Dual endothelin antagonist aprocitentan for resistant hypertension (PRECISION): a multicentre, blinded, randomised, parallel-group, phase 3 trial

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Summary

Background Resistant hypertension is associated with increased cardiovascular risk. The endothelin pathway has been implicated in the pathogenesis of hypertension, but it is currently not targeted therapeutically, thereby leaving this relevant pathophysiological pathway unopposed with currently available drugs. The aim of the study was to assess the blood pressure lowering efficacy of the dual endothelin antagonist aprocitentan in patients with resistant hypertension.

Methods PRECISION was a multicentre, blinded, randomised, parallel-group, phase 3 study, which was done in hospitals or research centres in Europe, North America, Asia, and Australia. Patients were eligible for randomisation if their sitting systolic blood pressure was 140 mm Hg or higher despite taking standardised background therapy consisting of three antihypertensive drugs, including a diuretic. The study consisted of three sequential parts: part 1 was the 4-week double-blind, randomised, and placebo-controlled part, in which patients received aprocitentan 12·5 mg, aprocitentan 25 mg, or placebo in a 1:1:1 ratio; part 2 was a 32-week single (patient)-blind part, in which all patients received aprocitentan 25 mg; and part 3 was a 12-week double-blind, randomised, and placebo-controlled withdrawal part, in which patients were re-randomised to aprocitentan 25 mg or placebo in a 1:1 ratio. The primary and key secondary endpoints were changes in unattended office systolic blood pressure from baseline to week 4 and from withdrawal baseline to week 40, respectively. Secondary endpoints included 24-h ambulatory blood pressure changes. The study is registered on ClinicalTrials.gov, NCT03541174.

Findings The PRECISION study was done from June 18, 2018, to April 25, 2022. 1965 individuals were screened and 730 were randomly assigned. Of these 730 patients, 704 (96%) completed part 1 of the study; of these, 613 (87%) completed part 2 and, of these, 577 (94%) completed part 3 of the study. The least square mean (SE) change in office systolic blood pressure at 4 weeks was –15·3 (SE 0·9) mm Hg for aprocitentan 12·5 mg, –15·2 (0·9) mm Hg for aprocitentan 25 mg, and –11·5 (0·9) mm Hg for placebo, for a difference versus placebo of –3·8 (1·3) mm Hg (97·5% CI –6·8 to –0·8, p=0·0042) and –3·7 (1·3) mm Hg (–6·7 to –0·8; p=0·0046), respectively. The respective difference for 24 h ambulatory systolic blood pressure was –4·2 mm Hg (95% CI –6·2 to –2·1) and –5·9 mm Hg (–7·9 to –3·8). After 4 weeks of withdrawal, office systolic blood pressure significantly increased with placebo versus aprocitentan (5·8 mm Hg, 95% CI 3·7 to 7·9, p<0·0001). The most frequent adverse event was mild-to-moderate oedema or fluid retention, occurring in 9%, 18%, and 2% for patients receiving aprocitentan 12·5 mg, 25 mg, and placebo, during the 4-week double-blind part, respectively. This event led to discontinuation in seven patients treated with aprocitentan. During the trial, a total of 11 treatment-emergent deaths occurred, none of which were regarded by the investigators to be related to study treatment.

Interpretation In patients with resistant hypertension, aprocitentan was well tolerated and superior to placebo in lowering blood pressure at week 4 with a sustained effect at week 40.

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Introduction

Hypertension is a leading cause of cardiovascular disease and mortality worldwide.[1] An estimated 1·3 billion people have hypertension,[2] of which approximately 10% have resistant hypertension,[3,4] representing a global public health concern.[5] For patients with resistant hypertension, guideline-recommended blood pressure targets are not achieved despite treatment with at least three antihypertensive medications of different classes, including a diuretic, a blocker of the renin–angiotensin system, and a long-acting calcium channel blocker.[4,6]

The failure to control blood pressure with currently available drugs suggests that relevant pathophysiological pathways remain unopposed. Indeed, the endothelin pathway has been implicated in the pathogenesis of hypertension,[7,8] but it is currently not targeted therapeutically. Yet, this pathway is activated in patients prone to developing resistant hypertension, such as

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See Online for appendix

Research in context

Evidence before this study

We searched PubMed for articles published from inception to Dec 31, 2020, for randomised trials, and open and observational studies on drug treatment for resistant hypertension, without language restrictions. We used the search terms "resistant hypertension", "randomised", "pharmacotherapy", "antihypertensive drugs", "endothelin antagonists", "steroidal mineralocorticoid receptor antagonist", "alpha-blocker", and "beta-blocker". Over the years, international guidelines have converged to define resistant hypertension as a condition where blood pressure targets are not achieved despite treatment with at least three antihypertensive medications of different classes, including a diuretic, a blocker of the renin–angiotensin system, and a long-acting calcium channel blocker. In patients with resistant hypertension, current guidelines recommend the use of the steroidal mineralocorticoid receptor antagonist, spironolactone, as the preferred fourth-line drug, with superior blood pressure lowering efficacy compared with α or β blockers. Spironolactone is associated with a risk of hyperkalaemia that has been shown in recent studies to be alleviated with the potassium binder patiromer. Alternatively, non-steroidal mineralocorticoid receptor antagonists could lower blood pressure without an increased risk of hyperkalaemia in patients who are not candidates for steroidal mineralocorticoid receptor antagonists due to advanced chronic kidney disease. Additional pharmacological drugs currently investigated for the treatment of resistant hypertension include brain aminopeptidase A inhibitors and aldosterone synthase inhibitors. However, despite the development of many new antihypertensive therapies, it has been over 30 years since an antihypertensive drug working via a new pharmacological pathway was last approved. Blockade of the endothelin pathway to lower blood pressure was suggested in the late 1990s but encouraging results from the first phase 3 pivotal trial with the endothelin receptor antagonist, darusentan, in resistant hypertension, were not confirmed.

Added value of this study

PRECISION, a multicentre, blinded, randomised, parallel-group, phase 3 study, supports the role of endothelin receptor blockade in the treatment of resistant hypertension. Although the endothelin pathway has been implicated in the pathogenesis of hypertension, it is currently not targeted therapeutically, and this could contribute to the failure to control blood pressure with currently available drugs.
The unique design of the study, including a 4-week double-blind, placebo-controlled treatment phase; a 32-week single-blind, active-treatment phase; and a 12-week double-blind, placebo-controlled withdrawal phase provides robust data on short-term and, importantly, long-term safety and efficacy of the dual endothelin receptor antagonist aprocitentan with both office and ambulatory blood measurement. The safety profile, together with the long half-life (44 h), and low potential for drug–drug interactions observed in the clinical pharmacology programme, is conducive for a chronic treatment to be used for patients who often have several comorbidities and are treated with multiple pharmacological therapies. The effect shown in this study was consistent across multiple key subpopulations.

Implications of all the available evidence

The study establishes dual endothelin receptor antagonism with aprocitentan as a well tolerated and effective therapeutic approach to achieve sustained blood pressure lowering in addition to guideline-recommended triple antihypertensive therapy, with both office and ambulatory blood pressure measurements.

Black patients, patients with obesity or obstructive sleep apnoea,[9–11] and in comorbid conditions frequently associated with resistant hypertension such as diabetes and chronic kidney disease.[12–15] Blocking the endothelin pathway could represent a new mode of action to lower blood pressure in resistant hypertension. Initial studies with the endothelin receptor antagonists bosentan[16] and darusentan[17–18] have shown a blood pressure lowering effect in patients with essential hypertension, resistant hypertension, or both, with no reflex neurohormonal activation. However, promising results with darusentan as an add-on therapy in resistant hypertension were not confirmed in a second phase 3 study.[19]

Aprocitentan is a once-daily, orally active, dual endothelin A and B receptor antagonist, with a half-life of 44 h and low drug–drug interaction potential.[20,21] In a phase 2 dose-finding study in patients with hypertension, aprocitentan, administered as monotherapy, in the range of 10–25 mg provided the most favourable profile combining effective blood pressure lowering with low rates of fluid retention.[22] The doses of 12·5 mg and 25 mg were chosen for further investigation and for simplicity. The Parallel-Group, Phase 3 Study with Aprocitentan in Subjects with Resistant Hypertension (PRECISION) was subsequently designed to investigate the short-term antihypertensive effect of aprocitentan and its sustainability in patients with resistant hypertension.[23]

Methods

Study design

PRECISION was a multicentre, blinded, randomised, parallel-group, phase 3 study. Study enrolment was done in hospitals or research centres in Europe, North America, Asia, and Australia. It was designed to evaluate whether aprocitentan, added to three antihypertensive medications of different classes, reduces blood pressure compared with placebo in patients with resistant hypertension after 4 weeks of double-blind treatment, and whether this effect is sustained at week 40. It included a randomised treatment part (part 1, 4 weeks), followed by a single-blind

active-treatment part (part 2, 32 weeks), and a re-randomised withdrawal part (part 3, 12 weeks). The study design (appendix p 30) has been described previously.[23]

Patients provided written informed consent before enrolment. The study protocol was approved by local ethics committees or institutional review boards. The study was performed in full compliance with the International Conference on Harmonization Good Clinical Practice Guideline, the principles of the Declaration of Helsinki, and the laws and regulations of the countries in which it was performed.

Participants

Eligible study participants have been described previously:[23] They were required to have a history of uncontrolled office blood pressure, despite taking at least three antihypertensive medications within 1 year before screening, all from different pharmacological classes for at least 4 weeks before screening. Sitting systolic BP (SBP) of 140 mm Hg or higher assessed by standardised unattended automated office blood pressure (thereafter called office blood pressure) measurement (mean of 3 measurements after a 5-min rest) was required at the start of all pre-randomisation periods. During screening, all patients switched their individual antihypertensive therapies (except β blockers) to standardised background therapy, a single-pill triple-combination of a calcium channel blocker (amlodipine), an angiotensin receptor blocker (valsartan), and a diuretic (hydrochlorothiazide), at fixed doses of either 5 mg, 160 mg, or 25 mg; or 10 mg, 160 mg, or 25 mg, respectively. The protocol required to use the maximally tolerated standardised background therapy dose.

Randomisation and masking

Randomisation, assessments, procedures, and treatment adherence have been described previously.[23] Briefly, investigators enrolled patients into the study. Randomisation was implemented by an interactive Response Technology system with the randomisation groups and ratios described subsequently. The re-randomisation that occurred at the beginning of part 3 was stratified according to the randomised treatment assigned in part 1. Study treatment (aprocitentan or placebo) was provided as identical tablets of 12·5 mg and 25 mg aprocitentan or matching placebo.

Procedures

The study included four consecutive phases (appendix p 30).[23] Phase 1 (4–12 weeks) was a screening period during which patients first continued their individual background therapy and then received standardised background therapy for at least 4 weeks. Phase 2 (4 weeks) was a single (patient)-blind run-in period, in which placebo was added to standardised background therapy. Phase 3 (48 weeks) was the active-treatment period consisting of three sequential parts: part 1 was the 4-week double-blind, randomised, and placebo-controlled part, in which patients received aprocitentan 12·5 mg, aprocitentan 25 mg, or placebo in a 1:1:1 ratio; part 2 was a 32-week single (patient)-blind part, in which all patients received aprocitentan 25 mg; and part 3 was a 12-week double-blind, randomised, and placebo-controlled withdrawal part, in which patients were re-randomised to aprocitentan 25 mg or placebo in a 1:1 ratio. Phase 4 was a safety follow-up period covering the 30 days after the last study treatment dose, during which patients continued standardised background therapy.

Outcomes

Changes from baseline to week 4 (part 1), and from withdrawal baseline (week 36) to week 40 (part 3), in mean trough sitting office SBP were the primary and key secondary endpoints, respectively. The rationale for a 40-week endpoint was to replicate the time period for the primary efficacy evaluation. Other secondary endpoints included changes at week 4 and week 40 in mean trough sitting office diastolic BP (DBP) and in 24 h SBP and DBP measured by ambulatory blood pressure monitoring. Changes from withdrawal baseline (week 36) to weeks 38, 44, and 48 in mean trough sitting office SBP and DBP and urine albumin–creatinine ratio were other efficacy endpoints. Adverse events were defined using the Medical Dictionary for Regulatory Dictionaries (version 24.1).

Statistical analysis

Statistical analyses and protocol changes have been published previously.[23] The sample size was driven by the power for the key secondary endpoint. The within-group SD for the change from withdrawal baseline (week 36) to week 40 in mean trough SBP (measured as office blood pressure) was expected to be around 15 mm Hg.[22] With a type I error of 0·05 (two sided), the sample size needed for 90% power to detect a difference of 5 mm Hg between aprocitentan 25 mg and placebo was 380 patients. Assuming a drop-out rate of 37% during the 9 months between randomisation and start of the withdrawal part, to have 380 patients in the withdrawal part, a total of 600 patients needed to be randomly assigned (200 in each of the three groups in the withdrawal part). Therefore, for the primary endpoint, the power to detect a difference of 6 mm Hg was over 90% (for 5·5 mm Hg, 6 mm Hg, or 6·5 mm Hg, the power was 92%, 96% and 98%, respectively). Ultimately, 730 patients were randomly assigned. The over-running was caused by the addition of sites to compensate for lower recruitment due to the COVID–19 pandemic. Briefly, the primary and key secondary analyses were investigated using a mixed model with factors for treatment group, visit, and treatment by visit interaction, and covariates for baseline or withdrawal baseline SBP and the interaction between baseline or withdrawal baseline and visit using the missing-at-random assumption. The key secondary

analysis included the randomised treatment in the double-blind part as an additional factor for stratum. To maintain an overall type I error at 0·05, two-sided significance levels were set at 0·025 for the primary endpoint, which assessed the efficacy of two aprocitentan doses, and at 0·05 for the key secondary endpoint. No multiplicity adjustment was applied to the analysis of other variables.

Sensitivity analyses assessed the impact of deviations from the missing-at-random assumption of the mixed models for repeated measures and the impact of premature discontinuation of double-blind treatment or the addition of a diuretic or antihypertensive rescue medication. Supportive analyses evaluated the impact of protocol deviations and substitution rules. Exploratory analyses of prespecified subgroups were performed. The study is registered on ClinicalTrials.gov, NCT03541174.

Role of the funding source

The sponsors of this trial contributed to the design of the trial, data analysis, interpretation of data, manuscript writing, and the decision to submit the manuscript for publication. Data collection was done by Idorsia Pharmaceuticals.

Results

The PRECISION study was done from June 18, 2018, to April 25, 2022. Overall, 1965 individuals were screened at 193 sites in 22 countries, and 730 were randomly assigned (figure 1). Not meeting the inclusion criterion of an SBP of 140 mm Hg or higher was the most common reason for exclusion before randomisation (44% of all screened patients).[23] Of the 730 patients who were randomly assigned, 704 (96%) completed part 1; of these, 613 (87%) completed part 2 and, of these, 577 (94%) completed part 3 of the study.

Patient characteristics were similar across all treatment groups at randomisation (table 1) and re-randomisation (appendix pp 13–14). They were representative of the patients affected by resistant hypertension regarding age and comorbidities (appendix p 15). Black or African American patients represented 11% of all randomly assigned participants and 37% (78 of 211) of the participants from the USA, which is higher than the distribution of Black people in the USA. At screening, 63% of all patients who were randomly assigned were prescribed four or more antihypertensive drugs and 63% were receiving a β blocker, as described previously.[23] At randomisation, 516 (71%) of 730 patients received the highest dose of standardised background therapy (amlodipine 10 mg) and 423 (58%) of 730 patients continued their β blocker treatment.

The time course of changes in office SBP and DBP during the 3 study parts illustrates the short-term (4 weeks) and sustained (up to 48 weeks) blood pressure lowering effects of aprocitentan (figure 2). After 4 weeks of treatment in the double-blind part 1, the primary endpoint was met. The least square mean (SE) change in office SBP at 4 weeks was –15·3 (0·9) mm Hg for aprocitentan 12·5 mg, –15·2 (0·9) mm Hg for aprocitentan 25 mg, and –11·5 (0·9) mm Hg for placebo, for a difference versus placebo of –3·8 (1·3) mm Hg (97·5% CI –6·8 to –0·8, p=0·0042) and –3·7 (1·3) mm Hg (–6·7 to –0·8, p=0·0046), respectively (figure 2 and appendix p 16). Office DBP also decreased with both aprocitentan doses compared with placebo (–3·9 mm Hg, 95% CI –5·6 to –2·3 for the 12·5 mg dose; –4·5 mm Hg, 95% CI –6·1 to –2·9 for the 25 mg dose, respectively). Office SBP and DBP were maintained during part 2 in patients previously receiving aprocitentan and decreased within the first 2 weeks of part 2 before stabilising in those previously receiving placebo. In part 3, office SBP after 4 weeks of withdrawal (the key secondary endpoint) increased significantly with placebo compared with aprocitentan (5·8 mm Hg, 95% CI 3·7 to 7·9, p<0·0001). Office DBP also increased with placebo compared with aprocitentan (5·2 mm Hg, 95% CI 3·8 to 6·6, p<0·0001). The difference between the two groups remained up to week 48.

The results of all sensitivity and supportive analyses (appendix pp 17–20) confirmed the robustness of the main analysis. In particular, the exclusion of patients resulting from the premature discontinuation of double-blind treatment or the addition or increase in dose of a diuretic or the use of rescue medication for blood pressure increase did not affect the primary and key secondary results.

The results from ambulatory blood pressure monitoring confirmed those derived from office measurements. At the end of part 1, aprocitentan, after placebo correction, decreased both the 24 h ambulatory SBP (–4·2 mm Hg, 95% CI –6·2 to –2·1 for the 12·5 mg dose; –5·9 mm Hg, –7·9 to –3·8 for the 25 mg dose; figure 3) and DBP (–4·3 mm Hg, 95% CI –5·7 to –3·0 for the 12·5 mg dose; –5·8 mm Hg, 95% CI –7·1 to –4·5 for the 25 mg dose; appendix p 31). The placebo-corrected SBP lowering effect was –5·1 mm Hg and –7·4 mm Hg during the night time and –3·8 mm Hg and –5·3 mm Hg during the daytime, for the 12·5 mg and 25 mg doses, respectively (figure 3C).

In part 3, after 4 weeks of withdrawal (week 40), both the 24 h ambulatory SBP and DBP increased with placebo compared with aprocitentan (6·5 mm Hg, 95% CI 4·6 to 8·5 [figure 3]; 6·8 mm Hg, 95% CI 5·5 to 8·0, respectively [appendix p 31]).

For the primary and key secondary efficacy analyses, a treatment effect consistent with that in the overall study population was observed across the majority of subgroups (appendix pp 32–34). Notably, a greater decrease in SBP was seen at week 4 for older patients (aged ≥75 years), and for patients with macro-albuminuria (urine albumin–creatinine ratio >300 mg/g) and chronic kidney disease stage 3–4 (estimated glomerular filtration rate [eGFR] 15 to <60 mL/min per 1·73 m^2). No difference in treatment effect was detected between patients with or without β blocker treatment at screening. Regarding race,

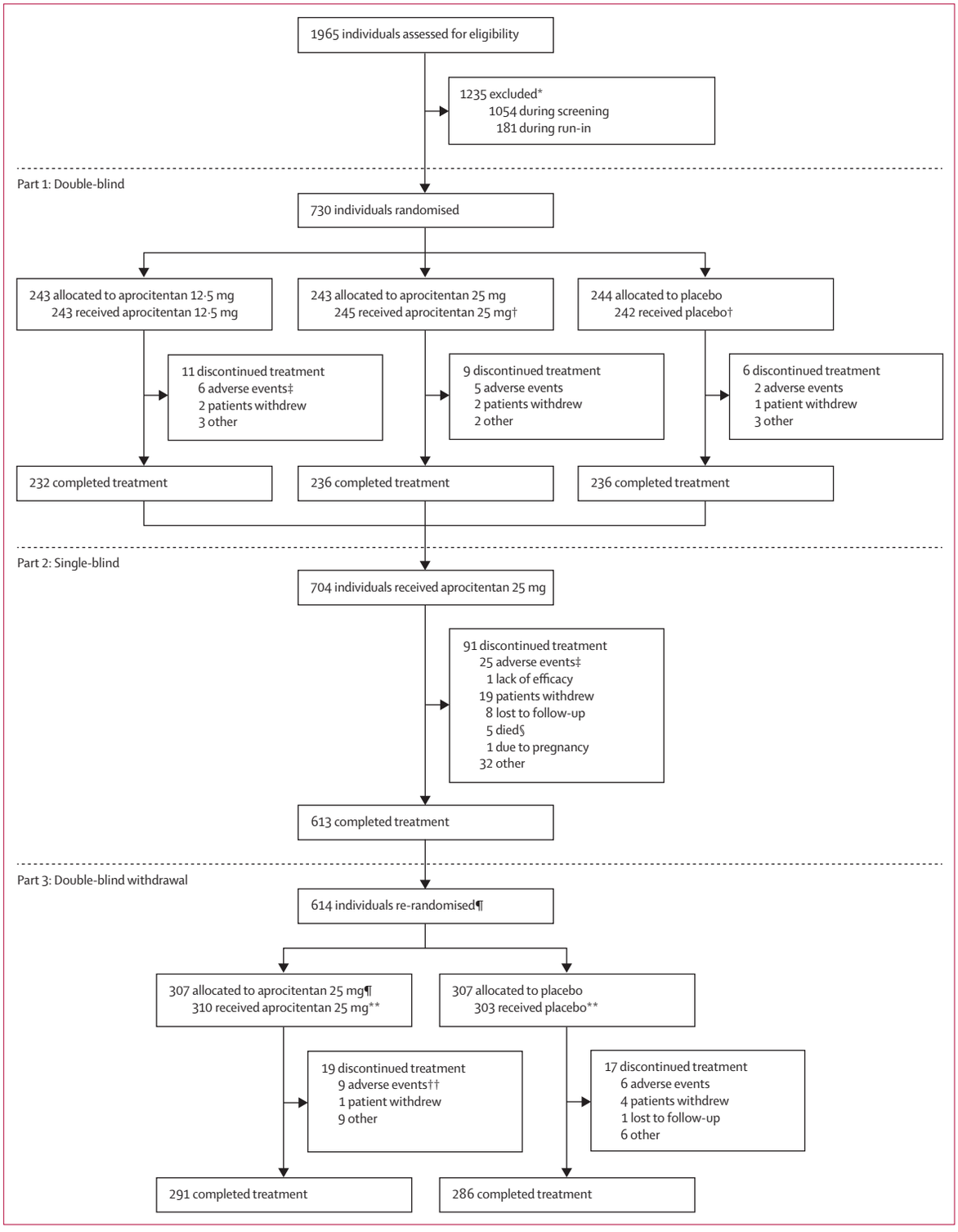

Figure 1: **PRECISION study profile**

Efficacy analyses were done by allocated treatment groups and safety analyses by received treatment groups. *Exclusion from screening and run-ins have been described previously.[23] †Two patients randomised to placebo received at least one dose of aprocitentan 25 mg during part 1 and were attributed to the aprocitentan 25 mg group. ‡One adverse event was due to COVID-19. §Four adverse events and one death were due to COVID-19. ¶One patient who had discontinued study treatment in part 2 was re-randomised in error to the aprocitentan 25 mg group in part 3 but did not receive study treatment. **Four patients randomised to placebo received at least one dose of aprocitentan 25 mg during part 3 and were attributed to the aprocitentan 25 mg group. ††One adverse event and four other events were due to COVID-19.

	Aprocitentan 12·5 mg (n=243)	Aprocitentan 25 mg (n=243)	Placebo (n=244)
Age at screening, years			
Mean age at screening	61·2 (10·3)	61·7 (10·4)	62·2 (11·2)
18 to <65	143 (59%)	136 (56%)	130 (53%)
65 to <75	78 (32%)	85 (35%)	86 (35%)
≥75	22 (9%)	22 (9%)	28 (11%)
Gender			
Men	144 (59%)	145 (60%)	145 (59%)
Women	99 (41%)	98 (40%)	99 (41%)
Geographical area			
Europe	153 (63%)	143 (59%)	152 (62%)
North America	76 (31%)	81 (33%)	75 (31%)
Asia or Australia	14 (6%)	19 (8%)	17 (7%)
Race or ethnicity			
White	203 (84%)	200 (82%)	202 (83%)
Black or African American	28 (12%)	28 (12%)	26 (11%)
Asian	11 (5%)	14 (6%)	13 (5%)
Other†	1 (0)	1 (0)	3 (1%)
BMI at screening, kg/m^2			
Mean BMI	33·6 (6·2)	34·3 (6·8)	33·3 (5·6)
Low to overweight (<30)	75 (31%)	70 (29%)	79 (32%)
Obese (30 to <40)	135 (56%)	132 (54%)	132 (54%)
Severely obese (≥40)	33 (14%)	41 (17%)	33 (14%)
Estimated glomerular filtration rate at baseline between 15 and <60 mL/min per 1·73 m^2	55 (23%)	61 (25%)	46 (19%)
Urine albumin–creatinine ratio at baseline, mg/g‡			
<30	144 (60%)	155 (65%)	154 (65%)
30 to 300	63 (26%)	55 (23%)	56 (24%)
>300	34 (14%)	28 (12%)	28 (12%)
Medical history			
Diabetes	131 (54%)	137 (56%)	127 (52%)
Ischaemic heart disease	73 (30%)	79 (32%)	73 (30%)
Congestive heart failure	48 (20%)	51 (21%)	44 (18%)
Sleep apnoea syndrome	33 (14%)	39 (16%)	31 (13%)
Stroke§	20 (8%)	21 (9%)	16 (7%)
≥4 antihypertensive drugs at screening*	151 (62%)	158 (65%)	151 (62%)
Unattended automated office blood pressure at baseline, mm Hg			
Systolic blood pressure	153·2 (8·8)	153·3 (9·0)	153·3 (9·0)
Diastolic blood pressure	87·9 (9·4)	87·7 (9·7)	87·1 (9·9)
Ambulatory blood pressure monitoring at baseline, mm Hg¶			
24 h systolic blood pressure	137·7 (13·3)	137·6 (15·2)	137·1 (13·6)
24 h diastolic blood pressure	83·5 (8·7)	82·5 (10·0)	82·5 (9·1)

Data are mean (SD) or n (%). *The overall patient characteristics and antihypertensive drugs at screening have been previously published.[23] †Includes American Indian or Alaska Native; Native Hawaiian or other Pacific Islander; other; and not reported. ‡The number of patients used to calculate the urine albumin–creatinine ratio were: 241 (99%) patients for aprocitentan 12·5 mg; 238 (98%) patients for aprocitentan 25 mg; and 238 (98%) patients for placebo. §Includes ischaemic and haemorrhagic strokes and excludes other CNS disorders. ¶The number of patients used to calculate the ambulatory blood pressure monitoring at baseline were: 206 (85%) patients for aprocitentan 12·5 mg; 207 (85%) patients for aprocitentan 25 mg; and 220 (90%) patients for placebo.

Table 1: **Characteristics of the randomised patients***

Black or African American patients compared with other patients tended to have a lower response to aprocitentan at week 4, and a stronger response at week 40, after 4 weeks of placebo-controlled withdrawal. The ambulatory blood pressure monitoring results in Black or African American patients were consistent with those observed in the overall population across study parts (appendix pp 21–22).

At the end of part 1, a reduction of –28% and –31% in the urine albumin–creatinine ratio was observed for the 12·5 mg and 25 mg aprocitentan groups, respectively, and an increase of 5% was observed for the placebo group (appendix p 35). In part 2, the reduction was maintained for all patients. In part 3, after 4 weeks of withdrawal, the ratio increased with placebo compared with aprocitentan. This antiproteinuric effect of aprocitentan tended to be greater in patients with chronic kidney disease stage 3–4 versus patients with an eGFR of 60 mL/min per 1·73 m^2 or more (appendix pp 23–24).

Aprocitentan was well tolerated (appendix pp 25–27). The most frequent adverse event was oedema or fluid retention occurring mainly during the first 4 weeks of treatment (appendix pp 36–37). Before randomisation, 70 (10%) of 730 patients had an ongoing medical condition of oedema or fluid retention and 35 (5%) of 730 had experienced an adverse event of oedema or fluid retention. Oedema or fluid retention was reported more frequently with aprocitentan than with placebo in a dose-dependent manner (9·1%, 18·4%, and 2·1% for patients receiving aprocitentan 12·5 mg, 25 mg, and placebo, during the 4-week part 1, respectively; 18·2% for patients receiving aprocitentan 25 mg during the 32-week part 2; and 2·6% and 1·3% for patients on aprocitentan 25 mg and placebo, during the 12-week part 3, respectively, table 2). Oedema or fluid retention was generally mild to moderate and diuretic treatment was added as needed (appendix p 28). Oedema or fluid retention was more frequent in patients with chronic kidney disease stage 3–4 (appendix pp 36–37). Discontinuation due to oedema or fluid retention was reported for seven patients receiving aprocitentan 25 mg during parts 1–3 (one of 245 patients in part 1, five of 704 patients in part 2, and one of 310 patients in part 3; appendix p 28).

A total of 13 deaths were reported, two of which were not considered treatment-emergent. Of the 11 treatment-emergent deaths, none were regarded by the investigators to be related to study treatment; five were cardiovascular deaths, five were COVID-19-related, and one patient died of procedural intestinal perforation.

Eleven patients required admission to hospital for heart failure (two [0·8%] of 245 receiving aprocitentan 25 mg during part 1; six [0·9%] of 704 during part 2; and two [0·6%] of 310 receiving aprocitentan 25 mg and one [0·3%] of 303 receiving placebo during part 3); none of the cases were fatal. All patients had a high-risk cardiovascular medical history including diabetes (11 [100%] of 11), chronic kidney disease stage 3–4 (6 [55%] of 11), and pre-existing heart failure (5 [45%] of 11). Two (18%) of 11 patients discontinued from study treatment due to heart failure. Major cardiovascular events (appendix p 29) included the five cardiovascular deaths.

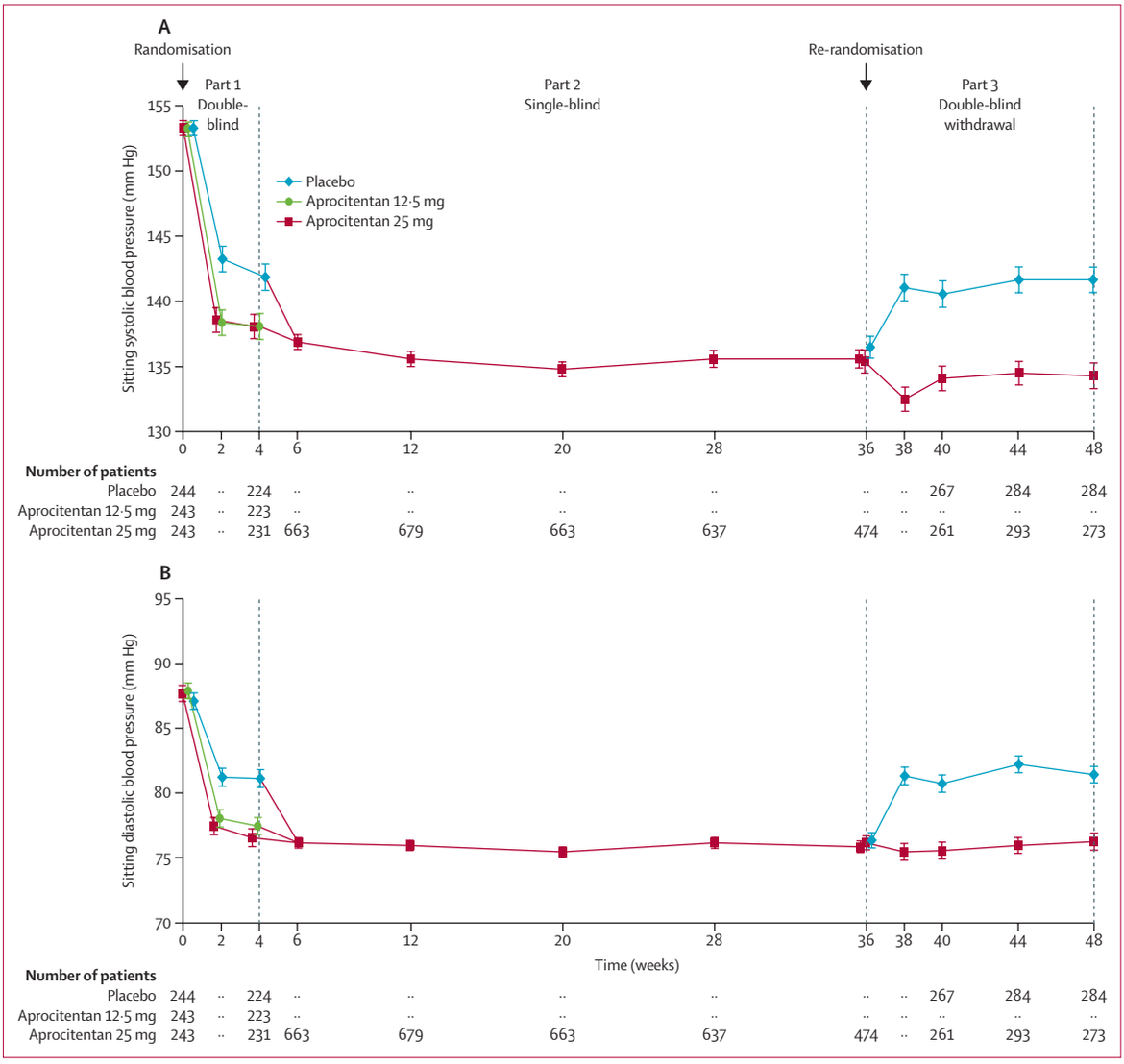

Figure 2: **Sitting systolic and diastolic blood pressures measured as unattended automated office blood pressure over time**
Blood pressure was measured at trough, before taking the study treatment and the standardised background antihypertensive therapy. Bars are standard error of the mean. Values are offset from each other for readability.

No signs of hepatotoxicity were observed (table 2). Haemoglobin concentrations decreased and estimated plasma volume increased to a similar degree with both aprocitentan doses (–8·0 g/L, –8·5 g/L, and –0·4 g/L for haemoglobin; and 10·5%, 11·2%, and 0·51% for estimated plasma volume, with aprocitentan 12·5 mg, aprocitentan 25 mg, and placebo, respectively) during part 1, stabilised during part 2 and reversed upon withdrawal during part 3 (appendix pp 38–39). Slight increases in N-terminal pro-brain natriuretic peptide (NT-proBNP) and mid-regional pro-atrial natriuretic peptide (MR-proANP) were observed in part 1 with aprocitentan, followed by stabilisation during part 2 and reversal during part 3 (appendix pp 40–41). A moderate increase in bodyweight with both aprocitentan doses and a decrease with placebo were observed during part 1 (appendix p 42). The eGFR decreased slightly with aprocitentan in part 1 versus placebo, stabilised in part 2, and decreased further in the aprocitentan group in part 3 while remaining stable in the placebo group (appendix p 43). A marginal decrease in heart rate was apparent in all treatment groups during part 1 and maintained during part 2 (appendix p 44).

Discussion

This phase 3 study, in patients with resistant hypertension receiving standardised antihypertensive treatment including a diuretic, showed that the addition of aprocitentan lowered both standardised automated office and 24 h ambulatory blood pressure compared with placebo after 4 weeks of initial treatment. This blood pressure lowering

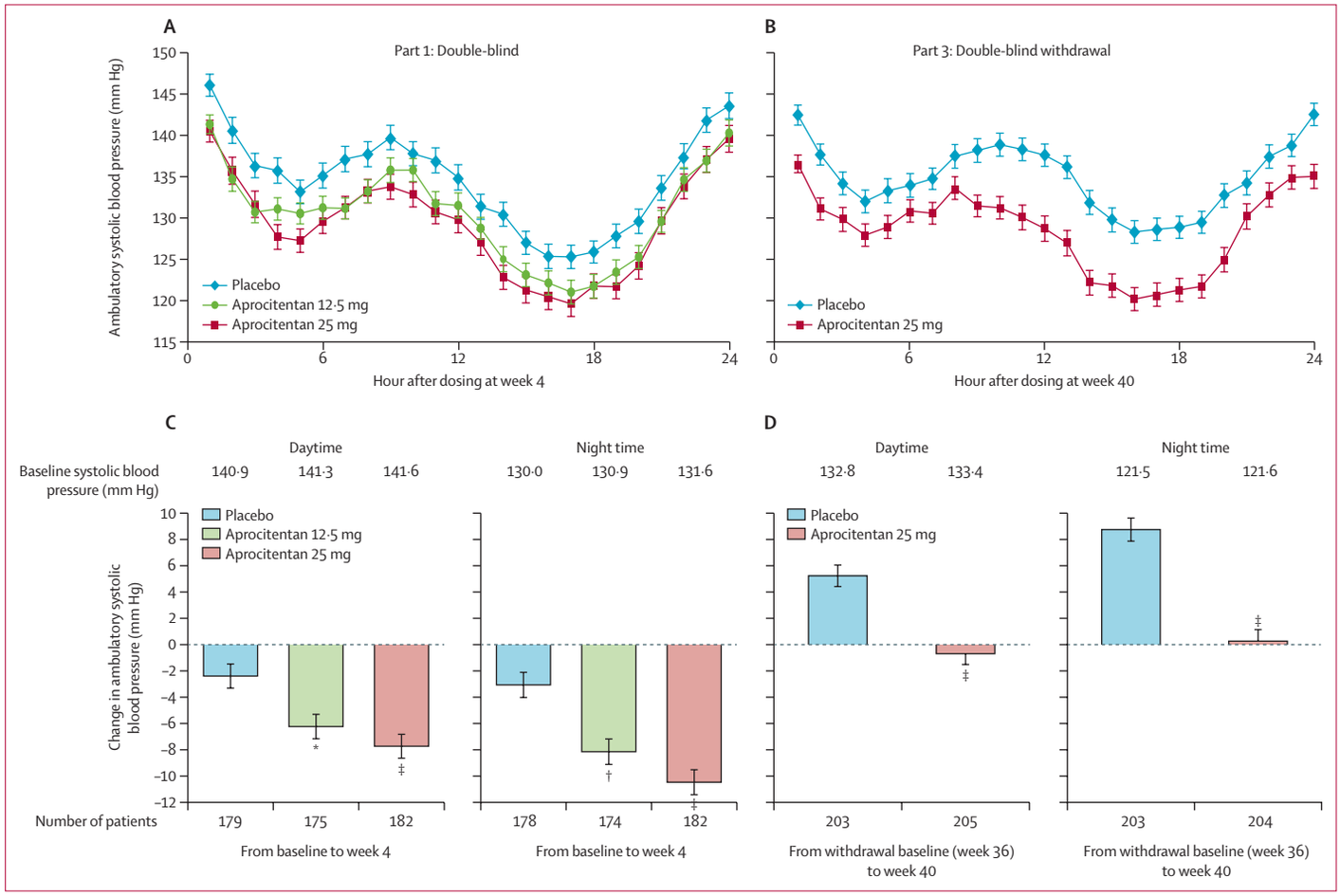

Figure 3: **Systolic blood pressure measured by 24-h ambulatory blood pressure monitoring after dosing (occurring after all visit assessments have been performed) at week 4 and week 40, and corresponding least square mean changes in daytime and night time ambulatory blood pressure from baseline to week 4 and week 40**
Bars are standard error of the mean. No correction for multiplicity was applied to the analysis of ambulatory blood pressure. *p=0·0033. †p=0·0002. ‡p<0·0001 (for comparison with placebo).

effect was maintained over a period of 48 weeks supporting long-term tolerability and efficacy of aprocitentan. A pronounced reduction was observed for nocturnal blood pressure, which is superior to other blood pressure measures in predicting cardiovascular mortality.[24,25] The clinical benefit is amplified by the high cardiovascular risk of the population enrolled.[4,26]

A 5 mm Hg reduction in office SBP has been associated with a 10% relative risk reduction in major cardiovascular events.[27] This is of particular relevance in patients with resistant hypertension at high risk of cardiovascular events.[4,26] Indeed, our study cohort had features characteristic of resistant hypertension, including obesity, comorbidities (such as diabetes, chronic kidney disease, albuminuria, and previous cardiovascular events), and high blood pressure despite at least three, but commonly four or more antihypertensive medications.

Ambulatory blood pressure monitoring is considered superior to other measurement modalities in assessing blood pressure levels and changes with treatment as it is less prone to a placebo effect and provides the most accurate prediction of cardiovascular outcomes, the latter relating particularly to night time blood pressure.[24,25] In this context, it is reassuring that ambulatory monitoring confirmed the blood pressure lowering efficacy observed with office blood pressure measurement and revealed a dose–response relationship. Notably, reduction in ambulatory blood pressure was most pronounced during night time, which might relate to additional reduction of cardiovascular risk. Furthermore, we also confirmed a lower placebo effect with this technique.

The study design,[23] including thorough confirmation of resistant hypertension with standardised background therapy and monitoring of treatment adherence, is a strength of the study. Several shortcomings of previous studies were addressed by introducing a three-part design that sequentially included a short double-blind placebo-controlled treatment part (4 weeks), a long single-blind active-treatment part (32 weeks), and a double-blind placebo-controlled withdrawal part (12 weeks), thereby allowing for an evaluation of the sustainability of the antihypertensive effect of aprocitentan over a period of

48 weeks. The withdrawal phase is of particular interest because it confirmed the sustained efficacy of aprocitentan to lower blood pressure, whereas a substantial rise in blood pressure was evident in the placebo group. Another strength of the study is the worldwide inclusion of patients who were representative of the population typically affected by resistant hypertension (appendix p 15).[6] Adherence to study medication has been monitored rigorously by pill counting, observed pill intake before ambulatory blood pressure monitoring, and urine samples for detection of background medication intake.[23]

A progressive reduction in eGFR and increased albuminuria indicate progressive loss of renal function. Both are independent and additive predictors of increased cardiovascular risk and progression of renal disease.[28] A reduced incidence of cardiovascular events and slower progression of renal disease has been reported with a treatment-induced reduction in urinary protein excretion in both patients who are diabetic and not diabetic, especially for micro-albuminuria.[29] At baseline, 37% of study participants showed evidence of micro or macro albuminuria. A substantial reduction in urine albumin–creatinine ratio of 28% and 31% was observed for the 12·5 mg and 25 mg aprocitentan doses, respectively, whereas urine albumin–creatinine ratio increased by 5% with placebo in the double-blind part 1 (appendix p 35). This antiproteinuric effect of aprocitentan tended to be greater in patients with chronic kidney disease stage 3–4 versus patients with eGFR of 60 mL/min per 1·73 m² or higher (appendix pp 23–24), perhaps highlighting the potential of aprocitentan to reduce organ damage even in patients with moderate-to-severe chronic kidney disease, in whom blood pressure control is particularly difficult to achieve.[30] Importantly, the antiproteinuric effect was sustained during the single-blind part 2, during which all participants were on 25 mg aprocitentan. The subsequent increase in patients re-randomised to placebo in the double-blind withdrawal part 3 substantiates this notion and indicates that the changes in urine albumin–creatinine ratio are associated with aprocitentan-induced blood pressure lowering as shown for other endothelin antagonists.[31,32]

As anticipated for an endothelin receptor antagonist, oedema or fluid retention was the most common adverse event reported with aprocitentan within the first 4 weeks of treatment and led to the discontinuation of seven patients during the study. The incidence was dose related, suggesting that 12·5 mg might represent a preferred dose for initiation of therapy. With the addition or up-titration of diuretic therapy, this event was clinically manageable. In this population with multiple comorbidities, half of the incident cases of hospitalisation for heart failure were reported for patients with pre-existing heart failure, highlighting the potential importance of adequate diuretic therapy before initiating aprocitentan in these patients. As expected with any endothelin antagonist, a decrease in haemoglobin concentration was observed, which was reversible and associated with an estimated plasma volume increase of 10–11% throughout the study, with limited impact on NT-proBNP and MR-proANP in this population with high cardiovascular risk.

	Aprocitentan 12·5 mg	Aprocitentan 25 mg	Placebo
Part 1: Double-blind	243	245	242
Patients with at least one event	30 (12·3%)	47 (19·2%)	7 (2·9%)
Oedema or fluid retention	22 (9·1%)	45 (18·4%)	5 (2·1%)
Anaemia or haemodilution	9 (3·7%)	3 (1·2%)	0
Hepatic disorder	0	1 (0·4%)	2 (0·8%)
Part 2: Single-blind	..	704	..
Patients with at least one event	..	185 (26·3%)	..
Oedema or fluid retention	..	128 (18·2%)	..
Anaemia or haemodilution	..	63 (8·9%)	..
Hepatic disorder	..	16 (2·3%)	..
Part 3: Double-blind withdrawal	..	310	303
Patients with at least one event	..	18 (5·8%)	15 (5·0%)
Oedema or fluid retention	..	8 (2·6%)	4 (1·3%)
Anaemia or haemodilution	..	6 (1·9%)	4 (1·3%)
Hepatic disorder	..	4 (1·3%)	7 (2·3%)

Data are n or n (%). Events are defined using the Medical Dictionary for Regulatory Activities (version 24.1). Safety analyses were done according to the received treatment group.

***Table 2*: Treatment-emergent adverse events of special interest**

Following the PATHWAY-2 study,[33] recent guidelines recommend spironolactone as the preferred fourth-line drug for patients with resistant hypertension.[4,6] Indeed, compared with placebo, spironolactone reduced home SBP by 8·7 mm Hg after 12 weeks of treatment. Spironolactone was also superior to both doxazosin and bisoprolol in lowering home SBP.[33] Although the risk of hyperkalaemia was low in the 12-week treatment period with spironolactone in PATHWAY-2 (the patients had an eGFR of 91·1 mL/min at baseline), there is a lack of longer-term efficacy data and concerns remain with regard to tolerability. Endothelin is a mediator of aldosterone and catecholamine release and aprocitentan could provide alternative therapy without risk of hyperkalaemia. In the absence of a direct comparison between spironolactone and aprocitentan and given the evidence in favour of aprocitentan from this study providing well tolerated, effective, and sustained blood pressure lowering in addition to guideline-recommended therapy, there is now an important additional treatment option for the cohort of patients at high risk with resistant hypertension, targeting a currently unopposed pathophysiological pathway.

A potential limitation of the study is that the two fixed doses of the amlodipine–valsartan–hydrochlorothiazide single-pill combination were not at the maximum-recommended dose for valsartan in all countries due to different local regulatory requirements. It is possible that the use of higher doses of hydrochlorothiazide or more potent diuretics (such as chlorthalidone) would have resulted in fewer adverse events related to fluid retention. However, further diuretics could be increased or added in case of clinically relevant fluid retention or as rescue medication for blood pressure increase. Notably, sensitivity analyses revealed that the addition or increase in dose of diuretics or use of rescue medication for blood pressure increase did not affect the primary and key secondary results.

The lack of a placebo control in the 32-week single-blind part 2 of the current study might be considered a limitation of the trial. Indeed, in a previous trial comparing the selective endothelin A receptor antagonist darusentan with placebo and the central α-2 agonist guanfacine in patients with resistant hypertension,[19] there was no difference in the predetermined endpoint of the mean decrease in sitting SBP at 14 weeks between darusentan (15 mm Hg [SE 14]) and placebo (14 mm Hg [14]). The unexpected placebo response was observed over time, particularly after week 8.[19] However, in the present study, re-randomisation to placebo or aprocitentan 25 mg in part 3, a double-blind, placebo-controlled, randomised withdrawal treatment period, clearly showed sustained blood prssure lowering with aprocitentan and a significant increase in blood pressure with placebo (5·8 mm Hg, 95% CI 3·7 to 7·9, p<0·0001). Similar differences were observed with ambulatory blood pressure monitoring. It therefore seems unlikely that the addition of a placebo control during part 2 would have made a substantial difference to the current findings.

Aprocitentan, by targeting a currently unopposed pathophysiologic pathway, provided clinically meaningful lowering of SBP and DBP in patients with treatment-resistant hypertension over 48 weeks with manageable adverse effects. Aprocitentan represents a novel, effective, and well tolerated treatment for resistant hypertension.

Contributors

MPS and MB wrote the first draft of the manuscript. MS-S did the statistical analysis. MPS, MB, PD, and RFD contributed to the writing of the clinical study report and verified the data. KN and J-GW participated in the aprocitentan advisory committee. MB and PD designed the study. MPS, JMF, and J-GW recruited patients for the study. All authors were involved in the interpretation of the data. All authors had unrestricted access to all the data in the study. All authors agreed to the content of the manuscript, reviewed manuscript drafts, and approved the final version. All authors take final responsibility for the decision to submit for publication. The authors assume responsibility for the accuracy and completeness of the data and analyses, as well as for the fidelity of the study and this report to the protocol.

Declaration of interests

MPS has received institutional grants or contracts and personal consulting fees from Medtronic, Abbott Laboratories, and ReCor Medical; personal payment or honoraria from Medtronic, Abbott Laboratories, Merck, and Servier Laboratories; personal support for attending meetings, travel, or both from Medtronic and Abbott Laboratories; serves as the President of the High Blood Pressure Research Council of Australia; and is on the International Society of Hypertension scientific committee. MB is an employee of Idorsia Pharmaceuticals. MAW is has received consulting fees or performed research services for Janssen, Bristol Myers Squibb, CinCor, Medtronic, ReCor, and Ablative Solutions. PD and RFD are employees of Idorsia Pharmaceuticals and hold stock or stock options in Idorsia Pharmaceuticals. GLB has received consulting fees from Bayer, KBP BioSciences, Ionis Pharmaceuticals, Alnylam Pharmaceuticals, AstraZeneca, Quantum Genomics, Novo Nordisk, Janssen, Dia Medica Therapeutics, and InREGEN. JMF has received consulting fees from Ardelyx, Janssen, Amgen, FibroGen, Teva Pharmaceuticals, and ReCor Medical; and payment for a lecture at a continuing medical education event from Janssen. MS-S is an employee of Idorsia Pharmaceuticals. LPH is an employee of Janssen and holds stock in Janssen. KN has received personal honoraria from Bausch Health, Berlin-Chemie (Menarini Group), Egis, Gedeon Richter, Krka, Medtronic, Merck, Novo Nordisk, Polpharma, Recordati, and Servier Laboratories; and has participated in an advisory board for Idorsia Pharmaceuticals. J-GW declares no competing interests.

Data sharing

Individual deidentified participant data will not be shared. The redacted protocol and statistical analysis plan will be shared with *The Lancet* and will be posted along with the required summary results on the clinical trials registries. Additional requests for information should be directed to the corresponding author.

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