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


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 (>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 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.

Funding Gilead Sciences.

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.1,2 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.1 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.3 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.3

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,4,5 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...
blocks 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. 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. 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.

We undertook a randomised, double-blind trial comparing differing doses of darusentan with placebo in patients with treatment-resistant hypertension as previously defined. 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 (≥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 if 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/m² and 43 kg/m², and estimated glomerular filtration rates (GFR) of 30 mL/min/1.73 m² 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
Laboratory tests were done at baseline, after 2 weeks, and obtained every 20 min throughout the 24-h observations and at the end of the study. Automated readings were monitoring was done for all patients at randomisation drug concentration in the seated position by standard tolerability of darusentan.

estimated GFR. We also assessed the safety and 14 weeks of treatment, and change from baseline in 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 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.10,11 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

<table>
<thead>
<tr>
<th>Placebo (n=132)</th>
<th>Darusentan 50 mg (n=81)</th>
<th>Darusentan 100 mg (n=81)</th>
<th>Darusentan 300 mg (n=85)</th>
<th>All patients (N=379)</th>
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<td>62 (9)</td>
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<td>Albuminuria*</td>
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<td>30 (38%)</td>
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<td>Diuretic drugs</td>
<td>33 (99%)</td>
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<td>81 (100%)</td>
<td>84 (99%)</td>
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<td>ACEI or ARB</td>
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<td>78 (96%)</td>
<td>78 (96%)</td>
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<td>β blocker</td>
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<td>86 (11)</td>
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<td>66 (10)</td>
<td>65 (8)</td>
<td>68 (11)</td>
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<td>24-h SBP (mm Hg)†</td>
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<td>136 (11)</td>
<td>136 (13)</td>
<td>134 (15)</td>
</tr>
<tr>
<td>24-h DBP (mm Hg)†</td>
<td>78 (10)</td>
<td>81 (10)</td>
<td>79 (12)</td>
<td>77 (10)</td>
</tr>
</tbody>
</table>

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 included in the mean 24-h endpoint analyses.
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 β 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 pressure values at the end of the study: 143/81 mm Hg (SD 15/12) versus 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.

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Articles

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.

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

<table>
<thead>
<tr>
<th>Number of background antihypertensive drugs</th>
<th>Placebo (n=132)</th>
<th>Darusentan 50 mg (n=81)</th>
<th>Darusentan 100 mg (n=81)</th>
<th>Darusentan 300 mg (n=85)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exactly three (n=159)</td>
<td>–8·7 (1·6)</td>
<td>–15·1 (2·6); p=0·0136</td>
<td>–19·8 (3·1); p=0·0007</td>
<td>–18·3 (2·7); p=0·0009</td>
</tr>
<tr>
<td>≥Four (n=220)</td>
<td>–8·5 (1·8)</td>
<td>–17·4 (2·2); p=0·0017</td>
<td>–17·1 (2·3); p=0·0040</td>
<td>–17·9 (2·8); p=0·0070</td>
</tr>
</tbody>
</table>

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

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.
(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 μmol/L) and decreases in estimated GFR (ranging
drawn 3 to 6 mL/min/1.73 m²) 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
c oncentrations (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 con-
centrations 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-

![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).
resistant hypertension—a patient population believed to be at increased risk for cardiovascular events. 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, 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.

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—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. 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.

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. Since the 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 trial.
Investigators in the study could increase or add diuretic between these changes in haemoglobin and total protein. and blood total protein concentrations in patients haemodilution; we recorded decreases in haemoglobin retention occurred during the first 6 weeks of treatment, of fluid retention. Almost all reports of clinical fluid retention. Across the darusentan treatment groups, such as hydrochlorothiazide, are more powerful than are commonly prescribed drugs using agents such as chlorthalidone or loop diuretics that higher diuretic doses than are used at present, or consider drug should guide adjunctive diuretic therapy. Patients with blockers of the renin-angiotensin system,19 were more 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 chlorothalidone or loop diuretics that are more powerful than are commonly prescribed drugs such as hydrochlorothiazide.28

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,29 30 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, BIW, 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.

Trial Steering Committee

Data Monitoring Committee
William White (University of Connecticut, Farmington, USA), Jeffrey Bozer (SUNY Downstate, Brooklyn, USA), William Cushman (University of Tennessee, Memphis, USA), Stuart Pocock (University of London, London, UK), Anitha Vijayan (Washington University, St Louis, USA).

Cardiovascular and Hepatic Adjudication Committees
Glen Cooke (Ohio State University, Columbus, USA), Alan Miller (University of Florida, Jacksonville, USA), Merrick Kukin (St Luke's-Roosevelt Hospitals, New York City, USA), James Freston, Paul Watkins (University of North Carolina, Chapel Hill, USA), Laurie DeLeve (University of Southern California, Los Angeles, USA).

Investigators by country

Conflicts of interest
M&W received consulting and lecturing fees from Gilead Sciences, Boehringer Ingelheim, Daiichi Sankyo, Forest, GlaxoSmithKline, Eli Lilly, and Novo. 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; he served as a consultant for GlaxoSmithKline, Merck, Novartis, Boehringer-Ingehelm, TiktaLabs, Abbott, Walgreen’s, Bristol-Myers Squibb/Sanofi-Aventis, and Forest, in addition to Gilead Sciences; and has spoken on speakers bureaus for Novartis and GlaxoSmithKline. HK has consulted for Merck KGA, Pfizer, Novartis, Roche, Novo, 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. LHJ has been an adviser to Gilead Sciences on this project. JVL, BIAW, and MSW are current or former employees of Gilead Sciences. BIAW holds stocks in Gilead Sciences.

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