Sciences. BLW holds stocks in Gilead Sciences.

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#### References

- Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure. *Hypertension* 2003; 42: 1206–52.
- Mancia G, DeBacker G, Dominiczak A, et al. 2007 guidelines for the management of arterial hypertension: the task force for the management of arterial hypertension of the European Society of Hypertension (ESH) and the European Society of Cardiology (ESC). *Eur Heart J* 2007; 28: 1462–536.
- Calhoun DA, Jones D, Trexter S, et al. Resistant hypertension: diagnosis, evaluation, and treatment. A scientific statement from the American Heart Association Professional Education Committee of the Council for High Blood Pressure Research. *Hypertension* 2008; 51: 1403–19.
- Saito Y, Nakao K, Mukoyama M, et al. Increased plasma endothelin level in patients with essential hypertension. *N Engl J Med* 1990; 322: 205.
- Haak T, Jungmann E, Felber A, et al. Increased plasma levels of endothelin in diabetic patients with hypertension. *Am J Hypertens* 1992; 5: 161–66.
- Schneider JG, Tilly N, Hierl T, et al. Elevated plasma endothelin-1 levels in diabetes mellitus. *Am J Hypertens* 2002; 15: 967–72.
- Krum H, Viskoper RJ, Lacourciere Y, et al. The effects of an endothelin-receptor antagonist, bosentan, on blood pressure in patients with essential hypertension. *N Engl J Med* 1998; 338: 784–90.
- Nakov R, Pfarr E, Eberle S, on behalf of the HEAT Investigators. Darusentan: an effective endothelin receptor antagonist for treatment of hypertension. *Am J Hypertens* 2002; 15: 583–89.
- Black HR, Bakris GL, Weber MA, et al. Efficacy and safety of darusentan in patients with resistant hypertension: results from a randomized, double-blind, placebo-controlled dose-ranging study. *J Clin Hypertens* 2007; 9: 760–69.
- Wiens BL. A fixed sequence Bonferroni procedure for testing multiple endpoints. *Pharm Statistics* 2003; 2: 211–15.
- Wiens BL, Dmitrienko A. The Fallback procedure for evaluating a single family of hypotheses. *J Biopharm Stat* 2005; 15: 929–42.
- Weber MA, Bakris GL, Tarka EA, et al. Efficacy of a once-daily formulation of carvedilol for the treatment of hypertension. *J Clin Hypertens* 2006; 8: 840–49.
- Williams B, Lindholm LH, Sever P. Systolic blood pressure is all that matters. *Lancet* 2008; 371: 2219–21.
- Nishizaka MK, Zaman MA, Calhoun DA. Efficacy of low-dose spironolactone in subjects with resistant hypertension. *Am J Hypertens* 2003; 16: 925–30.
- Ouzan j, perault C, Lincoff AM, et al. The role of spironolactone in the treatment of patients with refractory hypertension. *Am J Hypertens* 2002; 15: 333–39.
- Saha C, Eckert GJ, Ambrosius WT, et al. Improvement in blood pressure with inhibition of the epithelial sodium channel in blacks with hypertension. *Hypertension* 2005; 46: 481–87.
- McGill JB, Rilly PA. Telmisartan plus hydrochlorothiazide versus telmisartan or hydrochlorothiazide monotherapy in patients with mild to moderate hypertension: a multicenter, randomized, double-blind, placebo-controlled parallel-group trial. *Clin Ther* 2001; 23: 833–50.
- Weir MR, Weber MA, Neutel JM, et al for the ACTION Study Investigators. Efficacy of candesartan cilexetil as add-on therapy in hypertensive patients uncontrolled on background therapy: a clinical experience trial. *Am J Hypertens* 2001; 14: 567–72.
- Sica DA, Gehr TWB. Angiotensin-converting enzyme inhibitors. In: Oparil S, Weber MA, eds. Hypertension, 2nd edn. Philadelphia: Elsevier, 2005: 669–82.
- Knepper MA, Kleyman T, Gamba G. Diuretics: mechanisms of action. In: Oparil S, Weber MA, eds. Hypertension, 2nd edn. Philadelphia: Elsevier, 2005: 638–52.
- Einhorn PT, Davis BR, Massie BM, et al, for the ALLHAT Collaborative Research Group. Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) heart failure validation study: diagnosis and prognosis. *Am Heart J* 2007; 153: 42–53.
- Psaty BM, Lumley T, Furberg CD, et al. Health outcomes associated with various antihypertensive therapies used as first line agents: a network meta-analysis. *JAMA* 2003; 289: 2534–44.