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Effects of a State- and Use-Dependent Nav1.7 Channel Blocker on Ambulatory Blood Pressure: A Randomized, Controlled Crossover Study

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Abstract

Vixotrigine is a state- and use-dependent Nav1.7 channel blocker being investigated for the treatment of neuropathic pain conditions. This randomized, double-blind, placebo-controlled crossover trial was designed to evaluate changes in blood pressure with the administration of vixotrigine using ambulatory blood pressure monitoring (ABPM). Eligible participants were healthy adults 18 to 65 years of age without evidence of baseline systolic blood pressure (SBP) persistently > 140 mm Hg or diastolic blood pressure (DBP) persistently > 90 mm Hg. Vixotrigine (400 mg [men], 300 mg [women]) or placebo was administered orally twice daily for 36 days. Following a 7-day washout period, participants crossed over to the other treatment. Each dosing period was preceded by 1 inpatient visit and 1 outpatient baseline visit. Two 14-hour inpatient ABPM sessions occurred on days 14 and 35, with a return to the clinic the morning of days 15 and 36 for initiation of outpatient ABPM, which assessed blood pressure and heart rate every 15 minutes. Adverse events were collected throughout the study. The primary end point was the change from baseline in 24-hour mean SBP and DBP on day 36. Sixty participants were enrolled; 10 withdrew from the study owing to adverse events, investigator discretion, or withdrawal of consent. From baseline to day 36, mean changes in average SBP and DBP (vixotrigine treated) were -0.33 and 0.20 mm Hg, respectively. Adverse event rates were comparable for vixotrigine and placebo; the most common adverse events were headache, dizziness, and nausea. Vixotrigine administration is not associated with a clinically important increase in blood pressure.

Keywords

adverse event, blood pressure, Nav1.7, pain, pharmacokinetics, sodium channel blocker, state-dependent, vixotrigine

Vixotrigine (formerly BIIB074) is a state- and use-dependent Nav1.7 channel blocker[1] in development for the treatment of trigeminal neuralgia and other neuropathic pain conditions. Studies in individuals with trigeminal neuralgia (ClinicalTrials.gov identifier NCT01540630)[2] and painful lumbosacral radiculopathy (NCT01561027)[3] have provided preliminary efficacy and safety data for vixotrigine, and further clinical investigation in individuals with neuropathic pain, including these conditions, is planned.

Results from the first human studies of this drug indicated that its overall tolerability and pharmacokinetic (PK) profile support twice-daily dosing without a need for lengthy titration. Small increases in clinic blood pressure (BP) were observed in these first-in-human studies in doses ranging from 150 to 450 mg twice daily. Although observed increases in systolic BP were small (<3 mm Hg), further investigation was warranted to better define an off-target effect of vixotrigine on BP and, if an effect was present, to determine its durability.

We report the results of the present study of a placebo-controlled, randomized crossover trial designed to address whether vixotrigine increases BP, using both inpatient and outpatient ambulatory blood pressure monitoring (ABPM) in healthy participants treated with vixotrigine for 36 days. ABPM is an effective means to evaluate potential off-target effects of a noncardiovascular drug on BP.[4] The use of ABPM had the advantage of providing numerous BP measurements over time after drug administration when participants were in their own environment (outpatient) and performing activities of daily living. Additional

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benefits of ABPM include: (1) the ability to obtain BP measurements during the night/sleep, (2) superior reproducibility compared with single or duplicate measurements in the clinic or medical care environment, and (3) a stronger relationship with cardiovascular events and hypertensive target organ damage.[5] The study also aimed to determine population PK-pharmacodynamic parameters that describe the effect of vixotrigine plasma concentrations on BP and to further characterize the overall safety and PK profile of vixotrigine.

Methods

Study Design

The study was approved by an independent institutional review board (IntegReview IRB, Austin, Texas) and conducted at 1 clinical site (Buffalo Clinical Research Center, Buffalo, New York). All participants provided written informed consent that was reviewed and approved by an independent institutional review board, and the study was conducted in accordance with the International Conference on Harmonization principles of Good Clinical Practice and principles of the Declaration of Helsinki.

Prior to this study, no women had received vixotrigine. For this reason, PK following a single dose of vixotrigine 400 mg was assessed in female participants 1 week before the period 1 baseline visit. Based on these findings, some women were predicted to exceed the predefined PK limit (identified during preclinical work in animals: area under the plasma concentration-time curve [AUC] 97 μg·h/mL) when receiving 400 mg twice daily at steady state. Although these data were limited, women in this study received a lower dose (300 mg twice daily) than men (400 mg twice daily) based on the observed slightly higher exposure.

This was a phase 1 randomized, double-blind, placebo-controlled, repeat-dose, 2-period crossover study to investigate the effects of vixotrigine 300 to 400 mg twice daily on ambulatory blood pressure (ABP) and heart rate in healthy participants (Figure 1). The study design included: (1) a screening period (to occur a maximum of 30 days before the first baseline assessment), (2) two 36-day treatment periods separated by a 7-day washout, and (3) a follow-up period of 7 to 14 days after the last dose. Each 36-day treatment period was preceded by 1 inpatient visit and 1 outpatient baseline visit. Patients remained at the study center for two 3-day periods and 6 overnight stays in each treatment period. This trial is registered with ClinicalTrials.gov (NCT00955396).

Study Population

Eligible participants were healthy men or women aged between 18 and 65 years. The following criteria were applied for eligibility: body weight at least 50 kg; body mass index within the range 19 to 40 kg/m^2; no significant abnormalities on clinical examination, clinical chemistry, or hematology parameters; not of childbearing potential, or willing to use agreed methods of contraception. Participants with systolic BP (SBP) persistently > 140 mm Hg and/or diastolic BP (DBP) > 90 mm Hg determined on 3 occasions at least 5 minutes apart were not eligible for participation.

Participants had to abstain from taking prescription or nonprescription drugs within 7 days (14 days if the drug was a potential enzyme inducer) or 5 half-lives, whichever was longer, before the first dose of study medication until completion of the follow-up visit, unless in the opinion of the investigator and sponsor, the medication would not interfere with the study.

Randomization and Blinding

Participants were assigned to treatment sequences in accordance with a randomization schedule generated by Discovery Biometrics (Research Triangle Park, North Carolina) prior to the start of the study. Study treatment was vixotrigine 400 mg twice daily for men/300 mg twice daily for women or placebo for 36 days administered in the fasted state with 240 mL of water. Prior to dosing, participants were randomized into 1 of the following treatment sequences: vixotrigine (period 1) followed by placebo (period 2) or placebo (period 1) followed by vixotrigine (period 2). Periods 1 and 2 were double-blind to patients, study personnel, and the sponsor/clinical research organization.

Assessments

At screening, demographic data were collected, vital signs were measured, a 24-hour ABP monitor was placed, and 12-lead electrocardiography (ECG) was performed. A schedule of assessments and BP measurements collected during each treatment period is outlined in Supplementary Table S1. A complete physical examination, ECG, and vital signs were documented at the follow-up visit.

Blood pressure. ABP was measured while participants were outpatients and inpatients (Supplementary Table S1). The ABPM device (Spacelabs, Inc, Redmond, Washington) was typically placed on the nondominant arm, and measurements were taken every 15 minutes.

Bioanalytical. Blood samples were collected at prespecified times (Supplementary Table S1). Analysis was performed by Worldwide Bioanalysis, DMPK, GlaxoSmithKline, Verona, Italy, using a validated analytical method based on protein precipitation followed by high-performance liquid chromatography with tandem mass spectrometric detection analysis. The vixotrigine

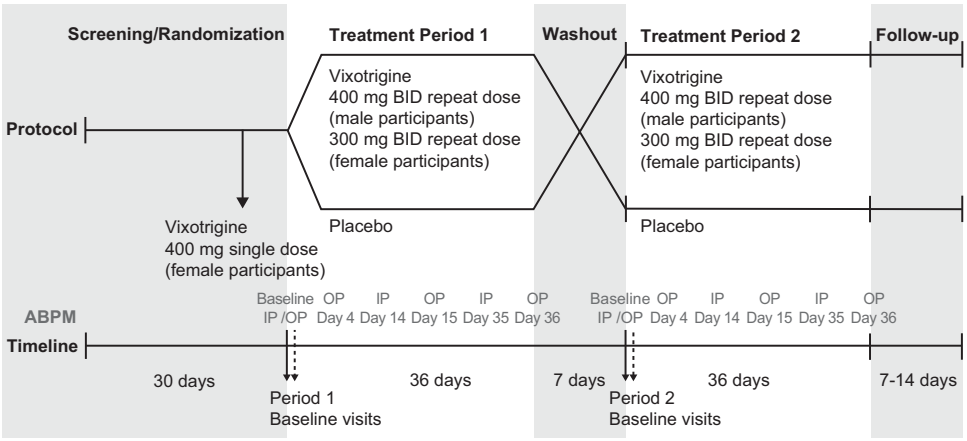

Figure 1. Study design. The vixotrigine 400-mg single dose for female participants was administered 7 days prior to the treatment period 1 baseline visit. There are 2 baseline visits: 1 inpatient visit and 1 outpatient visit. The solid arrow indicates the 14-hour inpatient baseline visit; the dotted arrow indicates the 24-hour outpatient baseline visit. ABPM, ambulatory blood pressure monitoring; BID, twice daily; IP, inpatient; OP, outpatient.

assay lower limit of quantification was 10 ng/mL, and the upper limit of quantification was 10 000 ng/mL.

Safety. Safety was assessed through monitoring of adverse events (AEs), vital signs, ECG, and laboratory safety tests (including clinical chemistry).

Statistical Analysis

The primary end point was the change from baseline in mean 24-hour ambulatory SBP and DBP on day 36. Secondary outcome measures included change in the 24-hour mean outpatient SBP and DBP from baseline to days 4 and 15; change in the 24-hour mean ambulatory heart rate from baseline to days 4, 15, and 16; and inpatient change in mean SBP and DBP within a 12-hour dosing interval from baseline to days 14 and 35. In addition, outlier analyses were performed using the proportion of participants whose 24-hour SBP and DBP increased by less than 5, 5 to 9, 10 to 14, 15 to 19, and more than 20 mm Hg compared with baseline.

The safety population was the primary analysis population for this study and included all participants who received 1 or more doses of vixotrigine. The PK population was defined as participants in the safety population for whom a PK sample was obtained and analyzed.

Means were calculated for ABP for the 12-hour period (inpatient) and the 24-hour period (outpatient day) as well as for discrete periods of the day (6:00 AM to 10:00 PM) and night (10:00 PM to 6:00 AM) following repeat dosing. Means were also calculated for the ABPM at baseline (per period) and the applicable baseline fitted in the model.

Noninferiority was based on the 1-sided 95% confidence interval (CI) for vixotrigine-placebo excluding an effect of at least 5 mm Hg in SBP. Sixty study participants were needed to obtain a minimum of 48 participants evaluable for ABPM during the repeat-dose phase for at least 90% power, assuming a within-participant standard deviation of 8.2 mm Hg based on a prior ABPM study with another pain medication.

ABPM data were analyzed using a repeated-measures mixed-effects model, whereby fixed effects were treatment, day, treatment × day, period, average baseline × day, period-adjusted baseline × day, sex, and treatment × sex; random effect was participant; and repeated effect was day. All summary statistics were carried out using SAS 8.02 for UNIX running under the Harmonisation of Analysis and Reporting Program environment.

The pharmacokinetic parameters of vixotrigine were evaluated following a single oral dose in healthy female participants and following repeated oral doses given twice daily to healthy male and female participants. Concentration-time data were analyzed by noncompartmental methods with WinNonlin v5.

A PK/pharmacodynamic (PD) model was developed to describe the effect of plasma concentrations of vixotrigine on inpatient SBP and DBP. The first-order conditional estimation method with interaction was used. Visual predictive check was used to evaluate the predictive ability of the model. Full model details are found in the Supplementary Information.

Results

The disposition of the 60 enrolled participants is shown in Supplementary Figure S1. Of the enrolled study participants, 10 withdrew prematurely (7 because of an AE, 2 at the investigator's discretion, and 1 withdrew consent). The mean age of the population (n = 60) was 34.3 years, the mean BMI was 27.07 kg/m^2, and 40% were female (Supplementary Table S2). Baseline vital signs before dosing are shown in Table 1.

Table 1. Baseline Vital Signs on Day 1, Predose[a]

	Placebo n = 54	Vixotrigine 300-400 mg Repeat Dose n = 54
Systolic blood pressure, mm Hg		
Inpatient	116.9 (11.8)	117.1 (11.0)
Outpatient	117.6 (9.7)	118.6 (10.2)
Diastolic blood pressure, mm Hg		
Inpatient	78.6 (7.8)	77.5 (7.9)
Outpatient	73.3 (7.4)	73.0 (7.7)
Heart rate, beats/min		
Inpatient	79.5 (13.0)	78.3 (12.2)
Outpatient	74.0 (11.0)	73.9 (13.2)

Values are mean (standard deviation) unless stated otherwise.
[a]Vital signs were recorded on day 1 of each treatment period, predose time, in a standing position.

Table 3. Changes in Outpatient 24-Hour Blood Pressure From Baseline to Days 4, 15, and 36

	Visit (Day)	Least-Squares Mean: Vixotrigine 300-400 mg	Least-Squares Mean: Placebo	Mean Differences for Vixotrigine-Placebo	90%CI for Difference[a]
Systolic blood pressure, mm Hg	4	2.37	1.37	1.01	(-0.23 to 2.24)
	15	0.92	0.62	0.29	(-0.93 to 1.52)
	36	−0.33	0.18	−0.51	(-1.76 to 0.74)
Diastolic blood pressure, mm Hg	4	1.86	1.07	0.79	(-0.26 to 1.84)
	15	0.91	0.26	0.65	(-0.40 to 1.69)
	36	0.20	−0.09	0.29	(-0.78 to 1.35)

CI, confidence interval.
[a]Upper bound of 2-sided 90%CI equates to upper bound of 1-sided 95%CI.

Pharmacokinetics

Following single-dose administration to female participants, vixotrigine was characterized by rapid and extensive absorption (plasma concentrations were measurable in all female participants between 0.5 and 24 hours). Peak levels were achieved within 1.5 hours postdosing, and afterwards, plasma levels declined, with a median terminal half-life ($t_{1/2}$) of ~9 hours (Table 2). The AUC over the 24-hour dosing interval ($AUC_{0\text{-}24}$) was characterized by small between-participant variability (coefficient of variation [CV%] between participants, 20%-25%). $AUC_{0\text{-}24}$ and maximal plasma concentration (C_{max}) in men receiving a vixotrigine repeat dose at 400 mg twice daily were, on average, 10% and 11% to 19% higher, respectively, than in women receiving 300 mg twice daily on days 14 and 35. Dose-normalized AUC and C_{max} were, on average, 17% to 18% and 11% to 17%, respectively, lower in male than in female participants (Table 2).

Ambulatory Blood Pressure Monitoring

Outpatient ABPM. The changes from baseline in 24-hour BP on days 4, 15, and 36 are shown in Table 3. The mean change in average SBP from baseline to day 36 for vixotrigine-treated patients was -0.33 mm Hg. Noninferiority of vixotrigine compared with placebo was demonstrated for both outpatient 24-hour SBP and DBP (the 1-sided 95%CI for vixotrigine-placebo excluded an effect of at least 5 mm Hg). In fact, owing to the very low within-participant variability observed in these normal healthy participants (within-subject standard deviation [SDw], 3.8 mm Hg for SBP; and SDw, 2.9 mm Hg for DBP), the power of the study was larger than planned, and a smaller effect size than 5 mm Hg could be ruled out. The upper bound of the 1-sided 95%CI was less than 2 mm Hg for the majority

Table 2. Vixotrigine Pharmacokinetic Parameters

	Single Dose (400 mg)	Repeat Dose (Women: 300 mg Twice Daily; Men: 400 mg Twice Daily)					
		Day 1		Day 14		Day 35	
Parameter	Female (n = 22)	Female (n = 21)	Male (n = 33)	Female (n = 21)	Male (n = 33)	Female (n = 21)	Male (n = 33)
$AUC_{0\text{-}12}$, ng·h/mL[a]	24 200 (20.9)	16 200 (20.4)	19 100 (19.9)	29 200 (24.7)	32 100 (23.5)	27 400 (23.4)	30 100 (21.8)
$AUC_{0\text{-}24}$, ng·h/mL[a]	48 300 (20.9)	32 400 (20.4)	38 300 (19.9)	58 300 (24.7)	64 100 (23.5)	54 800 (23.4)	60 100 (21.8)
C_{max}, ng/mL[a]	3780 (20.4)	2570 (22.2)	3210 (22.1)	4030 (21.2)	4790 (24.1)	3990 (26.6)	4410 (21.6)
t_{max}, hours[b]	1.50 (0.50, 3.0)	1.50 (0.50, 3.0)	1.00 (0.50, 3.0)	1.50 (1.00, 3.0)	1.00 (0.50, 2.5)	1.00 (0.50, 2.5)	1.00 (0.50, 3.0)
$C_{12\,h}$, ng/mL[a]	ND	746 (20.8)	889 (23.6)	1440 (29.9)	1590 (28.3)	1310 (24.0)	1460 (26.4)
$AUC_{0\text{-}t}$, ng·h/mL[a]	32 800 (21.9)	ND	ND	ND	ND	ND	ND
$AUC_{0\text{-}\infty}$, ng·h/mL[a]	38 700 (24.1)	ND	ND	ND	ND	ND	ND
$t_{1/2}$, hours	8.91 (13.7)	ND	ND	ND	ND	ND	ND

$AUC_{0\text{-}24}$, area under the concentration-time curve over the 24-hour dosing interval; $AUC_{0\text{-}12}$, area under the concentration-time curve from 0 to hour 12; $AUC_{0\text{-}t}$, area under the concentration-time curve from 0 to last time of quantifiable concentration; $AUC_{0\text{-}\infty}$, area under the concentration-time curve from 0 extrapolated to infinity; $C_{12\,h}$, concentration at hour 12; C_{max}, maximal plasma concentration; ND, not determined; $t_{1/2}$, terminal half-life; t_{max}, time to maximal concentration.
[a]Geometric mean (coefficient of variation between participants).
[b]Median (minimum, maximum) values.

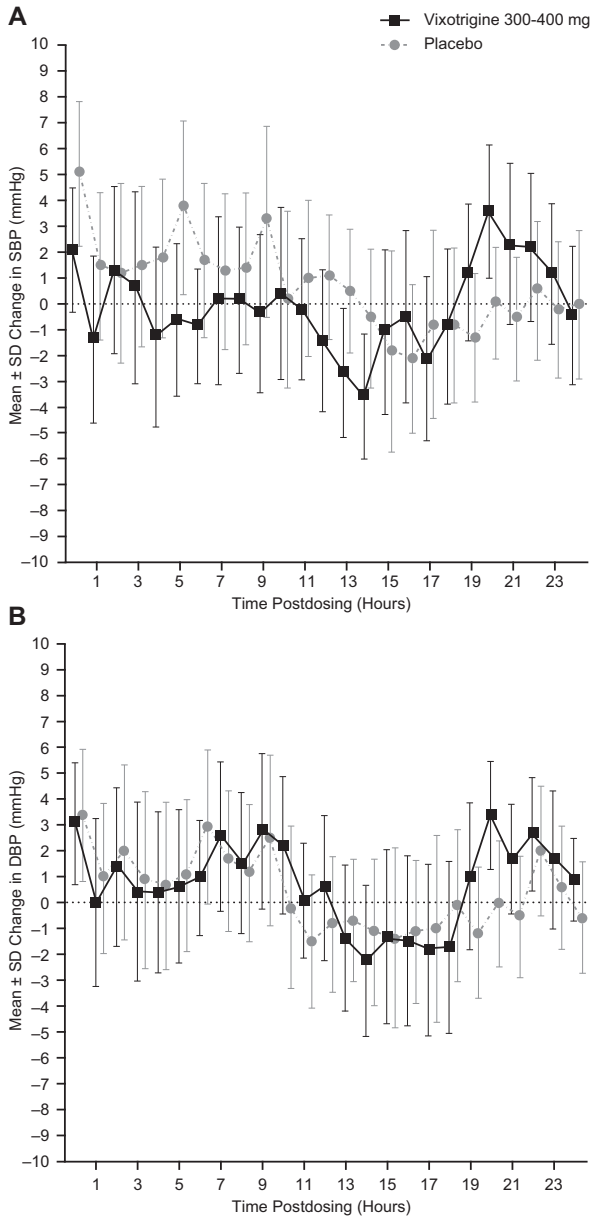

Figure 2. Mean ± SD change in outpatient 24-hour SBP (A) and DBP (B) from baseline to day 36. DBP, diastolic blood pressure; SBP, systolic blood pressure.

of SBP and DBP comparisons on days 4, 15, and 36, with the exception of SBP on day 4 (~2.2 mm Hg).

Changes from baseline in the hourly BPs over 24 hours at the end of the 36-day period are shown in Figure 2. These data demonstrate that vixotrigine and placebo had comparable effects on hourly BP. Changes from baseline in outpatient 24-hour SBP and DBP revealed a normal distribution (Figure 3), with the majority of SBP and DBP measurements on day 36 within 0 to 10 mm Hg of their associated time-matched baseline for both treatments.

To evaluate clinically relevant changes in BP, an outlier analysis was performed using proportions of participants whose BP increased by more than 10 mm Hg from baseline and who had a resultant absolute value of more than 130 mm Hg for SBP or more than 80 mm Hg for DBP. On day 36, 6.0% of BP values for placebo and 5.0% of observations for vixotrigine fell into this category for SBP, whereas 6.3% of observations for placebo and 6.9% of observations for vixotrigine fell into this category for DBP (Supplementary Table S3).

Inpatient ABPM. Analyses of inpatient 12-hour BP measurements showed comparable findings to the measurements obtained over the 24-hour ambulatory outpatient monitoring study (Figure 4). There were no significant differences between vixotrigine and placebo after 36 days of therapy. Similar to the outpatient ABPM results, the majority of inpatient 12-hour SBP and DBP measurements on day 35 were within 0 to 10 mm Hg of their associated time-matched baseline for both treatments. No observations showed an increase of 30 mm Hg or more for SBP, and only a few observations showed an increase of 20 mm Hg or more for DBP.

Inpatient ABPM measurements demonstrated an increase in change from baseline of 2.0 to 2.5 mm Hg on days 14 and 35 for SBP and DBP; similar findings were observed for heart rate. Noninferiority of vixotrigine compared with placebo was demonstrated because the 1-sided 95%CI for the difference vixotrigine-placebo excluded an effect of at least 5 mm Hg.

PK/PD modeling of ABPM inpatient data (for which observed plasma concentrations were available) indicated a statistically significant but minimal linear increase of DBP and SBP with increasing vixotrigine-observed plasma concentrations (Supplementary Figure S2). In the mixed-effects model, vital signs were linearly related to vixotrigine plasma concentrations, such that BP = slope × C + intercept, where intercept reflects the placebo values, considered normally distributed, and slope is the population slope, log-normally distributed. The slopes of the linear relationships were small (SBP, 0.000726 mm Hg/ng/mL [95%CI, 0.000387-0.00107 mm Hg/ng/mL]; DBP, 0.00111 mm Hg/ng/mL [95%CI, 0.000845-0.00137 mm Hg/ng/mL]).

General Safety Findings

The most common AEs during vixotrigine treatment were nervous system disorders such as headache and dizziness, followed by nasopharyngitis, nausea, and vomiting. The rate of AEs was comparable with placebo, particularly for the most common AE of headache (n = 11 [20%] for vixotrigine 300-400 mg twice daily repeat dose vs n = 10 [19%] for placebo). All AEs associated with vixotrigine 400 mg single

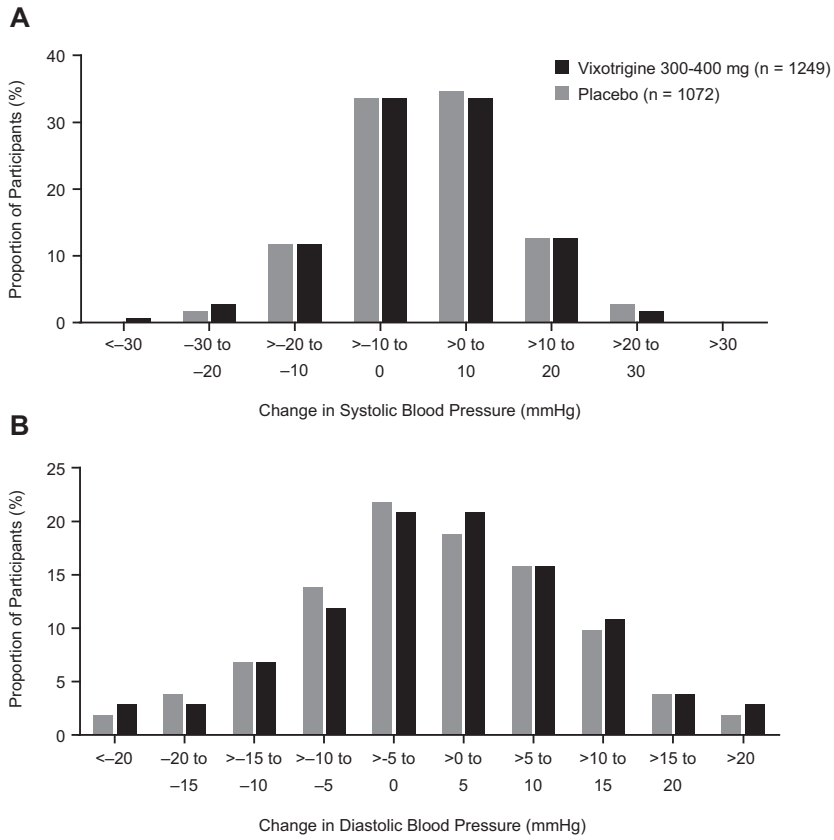

Figure 3. Proportion of observations with changes in outpatient 24-hour systolic blood pressure (A) or diastolic blood pressure (B) on day 36 compared with baseline. n, number of BP measurements.

dose in women were characterized as mild in nature. Table 4 summarizes AEs that occurred in more than 2 participants in any treatment group.

Of the 10 participants (17%) who were withdrawn from the study, 7 (12%) were withdrawn because of AEs (2 receiving placebo and 5 receiving vixotrigine at the time of withdrawal). For 1 participant receiving placebo, the AE started prior to dosing. One of the withdrawals was because of erythema multiforme in a participant who had received vixotrigine; this AE was nonserious and resolved after study discontinuation. No serious AEs were reported in this study. There were no clinically significant ECG changes in either treatment group, and the majority of ECG results from day 1 to day 35 were normal. Two participants receiving vixotrigine had elevation of alanine aminotransferase; in 1 participant, the elevation was greater than 3 times the upper limit of normal, and the patient was withdrawn from the study. The ALT elevation was resolving on follow-up.

Discussion

The results of this study demonstrate no clinically relevant changes in systolic or diastolic BP following repeat doses of vixotrigine for 36 days. Noninferiority was demonstrated, as defined by the 2-sided 90%CI (1-sided 95%CI) for vixotrigine-placebo excluding an effect of at least 5 mm Hg for both outpatient and inpatient ambulatory monitoring of SBP and DBP. In addition, further examination of the results demonstrated no difference between treatments in the proportion of participants who had a change from baseline that moved them into the stage 1 hypertension range, providing further evidence of a benign profile with respect to BP elevation. The PK/PD analyses relating inpatient BP measurement to observed plasma concentrations of vixotrigine indicated a weak relationship. Based on the model, doubling the vixotrigine concentration from 1000 to 2000 ng/mL would have a minimal effect on BP: at a vixotrigine concentration of 1000 ng/mL SBP is predicted to be 118.73 mm Hg and DBP 74.71 mm Hg, which increases to SBP 119.45 mm Hg and DBP 75.82 mm Hg at a vixotrigine concentration of 2000 mg/mL The inpatient BP analysis suggested that the mean increases in BP for vixotrigine versus placebo were approximately 2 to 3 mm Hg.

The 36-day treatment duration in this study was designed to determine whether tolerance developed for any potential effects of vixotrigine on SBP or DBP, because BP effects resolved by day 28 in the

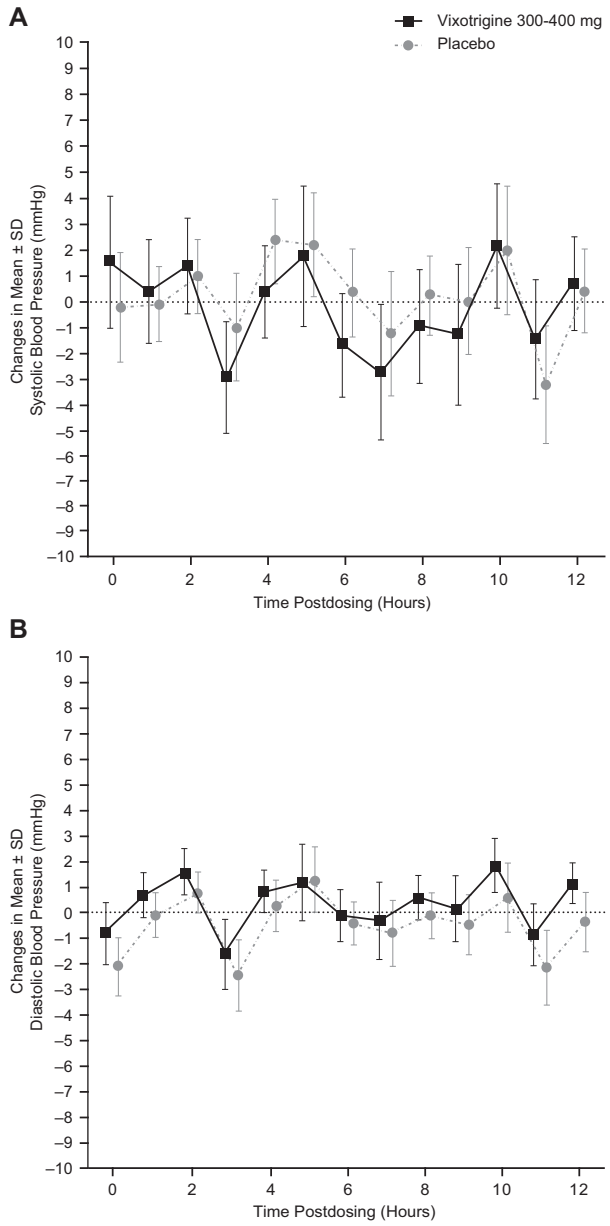

Figure 4. Mean ± SD change in inpatient 12-hour systolic blood pressure (A) and diastolic blood pressure (B) from baseline to day 35.

earlier phase 1 trial. The data from this study show some evidence of a decrease in the BP difference between vixotrigine and placebo between day 4 and day 35, although differences were small at all points. An additional point of note is that in preclinical safety/pharmacology studies there were no effects of vixotrigine on cardiovascular parameters in dogs (GSK, data on file). Other sodium channel blockers have only rarely been associated with increases in BP: carbamazepine, very rare (0.01%),[6] and lamotrigine, uncommon (0.1%-1%).[7] Thus, the body of evidence, encompassing clinical and preclinical studies, supports minimal effects of vixotrigine on BP and heart rate.

Table 4. Adverse Events Occurring in ≥2 Participants in Any Treatment Group

Preferred Term	Placebo n = 54	Vixotrigine 300-400 mg Twice-Daily Repeat Dosing n = 54	Vixotrigine 400-mg Single Dose n = 22
Participants with any adverse event	26 (48)	25 (46)	12 (55)
Headache	10 (19)	11 (20)	6 (27)
Dizziness	3 (6)	6 (11)	5 (23)
Nausea	2 (4)	4 (7)	3 (14)
Vomiting	2 (4)	3 (6)	1 (5)
Diarrhea	3 (6)	1 (2)	0
Nasopharyngitis	5 (9)	6 (11)	0
Oropharyngeal pain	1 (2)	2 (4)	0
Pyrexia	1 (2)	2 (4)	0
Fatigue	0	2 (4)	0
Pain in extremity	2 (4)	0	0
Rash	3 (6)	1 (2)	0
Hypersensitivity[a]	0	2 (4)	0

Data are n (%).

[a]Verbatim text: allergy symptoms. Neither event was considered to be drug related. One was nasal congestion/rhinorrhea attributed to seasonal allergy, and the other occurred during the washout period and involved wheezing following cat exposure.

ABPM was also measured within the inpatient setting to allow additional PK/PD analyses. Although small increases of DBP and SBP with increasing vixotrigine plasma concentrations were observed, the average increases were lower than 3 and 2 mm Hg for DBP and SBP, respectively, and of minimal clinical relevance. These inpatient results are consistent with those from the primary analysis of outpatient ABPM data.

As this investigation was performed in healthy individuals rather than a patient population with neuropathic pain and associated comorbidities, the generalizability of the findings may be limited. The current study population was also younger (mean age, 34.3 years) than the intended patient population; for example, peak onset age of trigeminal neuralgia is between 50 and 60 years[8] and for painful lumbosacral radiculopathy, individuals are most likely to develop symptoms between age 40 and 60 years.[9]

Conclusion

The results from this study provide assurance that vixotrigine administration is not associated with a clinically important hypertension signal in healthy, normotensive participants.

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Declaration of Conflicting Interests

Regan Fong and Joanne Palmer were employees of GlaxoSmithKline at the time of this study. Himanshu Naik and Deb Steiner are employees of Biogen. Charles Ballow received an investigator research grant to conduct this study. William B. White has nothing to declare. Medical writing support in the development of this article was provided by Valérie Boissel, PhD, and Linda Wagner, PharmD (Excel Scientific Solutions, Hammersmith, London, UK, and Southport, Connecticut) and funded by Biogen. Editorial support was provided by Jackie Parker of Excel Scientific Solutions, Southport, Connecticut and funded by Biogen.

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Author Contributions

Regan Fong contributed to the design and conduct of this study. Charles Ballow contributed to the conduct of this study. William B. White drafted parts of the manuscript and provided review and revision of the article. The other authors contributed to the interpretation of the study results and to the review and critical revision of the article. All authors approved the final version of the article for submission.

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.