Circulation

ORIGINAL RESEARCH ARTICLE

Efficacy and Safety of Firibastat, A First-in-Class Brain Aminopeptidase A Inhibitor, in Hypertensive Overweight Patients of Multiple Ethnic Origins

A Phase 2, Open-Label, Multicenter, Dose-Titrating Study

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BACKGROUND: Despite existing therapy, successful control of hypertension in the United States is estimated at less than 50%. In blacks, hypertension occurs earlier, is more severe, controlled less often and has a higher morbidity and mortality than in whites. Blacks are also less responsive to monotherapy with angiotensin-I converting enzyme inhibitors or angiotensin-II receptor type 1 blockers. Obesity, higher salt-sensitivity and low plasma renin activity are possible reasons of this poor blood pressure (BP) control, especially in blacks. The aim of the study was to assess efficacy and safety of firibastat, a first-in-class aminopeptidase A inhibitor preventing conversion of brain angiotensin-II into angiotensin-III, in BP lowering in a high-risk diverse hypertensive population.

METHODS: Two hundred fifty-six overweight or obese hypertensive patients, including 54% black and Hispanic individuals, were enrolled in a multicenter, open-label, phase II study. After a 2-week wash-out period, subjects received firibastat for 8 weeks (250 mg BID orally for 2 weeks, then 500 mg BID if automated office blood pressure (AOBP) >140/90 mm Hg; hydrochlorothiazide 25 mg QD was added after 1 month if AOBP ≥160/110 mm Hg). The primary end point was change from baseline in systolic AOBP after 8 weeks of treatment, and secondary end points include diastolic AOBP, 24-hour mean ambulatory BP and safety.

RESULTS: Firibastat lowered systolic AOBP by 9.5 mm Hg ($P<0.0001$) and diastolic AOBP by 4.2 mm Hg ($P<0.0001$). 85% of the subjects did not receive hydrochlorothiazide and were treated with firibastat alone. Significant BP reduction was found across all subgroups regardless age, sex, body mass index, or race. Systolic AOBP decreased by 10.2 mm Hg ($P<0.0001$) in obese patients, by 10.5 mm Hg ($P<0.0001$) in blacks, and 8.9 mm Hg ($P<0.0001$) in nonblacks. Most frequent adverse events were headaches (4%) and skin reactions (3%). No angioedema was reported. No change in potassium, sodium, and creatinine blood level were observed.

CONCLUSIONS: Our results demonstrate the efficacy of firibastat in lowering BP in a high-risk diverse population where monotherapy with angiotensin-I converting enzyme inhibitors or angiotensin-II receptor type 1 blockers may be less effective and support the strategy to further investigate firibastat in subjects with difficult-to-treat or potentially resistant hypertension.

CLINICAL TRIAL REGISTRATION: URL: https://www.clinicaltrials.gov. Unique Identifier: NCT03198793.

Key Words: angiotensin II ■ angiotensin III ■ angiotensin-converting enzyme inhibitors ■ blood pressure ■ hypertension ■ obesity

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Clinical Perspective

What Is New?

- Firibastat, the first orally active brain aminopeptidase A inhibitor, a new class of centrally acting renin-angiotensin system blocker, exhibits a marked blood pressure reduction after 8-week treatment in a high-risk diverse population.
- The efficacy of firibastat in lowering blood pressure is proved in all subgroups, particularly obese and black patients in whom monotherapy with blockers of the systemic renin-angiotensin system may be poorly effective.
- An 8-week open-label phase 2 study in overweight hypertensive patients including at least 50% of self-identified blacks or Hispanics with the use of automated office blood pressure monitoring to establish the primary end point.

What Are the Clinical Implications?

- The study supports the strategy to further investigate in clinical trials the use of firibastat and brain aminopeptidase A inhibitors to improve blood pressure control in subjects with difficult-to-treat or potentially resistant hypertension.

Hypertension (HTN) is a complex phenotype that arises from numerous genetic, environmental, behavioral, and even social origins. It is the world's leading risk factor for cardiovascular disease, stroke, disability, and death. Complications of HTN account for 10.4 million deaths and 218 million attributable disability-adjusted life-years worldwide every year.[1] National Center for Health Statistics data indicated that prevalence of HTN among all US adults aged >18 years was 29% and even higher among non-Hispanic black adults (40.6%).[2] Obesity is also a growing health concern because prevalence of obesity among adults increased from 30.5% to 39.6% over the last decades,[3] and because the relationship between overweight and high blood pressure (BP) was demonstrated prospectively in the 1960s in the Framingham Heart Study.[4]

Effective BP management has been shown to decrease cardiovascular risk and the incidence of stroke, heart attack and heart failure.[5] In the United States, antihypertensive medication is recommended for most adults with systolic BP ≥130 mm Hg or diastolic BP ≥80 mm Hg.[6] But, despite the availability of different therapeutic classes of effective and safe antihypertensive drugs, more than 50% of US adults taking antihypertensive medication have BP above the treatment goal.[7] Uncontrolled HTN is even more common in obese, black, and other minority patients, and among US hypertensive adults, 19.9% met the criteria for apparent treatment resistant HTN (BP above goal levels despite concurrent use of adequately dosed antihypertensive drugs of 3 different classes including a diuretic, or BP below goal levels while taking at least antihypertensive drugs of 4 different classes, including a diuretic).[8]

Obesity is associated with activation of both the sympathetic nervous system and the renin-angiotensin system (RAS) leading to HTN.[9] The systemic RAS plays a central role in BP regulation and sodium metabolism, and drugs targeting the systemic RAS, such as angiotensin-I converting enzyme inhibitors and angiotensin-II (Ang-II) receptor type-1 blockers, are clinically effective in lowering BP and preventing cardiovascular and renal morbidity, and mortality. Yet, these agents have been reported to be less effective as monotherapy or initial therapy in blacks, and in overweight or obese subjects.[10,11] Thus, international guidelines recommend that initial antihypertensive drug treatment in black patients should include a diuretic or a calcium channel blocker, either in combination or with a RAS blocker.[6,12]

Evidence supports the existence of a functional RAS in the brain, controlling cardiovascular functions and body fluid homeostasis.[13] Hyperactivity of the brain RAS and particularly hyperactivity of brain aminopeptidase A ([APA] glutamyl aminopeptidase), a membrane-bound zinc metalloprotease involved in vivo in the conversion of Ang-II into angiotensin-III, is implicated in the development and maintenance of HTN in various experimental animal models.[14–16] In these models, brain angiotensin-III exerts a tonic stimulatory control over BP and inhibition of brain APA activity leads to BP decrease.[17,18]

Firibastat, previously named QGC001 or RB150, is an orally active brain penetrating prodrug of EC33, a selective and specific inhibitor of APA. On entry into the brain, it is cleaved by brain reductases to generate 2 active molecules of EC33, which inhibit brain APA activity, block brain angiotensin-III formation, and decrease BP both in spontaneously hypertensive rats and in deoxycorticosterone acetate salt rats,[19,20] an experimental model of HTN associated with salt-sensitivity and low plasma renin levels, known to be poorly responsive to systemic RAS blockers.[21] In contrast, no effect on BP nor on heart rate was observed after repeated oral administrations of firibastat, even at doses >1000 mg/kg, in normotensive rats which are not displaying brain APA hyperactivation. In healthy volunteers, single oral doses of firibastat up to 2000 mg as well as twice-daily doses up to 750 mg were well-tolerated, and had no effect on BP, heart rate, and the systemic RAS activity.[22] A first pilot phase 2a study in 34 patients with mild-to-moderate HTN showed that 4-week administration of 1000 mg/d of firibastat (250 mg BID for 1 week, then uptitrated to 500 mg BID for 3 weeks) decreased daytime systolic ambulatory blood pressure (ABP) by 2.7 mm Hg and systolic office blood pressure by 4.7 mm Hg compared with placebo, with an acceptable safety profile.[23]

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The present clinical trial investigates over an 8-week open-label treatment period, the efficacy and safety of firibastat oral treatment up to 500 mg BID in a high-risk diverse population (overweight or obese patients with stage 2 primary HTN, including at least 50% self-identified black and Hispanic individuals).

METHODS

The data that support the findings of this study are available from the corresponding author on reasonable request.

Study Design

This was an 8-week open-label phase 2b study in 256 patients with stage 2 primary HTN carried out at 40 US centers. After screening, subjects entered a 2-week wash-out period and stopped all antihypertensive medication. All subjects who met the selection criteria after a 2-week wash-out period, with systolic BP between 145 and 170 mm Hg inclusive and diastolic BP ≤105 mm Hg through a fully automated unattended measurement technique, called automated office blood pressure (AOBP), were enrolled into the trial and received firibastat 250 mg BID for 2 weeks (Figure 1). If after 2 weeks of treatment, AOBP was ≤140/90 mm Hg, subjects remained at the same dose until day 56, otherwise the dose was increased to 500 mg BID. If after 1 month of treatment (day 28), AOBP was ≥160/110 mm Hg, hydrochlorothiazide (HCTZ) 25 mg once daily (QD) was combined with firibastat. AOBP was assessed after 2 weeks, 4 weeks, and 8 weeks. ABP measurements over 24 hours were assessed at baseline and at day 56 (end-of-treatment). The full description of the dosage titration scheme and the study treatment allocation rules for each study visit is provided in the supplemental publication material (Figure I in the online-only Data Supplement).

The study was approved by individual site and/or central institutional review boards, conducted under GCP/ICH and is listed in clinical trials.gov under NCT03198793.

Study Population

Eligible subjects were adult (over 18 years old) male or female patients with primary HTN, either treatment-naïve or treated, with systolic AOBP between 145 and 170 mm Hg and diastolic AOBP below 105 mm Hg after a 2-week wash-out treatment period, and a body mass index (BMI) between 25 and 45 kg/m^2. Subjects with renal dysfunction (estimated glomerular filtration rate less than 45 mL/min per 1.73 m^2) as well as subjects with type-I diabetes mellitus or uncontrolled type-2 diabetes mellitus (defined as glycohemoglobin HbA1C >8%), and subjects treated with short-acting insulin or sodium-glucose cotransporter-2 inhibitors were excluded. The study targeted to enroll at least 50% of self-identified blacks or Hispanics. A full description of the inclusion and exclusion criteria patients is provided in the Appendix in the online-only Data Supplement. All subjects screened provided written informed consent before participating in the trial.

Study Treatments

All antihypertensive medications taken by the subjects before enrollment were discontinued for the duration of the study. Adherence to firibastat treatment was measured using pills count. Serum potassium levels were measured in subjects receiving HCTZ and if levels were <4 mmol/L after 1 week (day 35), potassium supplementation was prescribed.

End Points and Assessments

The primary end point was the change from baseline to day 56 in seated systolic AOBP. AOBP measurements were performed using a validated automated oscillometric device (SunTech-CT40; SunTech Medical Inc.).[24] AOBP results from the recording of multiple BP readings with the patient resting alone seated in a quiet room of the clinic. The device was programmed to take 6 consecutive BP readings with 1-minute interval after an appropriate resting period (5 minutes). The first measurement was discarded, and the 5 next readings were averaged. Secondary end points included change in diastolic AOBP, 24-hour ABP, daytime and nighttime ABP, safety and laboratory tests. Twenty-four-hour ABP monitoring was performed using a validated device (OnTrak, Spacelabs Healthcare Ltd.),[25] with measurement frequency set at 30-minute intervals during the day (8:00 AM – 10:00 PM) and 60-minute intervals at night (10:00 PM – 8:00 AM). ABP monitoring was considered valid if at least 70% of all readings were successful, with at least 21 daytime and 6 nighttime successful readings.

Statistical Analysis

Efficacy analysis was performed on the intention-to-treat (ITT) population gathering all patients who took at least 1 dose of firibastat and had baseline measurements and at least 1 post-baseline AOBP measurement. Missing values were replaced according to the Last observation carried forward method. The per-protocol population clustered patients who completed 8 weeks on treatment without any major protocol violation. Safety population consisted of all patients who took at least 1 firibastat dose.

The primary end point was analyzed using a linear regression model with baseline systolic AOBP. An exploratory multivariate analysis of the primary end point was conducted using an ANCOVA model with baseline systolic AOBP, age, BMI as covariates and gender, race and pooled sites as factors. The primary efficacy end point was summarized by gender, age (≥65 or <65 years), BMI (25 to 30 or >30 kg/m^2), race (black or nonblack), estimated glomerular filtration rate (≥60 or <60 mL/min per 1.73m^2). For continuous secondary efficacy variables, the same analysis model was used. Significance

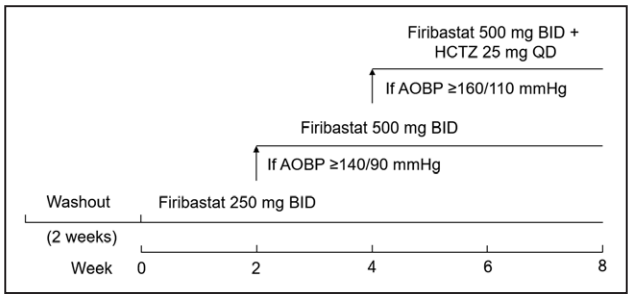

Figure 1. Study design.
AOBP indicates automated office blood pressure; BID, bis in die (ie, twice daily); HCTZ, hydrochlorothiazide; and QD, quaque die (ie, once a day).

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(α-level) was defined as $P<0.05$. Study sample size was based on an ANCOVA model with an assumed minimum change of 7 mm Hg and a SD of 12 mm Hg in the primary end point (change from baseline in AOBP) with 95% power. No adjustment for multiplicity were applied.

RESULTS

Patient Characteristics

Two hundred fifty-six subjects were enrolled into the trial and 254 patients received at least 1 dose of firibastat and had at least 1 postbaseline AOBP evaluation (ITT population). Two hundred eighteen subjects (85%) completed the study on-treatment (per-protocol population). Patient disposition is reported in Figure 2. Patient baseline characteristics are reported in Table 1.

At baseline, the mean age was 58.3±9.9 years, the mean BMI was 33.0±5.2 kg/m^2, 65% of the subjects were obese (BMI >30 kg/m^2), 54% self-identified as black or Hispanic, including 38% of self-identified blacks, and 28% with type-2 diabetes mellitus. Baseline AOBP were 153.9±7.3 mm Hg and 91.5±8.5 mm Hg for systolic and diastolic BP, respectively. At the end-of-treatment period, 37 subjects (14%) were treated with firibastat 250 mg BID, 178 subjects (70%) with firibastat 500 mg BID, and 39 subjects (15%) received combined therapy with HCTZ 25 mg QD.

Efficacy on AOBP and ABP

A significant decrease in the primary end point (change from baseline in seated systolic AOBP after 8-week treatment) was observed in the ITT population. Systolic AOBP and diastolic AOBP decreased continuously along the treatment period (Figure 3). Primary and secondary efficacy end point data are summarized in Table 2. After 8-week treatment the changes from baseline in BP levels were highly significant showing a decrease by 9.5 mm Hg (95% CI, −10.7; −7.3; $P<0.0001$) for systolic AOBP and by 4.2 mm Hg (95% CI, −5.5; −3.3) for diastolic AOBP ($P<0.0001$).

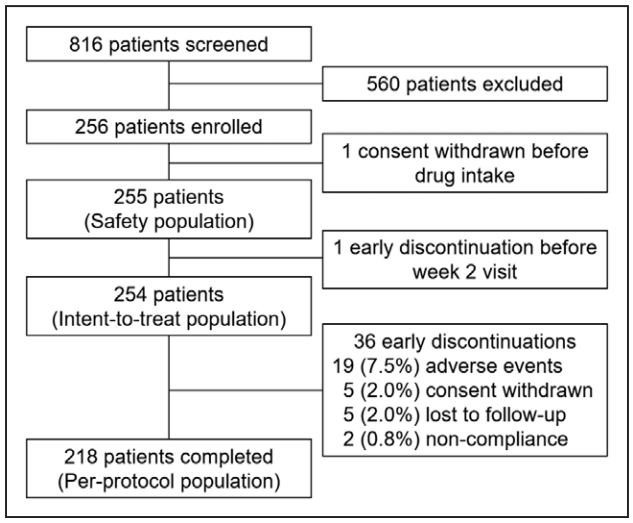

Figure 2. Patient flow diagram.

Table 1. Demographic Summary and Baseline Clinical Characteristics

Characteristic	All Patients (n=256)
Gender, M/F	140/116
Age, y	58.3±9.9
Age ≥65, n (%)	67 (26.2%)
Weight, kg	94.9±17.0
BMI, kg/m^2	33.0±5.2
Obese (BMI >30 kg/m^2), n (%)	166 (64.8%)
Self-identified minorities, n (%)	138 (53.9%)
Blacks, n (%)	98 (38.3%)
Type 2 diabetes mellitus, n (%)	73 (28.5%)
eGFR, ml/min/1.73 m^2	87.7±18.3
Systolic AOBP, mm Hg	153.9±7.3
Diastolic AOBP, mm Hg	91.5±8.5
Systolic daytime ABP, mm Hg	151.2±13.2
Diastolic daytime ABP, mm Hg	88.3±9.4
Previous antihypertensive therapy, yes/no	197/59
Monotherapy, n (%)	117 (59.4%)
Bitherapy, n (%)	80 (40.6%)

Data are expressed as mean±SD or proportions as appropriate. "Minorities" indicates black or Hispanic adults. ABP indicates ambulatory blood pressure; AOBP, automated office blood pressure; BMI, body mass index; and eGFR, estimated glomerular filtration rate.

A significant decrease in daytime ABP and in 24-hour ABP was also observed in the ITT population after 8-week treatment. A decrease from baseline by 3.1±13.0 mm Hg, ($P=0.0005$) for daytime systolic ABP and by 1.6±7.8 mm Hg ($P=0.003$) for daytime diastolic ABP was observed. No significant change in nighttime systolic and diastolic ABP was observed. The changes from baseline in 24 hour ABP levels showed a decrease by 2.7±12.4 mm Hg, ($P=0.002$) for systolic 24-hour ABP and by 1.4±7.2 mm Hg ($P=0.01$) for diastolic 24-hour ABP. Treatment did not affect heart rate (change from baseline of 0.9±12.3 bpm).

Results were consistent for the 215 subjects who received firibastat as a monotherapy. In these patients, systolic and diastolic AOBP decreased by −9.4±14.3 mm Hg and by −4.20±9.5 mm Hg respectively. Results from the per-protocol analysis as well as from the analysis in the completer population (no replacement by Last observation carried forward method of missing day 56 BP value) were similar to those obtained in the ITT population (Table I in the online-only Data Supplement).

Subgroup Analyses

Results of the subgroup analyses by age, sex, race, and estimated glomerular filtration rate did not reveal any predicting factor on BP lowering efficacy of treatment

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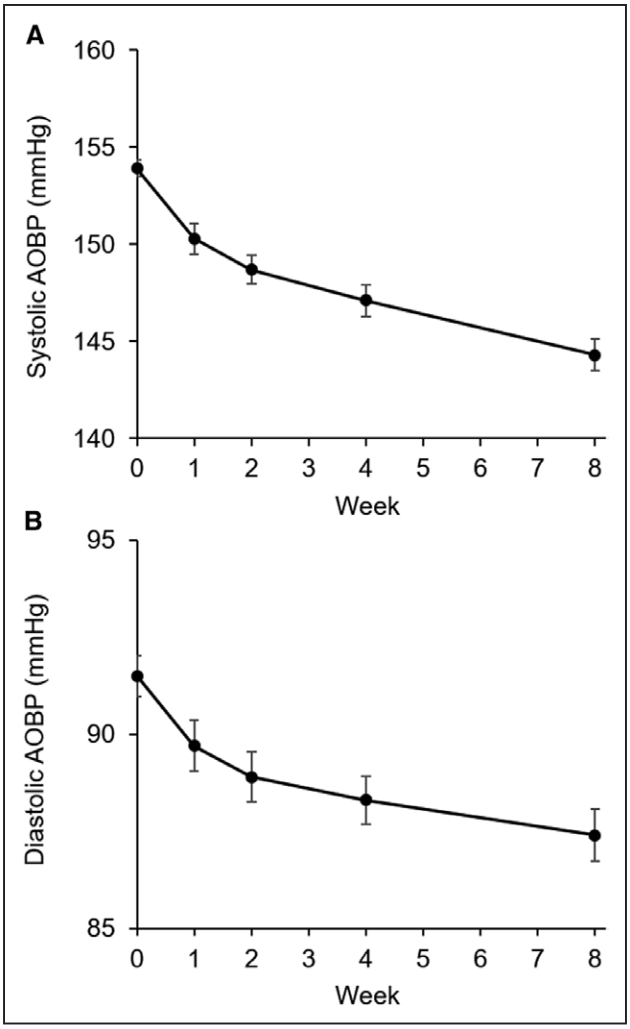

Figure 3. Systolic automated office blood pressure (A) and diastolic automated office blood pressure (B) in the intent-to-treat population (n=254) along 8-week treatment.
Values are presented as mean±standard error of mean. AOBP indicates automated office blood pressure.

(Figure 4). BP decrease was consistent across all the different subgroups. Decrease in systolic AOBP was similar in blacks (–10.5±14.7 mm Hg; $P<0.0001$) and in nonblacks (–8.9±14.1 mm Hg; $P<0.0001$), as well as in obese (–10.2±14.5 mm Hg; $P<0.0001$) versus overweight patients (–8.3±13.9 mm Hg; $P<0.001$).

Safety and Tolerability

One subject did not start study drug therefore 255 patients were considered for the safety population. Safety data are summarized in Table 3. Thirty-six subjects (14.1%) reported a related treatment-emergent adverse event. The most common treatment-emergent adverse events were headache (4%) and skin reaction (3%). Overall, 19 subjects (7.5%) stopped the medication attributable to adverse events. Five serious adverse events occurred during the study, but only 1 serious adverse event (a case of erythema multiforme) was considered by the investigator to be related to study medication. No deaths were reported during the study.

There were no major differences in the clinical laboratory tests performed at baseline or after 8-week treatment as illustrated in Table 4. No change in potassium, sodium, and creatinine blood level occurred. A nonsignificant increase in glucose blood level was observed in subjects treated either by firibastat alone or with concomitant HCTZ (Table II in the online-only Data Supplement).

Effects on Plasma Biomarkers

A nonsignificant reduction of –15.4 pg/mL in NT-proBNP (N-terminal pro-B-type natriuretic peptide) levels was observed between baseline (121.3±174.4 pg/mL) and Day-56 (106.0±171.8 pg/mL). An increase in high sensitivity C-reactive protein and high sensitivity troponin T (statistically significant but clinically irrelevant) was also seen (Table 4).

DISCUSSION

The results of the present study demonstrate that 8 weeks of oral treatment with firibastat, the first brain APA inhibitor, at doses up to 500 mg twice daily, effectively reduce BP in a high-risk diverse population of overweight and obese patients with stage 2 primary HTN and including at least 50% self-identified black and Hispanic individuals. Nevertheless, the study was conducted as an open-label study without any placebo arm which represents a limitation. But, in a placebo-controlled study with high cardiovascular risk subjects, both physicians and patients would have been reluctant to consider a placebo treatment for 10 weeks, which would have limited the enrolment of severe patients and jeopardized the purpose of result generalizability. The absence of an active control group with a standard therapy is another limitation of the study. Since the goal is to develop firibastat in difficult-to-treat HTN, this will be addressed in further trials either versus placebo or active control on top of other therapeutic classes.

AOBP was used in this study to establish the primary end point since this is a better technique than usual clinic BP. Contemporary guideline recommendations are based on the results of major randomized controlled outcome trials which all used clinic BP readings, as efficacy end point.[6,12] Although considered as the gold standard, ABP technique remains complicated especially in obese patients for whom it is difficult to obtain repeated valid measurements. In our study, only 181 patients (70%) could have both their baseline and end-of-study ABP recorded correctly. AOBP measurements were used in the Systolic Blood Pressure Intervention Trial which showed that a goal of intensive BP control to systolic AOBP <120 mm Hg resulted in significant

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Table 2. Baseline and Day-56 Automated Office Blood Pressures, Ambulatory Blood Pressure, and Heart Rate, and Changes From Baseline With Study Treatment

Hemodynamic Parameter	N	Baseline	Day-56	Change From Baseline	*P* Value
Systolic AOBP, mm Hg	251	154.0±7.3	144.4±14.1	–9.5±14.3	<0.0001
Diastolic AOBP, mm Hg	251	91.5±8.5	87.4±10.1	–4.2±9.4	<0.0001
Office HR, bpm	251	75.6±12.5	76.6±11.4	0.9±12.3	0.22
Systolic daytime ABP, mm Hg	181	151.3±13.2	148.2±14.2	–3.1±13.0	0.0005
Diastolic daytime ABP, mm Hg	181	88.7±9.4	87.1±9.7	–1.6±7.8	0.003
Systolic nighttime ABP, mm Hg	181	137.8±16.3	135.9±17.2	–1.9±14.9	0.11
Diastolic nighttime ABP, mm Hg	181	78.3±10.8	77.5±10.5	–0.9±9.0	0.28
Systolic 24h-ABP, mm Hg	181	146.8±13.4	144.1±14.4	–2.7±12.4	0.002
Diastolic 24h-ABP, mm Hg	181	85.2±9.3	83.8±9.3	–1.4±7.2	0.01

Data are expressed as mean±SD. ABP indicates ambulatory blood pressure; AOBP, automated office blood pressure, and HR, heart rate.

cardiovascular benefit in high-risk patients with HTN, compared with routine BP control to a goal below 140 mm Hg.[26] AOBP is now recommend as a method of choice of determining BP in a routine clinical practice by the Canadian guidelines for HTN diagnosis and management.[27] Firibastat treatment led to significant reductions of systolic and diastolic BP based on AOBP, and 24-hour and daytime ABP measurements. But, while AOBP was reported to mirror awake ABP,[28] we observed in our study a smaller but still significant decrease in daytime ABP than in AOBP. This finding needs further investigations. No effect on nighttime ABP was noticed which may be attributable to lower BP levels at night and may reflect less nominal effects of firibastat.

Of the 254 patients analyzed in the study, 39 patients (15%) had their systolic BP over 160 mm Hg after 4 weeks of firibastat treatment and therefore received a combination of firibastat and HCTZ for 4 additional weeks. The change from baseline in seated systolic AOBP after 8-week treatment for these 39 patients (–10.4±14.5 mm Hg) was similar to the one observed in the 254 patients overall (–9.5±14.3 mm Hg). These results suggest that firibastat does not inhibit the action of thiazide-type diuretics like HCTZ, and may suggest that greater antihypertensive effect and higher BP control could have been observed with the earlier initiation of the firibastat plus HTCZ combination.

Firibastat is the first drug candidate of a new class of centrally acting antihypertensive agents, brain APA inhibitors. Firibastat acts as an antihypertensive drug and not as a hypotensive agent. In hypertensive animals, firibastat was found to normalize brain APA activity, and by doing so, lowered BP through a triple mechanism of action that involves a decrease of the vasopressin release into the blood stream, a decrease of the sympathetic tone, and a stimulation of the baroreflex.[29] As such, firibastat appears as a promising alternative therapy for hypertensive subjects known to be associated with diminished response to drug monotherapy because of salt-sensitivity, low plasma renin activity, or sympathetic nervous system overactivity. Obesity is associated with activation of the sympathetic nervous system and with a reduction of baroreflex sensitivity, leading to HTN.[9,30] The efficacy of firibastat in lowering BP was proven in all subgroup analyses, including age, sex, ethnic origin, and weight. In particular, a statistically significant

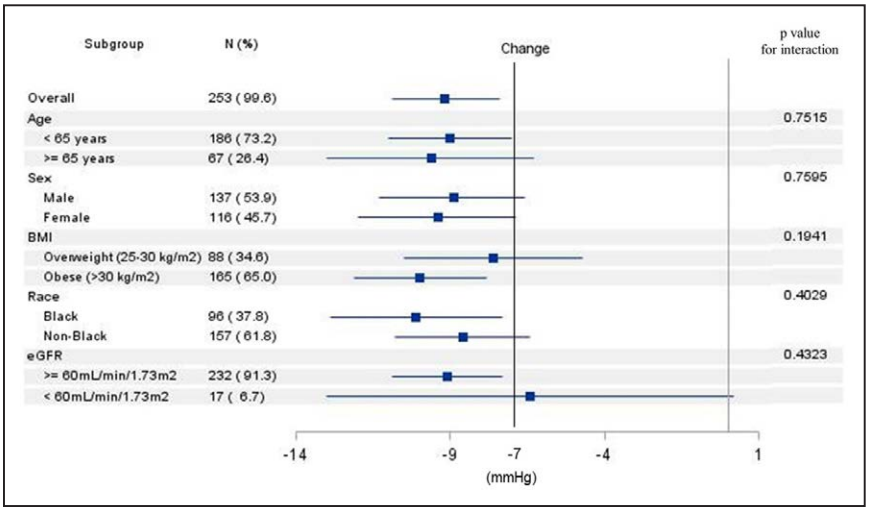

Figure 4. Comparison of changes in seated systolic automated office blood pressure (AOBP) measurements according to age, gender, body mass index (BMI), race, and renal function with estimated glomerular filtration rate (eGFR).

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Table 3. Summary of the Treatment-Emergent Adverse Events (n=255)

	Patients (%)
Patients with any TEAE	107 (42.0%)
Related TEAEs*	36 (14.1%)
Most common treatment related AEs	
Headache	11 (4.3%)
Skin reaction	8 (3.1%)
AE leading to discontinuation	19 (7.5%)
Headache	4 (1.6%)
Skin reaction	3 (1.2%)
Hypertension	3 (1.2%)
Dizziness/presyncope	4 (1.6%)
Diarrhea	2 (0.8%)
Other	3 (1.2%)
Serious AE	5 (2%)
Related serious AE	1 (0.4%)

AE indicates adverse event; and TEAE, treatment-emergent adverse events.
*Investigator determined.

decrease in systolic AOBP was found in obese patients (–10.4 mm Hg; $P<0.0001$), a population at higher risk for resistant HTN.[31]

Interestingly, no difference in BP reduction with firibastat was observed between black (–10.5 mm Hg; $P<0.0001$) and nonblack patients (–8.4 mm Hg; $P<0.0001$). No analysis was performed in other race/ethnicity subgroups like black Hispanics (3 subjects), who were all poorly represented. Firibastat appears also as a potential alternative therapy for blacks whose HTN is generally more difficult to control. HTN in blacks remains a major public health problem because of the high prevalence and premature onset of elevated BP, as well as the high burden of comorbid factors that lead to pharmacological treatment resistance (obesity, diabetes mellitus mellitus, decreased glomerular filtration rate, and albuminuria). Obesity, as well as cardiovascular and renal complications occur more frequently in blacks compared with whites, and the prevalence of resistant HTN is also more common in blacks than in whites.[3,32] Salt sensitivity and low renin levels are disproportionately manifest in blacks, particularly among those with HTN.[33]

The other principal finding of this study was that firibastat was well-tolerated, without any effect on potassium blood levels or renal function, confirming previous knowledge derived from smaller studies in healthy normotensive volunteers and mild-to-moderate hypertensive patients.[22,23] Variations in some clinical laboratory values were observed but were considered as nonclinically relevant despite calculated statistical significance. Specifically, the significant change in high sensitivity C-reactive protein remains unclear and difficult to interpret because of a known short term intraindividual variation.[34] Reversible skin rashes, among them 2 cases of erythema multiform, occurred in 8 patients and were considered by the investigators to be study medication related. Those skin reactions may be attributable to the molecular structure of EC33, the active metabolite of firibastat, exhibiting a zinc-binding sulfhydryl group, known to increase the frequency of skin rashes.[35,36] Overall, the cutaneous adverse drug reactions to firibastat were similar in intensity and frequency to those previously reported with angiotensin-I converting enzyme inhibitors and specifically captopril, Ang-II receptor type-1 blockers, calcium channel blockers, and β-blockers.[37–39] No angioedema, a known serious AE of angiotensin-I converting enzyme inhibitors although rare but more frequent in blacks, was reported.

Conclusions

Despite the open label, uncontrolled study design, the data obtained from both AOBP and ABP measurements provide strong evidence of the efficacy of brain APA inhibition for decreasing BP in a high-risk diverse population with a known reduced BP response to systemic

Table 4. Baseline and Day-56 Clinical Laboratory Findings, and Changes From Baseline With Study Treatment

Clinical Laboratory findings	Baseline	Day 56	Change From Baseline	*P* Value
Potassium, mmol/L	4.4±0.4	4.4±0.5	–0.03±0.5	0.42
Sodium, mmol/L	139.3±2.5	139.0±2.3	–0.2±2.3	0.13
Blood glucose, mg/dL	112.4±33.7	116.7±44.3	3.5±36.2	0.14
Creatinine, mg/dL	0.91±0.2	0.91±0.2	0.0±0.1	0.81
ALT, UI/L	21.8±16.5	25.1±16.3	3.7±10.4	0.001
AST, UI/L	19.1±9.7	21.1±11.3	2.3±7.4	0.001
Hs-CRP, mg/mL	4.96±7.6	5.61±8.2	0.66±8.2	0.0004
NT-proBNP, pg/mL	121.3±174.4	106.0±171.8	–15.4±132.6	0.89
Hs-troponin T, ng/mL	0.009±0.007	0.011±0.001	0.001±0.009	0.01

Data are expressed as mean±SD. ALT indicates alanine aminotransferase; AST, aspartate aminotransferase; Hs-CRP, high sensitivity C-reactive protein; Hs-troponin T, high sensitivity troponin T; and NT-proBNP, N-terminal probrain natriuretic peptide.

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RAS blockers such as angiotensin-I converting enzyme inhibitors or Ang-II receptor type-1 blockers. The results reported here are a useful guide to the design of a larger, randomized parallel-group trial to investigate the use of firibastat as add-on therapy to complex drug regimens for the treatment of difficult-to-treat or potentially resistant HTN to improve BP control and ultimately reduce morbidity and mortality rates among high-risk patients.

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