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ARTICLE

Safety, Tolerability and Pharmacokinetics of Single and Repeat Doses of Vixotrigine in Healthy Volunteers

Himanshu Naik[1,*], Deb J. Steiner[1,†], Mark Versavel[1,2,†], Joanne Palmer[3,†] and Regan Fong[4,†]

Neuropathic pain affects ~ 6.9–10% of the general population and leads to loss of function, anxiety, depression, sleep disturbance, and impaired cognition. Here, we report the safety, tolerability, and pharmacokinetics of a voltage-dependent and use-dependent sodium channel blocker, vixotrigine, currently under investigation for the treatment of neuropathic pain conditions. The randomized, placebo-controlled, phase I clinical trials were split into single ascending dose (SAD) and multiple ascending dose (MAD) studies. Healthy volunteers received oral vixotrigine as either single doses followed by a ≥ 7-day washout period for up to 5 dosing sessions (SAD, *n* = 30), or repeat doses (once or twice daily) for 14 and 28 days (MAD, *n* = 51). Adverse events (AEs), maximum observed vixotrigine plasma concentration (C_{max}), area under the concentration-time curve from predose to 24 hours postdose ($AUC_{0–24}$), time to C_{max} (T_{max}), and terminal half-life (*t1/2*), among others, were assessed. Drug-related AEs were reported in 47% and 53% of volunteers in the SAD and MAD studies, respectively, with dizziness as the most commonly reported drug-related AE. SAD results showed that C_{max} and AUC increased with dose, T_{max} was 1–2 hours, and $t_{1/2}$ was ~ 11 hours. A twofold increase in accumulation was observed when vixotrigine was taken twice vs. once daily (MAD). Steady-state was achieved from day 5 onward. These data indicate that oral vixotrigine is well-tolerated when administered as single doses up to 825 mg and multiple doses up to 450 mg twice daily.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?
☑ Neuropathic pain is a common condition; available treatments are of limited effectiveness and have multiple drug interactions and tolerability issues.

WHAT QUESTION DID THIS STUDY ADDRESS?
☑ These 2 phase I studies investigated the safety, tolerability, and pharmacokinetics (PKs) of vixotrigine administered as a single dose or in multiple doses in healthy volunteers.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?
☑ This study describes the safety, PKs, and tolerability of a voltage-dependent and use-dependent sodium channel blocker being developed for neuropathic pain conditions.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?
☑ These results support the further clinical development of vixotrigine, inform on dosing for clinical trials in individuals with neuropathic pain, and test the potential benefit of voltage-dependent and state-dependent sodium channel blockade in the treatment of neuropathic pain.

Neuropathic pain can arise from a lesion or disease of the somatosensory system, including peripheral fibers (Aβ, Aδ, and C fibers) and central neurons.[1] The signs and symptoms of neuropathic pain include allodynia, spontaneous paroxysmal pain, hyperalgesia, and, on occasion, causalgia or incessant burning pain.[2] The estimated prevalence of neuropathic pain in the general population is 6.9–10%.[3] Substantial impairment of quality of life is caused due to loss of function, anxiety, depression, sleep disturbance, and impaired cognition.[1]

Voltage-gated sodium channels (Navs) are complex transmembrane proteins responsible for the initiation and propagation of action potentials in neurons.[4] Gain-of-function changes produced by missense substitutions in the genes encoding Nav1.7–1.9 have been implicated in human pain syndromes through genetic studies.[5,6] Loss-of-function autosomal recessive mutations in the gene encoding the α-subunit of Nav1.7 result in congenital insensitivity to pain.[5,7] Sodium channel subtype Nav1.7 is expressed in peripheral sensory neurons innervating skin, viscera, and dorsal

†At the time of the study.
[1] Biogen, Cambridge, Massachusetts USA; [2] Convergence Pharmaceuticals Ltd., a Biogen company, Cambridge, UK; [3] GlaxoSmithKline, Harlow, UK; [4] GlaxoSmithKline, King of Prussia, Pennsylvania USA. Correspondence: Himanshu Naik (himanshu.naik@biogen.com)
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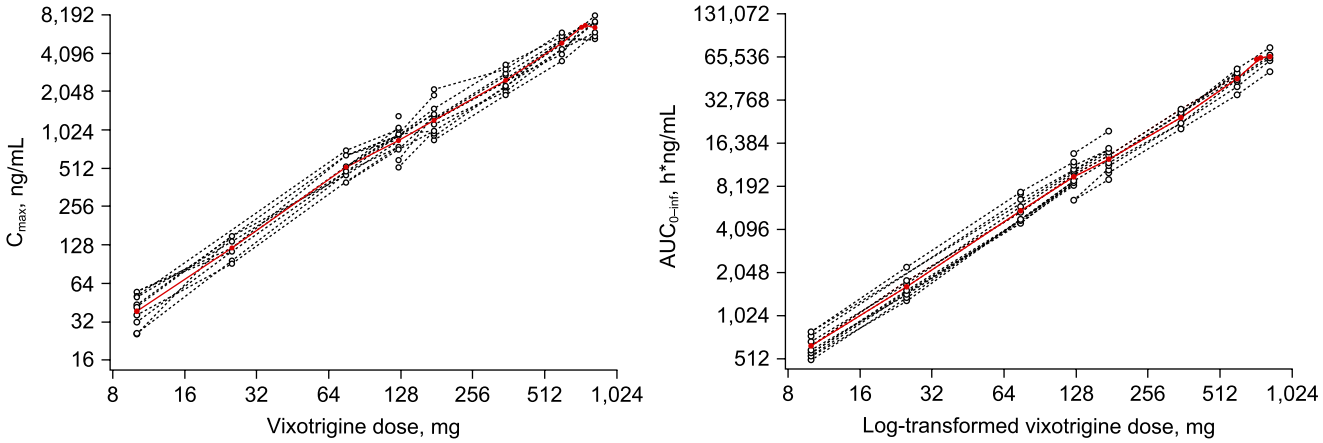

Figure 1 Systemic exposure of each vixotrigine dose in the single-dose study for maximum observed concentration (C_{max}) and area under the concentration-time curve from predose extrapolated to infinite time (AUC_{0-inf}).

root and trigeminal ganglia in the orofacial region, together with sympathetic neurons and olfactory epithelia.[8] Nav1.8 is a tetrodotoxin-resistant subtype, expressed in nociceptive sensory neurons.[8] Nav1.9, the most recently identified Nav subtype, is a marker of primary nociceptors, also expressed in the enteric nervous system.[8] Carbamazepine, which is known to target Nav channels, is used to treat neuropathic pain, in particular trigeminal neuralgia (TN),[2,9] although use is limited due to poor tolerability, need for titration, and potential pharmacological interactions.[9] Thus, there is a need for effective and well-tolerated treatments for neuropathic pain.

Vixotrigine is a voltage-dependent and use-dependent Nav channel blocker[10] currently under investigation for neuropathic pain conditions, including painful small fiber neuropathy and TN.[11,12] Several preclinical studies of vixotrigine have been completed to date. In rats, oral vixotrigine administered at 0.1–5 mg/kg produced a dose-related reversal of Freund's complete adjuvant-induced hypersensitivity to pain as measured by weight bearing. In this study, the minimum effective dose resulting in 50% of the maximum response was 1 mg/kg (Biogen, data on file). Following a single oral dose of ^{14}C-labeled vixotrigine in Sprague-Dawley rats at a target level of 30 mg freebase/kg, drug-related material was eliminated via urine (mean 58.1% of the dose) and feces (mean 35.9% of the dose). Elimination was rapid, with a mean of 92.9% of the dose recovered by 24 hours postdose (Biogen, data on file).

Here, we report the findings of 2 clinical studies designed to investigate the safety, tolerability, and pharmacokinetics (PKs) of vixotrigine in healthy volunteers, following either single escalating doses or repeat dosing. In addition, the effect of food on vixotrigine PK parameters was investigated in the repeat dosing study.

METHODS

The study protocol was reviewed and approved by an investigational review board for both the single-dose (SD) and repeat-dose studies. Study volunteers provided written informed consent. Both the single ascending dose (SAD) and multiple ascending dose (MAD) studies were phase I, randomized, placebo-controlled studies (NCT00488566 and NCT00908154, respectively). Study site details and investigators are provided in the **Supplementary Materials**.

Single ascending dose study procedures

This was a double-blind crossover study conducted at a single clinical site from May 2007 to May 2008. Volunteers and all site personnel were blinded to study treatment allocation

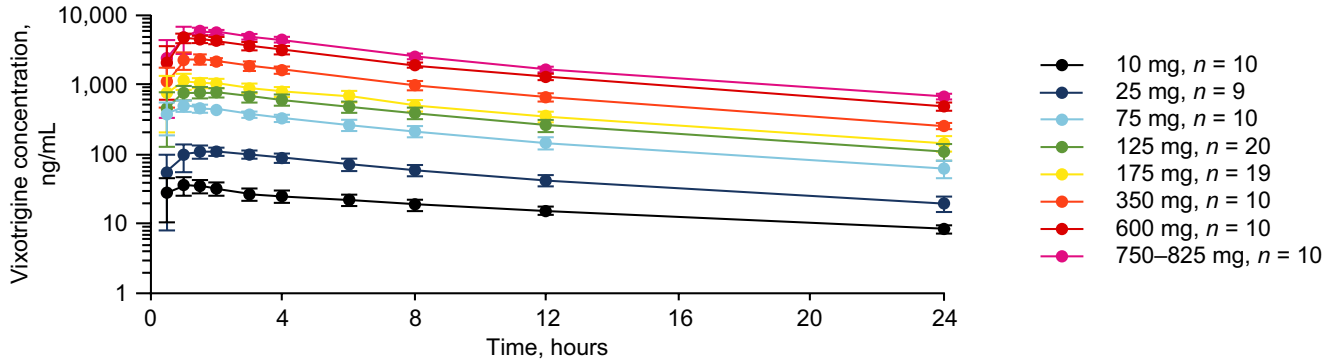

Figure 2 Vixotrigine concentrations by time and dose in the single-dose study.

Table 1 PK of vixotrigine doses in the single-dose study

	Vixotrigine									
PK parameter	**10 mg (*n* = 10)**	**25 mg (*n* = 10)**	**75 mg (*n* = 10)**	**125 mg (*n* = 20)**	**175 mg (*n* = 20)**	**350 mg (*n* = 10)**	**600 mg (*n* = 10)**	**725 mg[a] (*n* = 1)**	**750 mg[b] (*n* = 1)**	**825 mg (*n* = 7)**
AUC_{0-inf}, h*ng/mL[c]	633.7 (16.8)	1,653.4 (20.6)	5,592.8 (19.1)	9,731.7 (19.6)	12,802.8 (17.1)	24,953.5 (9.9)	47,022.5 (12.4)	63,550.5	64,583.6	66,200.4 (14.5)
AUC_{0-t}, h*ng/mL[c]	474.4 (20.8)	1,507.0 (21.4)	5,358.2 (19.5)	9,446.5 (20.0)	12,582.6 (17.3)	24,729.0 (10.1)	46,687.8 (12.5)	63,234.8	64,280.6	65,753.2 (13.4)
$t_{1/2}$, hours	17.1 (19.1)	17.2 (15.8)	12.6 (14.7)	12.9 (19.1)	11.8 (15.1)	11.3 (8.1)	10.8 (9.0)	9.8	10.4	10.7 (13.3)
C_{max}, ng/mL[c]	38.4 (27.6)	121.1 (18.4)	522.0 (19.1)	845.9 (20.6)	1,225.2 (24.0)	2,503.3 (17.1)	4,878.8 (15.8)	6,530.1	6,759.2	6,534.8 (14.9)
Median (min–max) T_{max}, hours	1.34 (0.50–2.05)	1.95 (0.50–2.98)	1.02 (0.50–2.00)	1.48 (0.48–2.12)	1.07 (0.47–2.18)	1.48 (1.00–2.05)	1.05 (0.98–2.10)	1.05 (1.05–1.05)	1.02 (1.02–1.02)	1.50 (1.00–2.12)

AUC_{0-inf}, area under the concentration-time curve from predose extrapolated to infinite time; AUC_{0-t}, area under the concentration-time curve from predose to the last quantifiable concentration; C_{max}, maximum observed concentration; max, maximum; min, minimum; PK, pharmacokinetic; $t_{1/2}$, terminal half-life; T_{max}, time to maximum observed concentration.

[a]One volunteer received 725 mg.

[b]One volunteer received 750 mg.

[c]Geometric mean (coefficient of variance %).

but sponsor personnel were unblinded to assist with appropriate dose selection decisions. Eligible volunteers were healthy men aged 18–65 years or healthy women with no childbearing potential aged 18–50 years. Volunteers were also required to be nonsmokers and have a body weight of > 50 kg and body mass index of 19–29.9 kg/m^2 (± 10%). Exclusion criteria included significant abnormalities found on clinical examination, or clinical chemistry or hematology parameters. The sample size of 10 participants per cohort is a commonly used number in early studies.[13]

The steps recommended in the US Food and Drug Administration's Guidance for Industry: Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers[14] were followed for the estimation of the starting dose. On normalizing the experimentally determined nontoxic dosage level for surface area, the most sensitive preclinical animal species examined was the dog. Using the conversion factor provided in the guidance, the nontoxic dosage level of 70 mg/kg/day in the dog translates to a human equivalent dose of 2,333 mg/day for a 60 kg human. Dividing this value by a conservatively estimated safety factor of 10, the maximum recommended starting dose of vixotrigine was determined to be 233 mg/day[14]; however, the results observed using vixotrigine in pain models indicate that a pharmacologically active dosage of vixotrigine is 1 mg/kg. This efficacious dose is expected to translate to a predicted clinical dose of 10 mg/day in a 60 kg human; thus, a starting dose of 10 mg q.d. was selected.[14]

Volunteers were recruited into 3 cohorts of 10 and treated with a starting dose of vixotrigine 10 mg or placebo in cohort 1 (**Figure S1**). In each dosing session, 8 volunteers received vixotrigine and 2 volunteers received placebo, except cohort 2, dosing session 3 (vixotrigine, *n* = 4; placebo, *n* = 6). The highest vixotrigine dose tested in 1 cohort was the initial dose in the subsequent cohort (**Figure S2**). Vixotrigine doses were escalated up to 825 mg, until predefined safety or PK stopping limits were reached. Plasma samples were taken at baseline and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 36, 48, and 72 hours after dosing. Each volunteer received a maximum of 4 vixotrigine doses and 1 placebo dose over 5 dosing sessions, with the exception of cohort 2 (2 vixotrigine doses and 1 placebo dose over 3 dosing sessions). Each session was separated by a ≥ 7-day washout period. Volunteers attended a follow-up visit ~ 7–14 days following the last dose of study medication.

The primary endpoints of the SAD study were to (i) evaluate vixotrigine safety and tolerability assessed through adverse events (AEs), vital signs (blood pressure, heart rate, and respiration rate), clinical laboratory evaluations (hematology, clinical chemistry, and urinalysis), and 12-lead electrocardiograms (ECGs); and (ii) evaluate the following vixotrigine PK parameters: area under the concentration-time curve from time 0 (predose) extrapolated to infinite time (AUC_{0-inf}), AUC from predose to last time of quantifiable concentration (AUC_{0-t}), maximum observed concentration (C_{max}), and time to C_{max} (T_{max}). Dose proportionality of AUC_{0-inf}, AUC_{0-t}, and C_{max} across doses was investigated by a power model[15,16] fitted by restricted maximum likelihood method, with log(dose) fitted as covariate. The intercept for volunteers was fitted as a random effect. Estimated mean slope (β) and 90% confidence intervals were constructed for each parameter.

Table 2 Vixotrigine PK parameters in the repeat-dose study

Vixotrigine regimen	Day	Median (min–max) T_{max}, hours	Geometric mean (%CVb) C_{max}, ng/mL	Geometric mean (%CVb) AUC_{0-24}, h*ng/mL	Geometric mean (%CVb) AUC, h*ng/mL	Geometric mean (%CVb) $t_{1/2}$, hours
150 mg q.d.	1[a]	1.50 (1.00–1.50)	1,017 (20.0)	8,789 (18.4)	10,442 (20.5)	9.2 (10.0)
	7[a]	1.03 (0.50–3.00)	1,216 (19.4)	11,633 (15.1)		9.4 (7.5)
	14[a]	1.02 (0.52–2.03)	1,238 (27.7)	11,184 (20.5)		8.6 (12.6)
400 mg q.d.	1[a]	1.50 (0.50–2.03)	3,310 (23.3)	27,993 (16.6)	34,195 (18.1)	10.0 (11.1)
	7[a]	1.03 (0.50–2.00)	3,772 (22.2)	34,850 (18.7)		10.5 (12.8)
	14[a]	1.50 (0.50–2.03)	3,590 (14.7)	33,265 (16.6)		9.9 (10.2)
	15 (with food)[a,b]	4.00 (1.02–6.00)	3,047 (23.0)	32,156 (17.6)		9.1 (10.3)
300–400 mg b.i.d.	1	1.02 (1.00–2.10)	3,799 (20.0)	22,629[c] (14.4)	37,342 (14.9)	12.7 (15.4)
	7[a]	1.48 (1.00–1.57)	4,660 (8.4)	33,061[c] (9.7)		7.8 (11.8)
	14[a]	1.50 (1.00–2.08)	4,760 (10.9)	34,052[c] (8.8)		7.2 (19.7)
	28[a]	1.02 (1.00–2.00)	4,846 (16.2)	34,193[c] (10.7)		9.1 (9.2)
350–450 mg b.i.d.	1	1.50 (1.00–2.10)	3,723 (23.9)	23,156[c] (22.0)	37,033 (25.2)	11.7 (6.7)
	7[a]	1.50 (1.00–2.02)	5,221 (17.7)	38,345[c] (16.7)		7.3 (15.7)
	14[a]	1.00 (0.50–2.00)	5,546 (14.0)	38,589[c] (15.6)		7.3 (10.4)

AUC, area under the concentration-time curve; AUC_{0-24}, area under the concentration-time curve from time 0 (predose) to 24 hours; C_{max}, maximum observed concentration; CVb, coefficient of biological variation; max, maximum; min, minimum; PK, pharmacokinetic; $t_{1/2}$, terminal half-life; T_{max}, time to maximum observed concentration.
[a]PK sampling up to 24 hours postdose.
[b]High-fat meal.
[c]AUC from time 0 to 12 hours.

Multiple ascending dose study procedures

This single-blind study included 4 cohorts of parallel staggered doses. Eligible volunteers were healthy men or healthy women with no childbearing potential aged 18–55 years, and a body weight ≥ 50 kg and body mass index ≥ 19 kg/m^2 and ≤ 29 kg/m^2. No significant abnormalities on clinical examination or through evaluation of clinical chemistry or hematology parameters were permitted.

Vixotrigine was supplied as 50, 100, or 200 mg film-coated brownish yellow tablets. Placebo tablets visually matched the active tablets and all tablets were taken with 240 mL of water. Twelve volunteers in each of 4 parallel-dose cohorts were randomized to vixotrigine or placebo in a 9:3 ratio. For all cohorts, a screening phase preceded study treatment and a follow-up visit was conducted 7–14 days after the last dose. Cohort 1 received one 14-day repeat-dose phase (vixotrigine 150 mg q.d. or placebo). Cohort 2 received one 14-day repeat-dose phase (vixotrigine 400 mg q.d. or placebo). An additional dose of study drug was administered on day 15, within 30 minutes of consuming a high-fat breakfast. Cohort 3 received an SD and 28-day repeat-dose of vixotrigine 300–400 mg b.i.d. (doses individually adjusted to keep the AUC below the originally defined PK limits) or placebo, with a morning dose given for the SD and on day 28 of the repeat-dose period. Cohort 4 received an SD and 14-day repeat-dose of vixotrigine 350–450 mg b.i.d. (doses individually adjusted to keep below the PK limits for C_{max} and AUC) or placebo, with a morning dose given for the SD and on day 15 of the repeat-dose period. In addition, an assessment of exploratory endpoints (mechanical pain threshold, and pressure pain threshold and tolerance) was completed after day 1 and day 15 SD (see **Supplementary Material Table S1** and **Figure S3**). Volunteers in cohorts 3 and 4 received the same treatment allocation (vixotrigine or placebo) in the SD and repeat-dose periods, which were separated by ≥ 7 days. Predose blood samples were drawn and at prespecified time points to measure plasma vixotrigine levels (0, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, and 24 hours; cohorts 1 and 4: days 1, 7, and 14; cohort 2: days 1, 7, 14, and 15; cohort 3: days 1, 7, 14, and 28).

The primary endpoints of the repeat-dose study were (i) to evaluate the safety and tolerability of vixotrigine by monitoring AEs and concomitant medication, 12-lead ECGs, lead II monitoring, 24-hour Holter monitoring, vital signs, and laboratory parameters; and (ii) PK parameters estimated from plasma concentration-time profiles for each analyte: C_{max}, T_{max}, and AUC from time 0 (predose) to 24 hours after dosing (AUC_{0-24}; q.d. dose), AUC from time 0 (predose) to 12 hours after dosing (b.i.d. dose), and terminal half-life ($t_{1/2}$).

For both studies, plasma concentrations of vixotrigine were determined using liquid chromatography-tandem mass spectrometry after protein precipitation extraction, according to validated analytical methods at LGC (Fordham, UK).[17] The lower limit of quantification for vixotrigine was 10 ng/mL. PK parameters were derived using noncompartmental analyses with WinNonlin software (Certara, Princeton, NJ) version 5.0.1. Statistical analyses used SAS (Cary, NC) version 9.1.

RESULTS

Thirty male volunteers were randomized in the SAD study, treated with vixotrigine 10–825 mg, and completed treatment as planned (**Table S2**). One volunteer received vixotrigine 600 mg twice during the study. In the repeat-dose study, 51 male volunteers were enrolled

and received placebo (n = 12; 3 volunteers per cohort) or vixotrigine (12, 9, 9, and 9 in cohorts 1, 2, 3, and 4, respectively; **Table S2**). Three additional volunteers were included in cohort 1 to replace 3 volunteers who were withdrawn from the study early due to reaching protocol-defined stopping criteria.

PK analysis

Single ascending dose PK

No quantifiable vixotrigine concentrations were reported in predose plasma samples, indicating no carryover between dosing periods. Vixotrigine was rapidly and extensively absorbed, with C_{max} generally achieved at 1–2 hours postdose. Dose proportionality was approximate (**Figure S4**); although statistical significance was not confirmed for vixotrigine 10–825 mg, AUC_{0-inf} showed no relevant deviation from dose proportionality (estimate of the slope from the power model, 1.088). The deviation from dose proportionality for C_{max} was larger but still of limited importance (slope, 1.202). Following the maximal vixotrigine dose for this study (825 mg), C_{max} and AUC_{0-inf} were 6.53 µg/mL and 66.2 µg*h/mL, respectively (**Figure 1**). The estimated values for oral clearance and volume of distribution were 13.8 L/hr and 262 L, respectively. The concentration of vixotrigine increased with dose (**Figure 2**) and there were no dose-dependent changes in total clearance of vixotrigine from plasma or volume of distribution, indicating linear kinetics. Vixotrigine appeared to have moderate plasma clearance and tissue distribution, with a $t_{1/2}$ of ~ 11 hours (**Table 1**).

Multiple ascending dose PK

Repeat-dose PK parameters for vixotrigine are summarized in **Table 2**. PK characteristics of single oral doses of vixotrigine 150–400 mg were in alignment with those reported in the SD study. T_{max} was achieved in ~ 2 hours postdose and $t_{1/2}$ was 9–13 hours. Accumulation was observed following repeat vixotrigine doses; dose-proportional increases in exposure, as measured by AUC_{0-24} and C_{max}, were approximate (**Figure S6**). As expected, accumulation was higher after b.i.d. dosing by approximately twofold compared with q.d. dosing (**Figure 3**). Steady-state of vixotrigine was generally achieved for all repeat-dose regimens from day 5 onward. When administered a high-fat meal, vixotrigine 400 mg q.d. AUC_{0-24} decreased by 3%, C_{max} decreased by 15%, and T_{max} was delayed by an average of 2.5 hours (**Figure S5**). Similar to SD PK, no dose-dependent changes in oral clearance and volume of distribution were observed following repeat-dose administration of vixotrigine.

Safety and tolerability

Single ascending dose safety and tolerability

In the SD study, vixotrigine doses up to 825 mg were well-tolerated in healthy volunteers (**Table 3**). Twenty-three (77%) volunteers reported at least 1 AE. Dizziness was the most commonly reported AE (n = 11; 37%), with a higher incidence at higher vixotrigine doses (600 and 825 mg, reported by 4 of 10 (40%) and 5 of 7 (71%) volunteers, respectively). No other AEs appeared to increase with dose. Drug-related AEs were reported by 14 (47%) volunteers (**Table 3**); dizziness was again the most commonly reported AE (n = 9; 30%).

The majority of AEs following vixotrigine administration were mild in nature, except for 8 events (4 for dizziness and 1 for each of somnolence, headache, diarrhea, and vasovagal syncope associated with sinus node pause) that were rated as moderate. No deaths, serious AEs, withdrawals due to an AE, drug-related serious AEs, or clinically significant changes in ECG values or clinical laboratory evaluations were reported.

Multiple ascending dose safety and tolerability

Repeat vixotrigine doses were well-tolerated at all dose levels up to 450 mg in healthy volunteers (**Table 4**). An AE was reported by 11 (92%) placebo-treated volunteers and by 9 (75%), 6 (67%), 9 (100%), and 7 (78%) volunteers treated with vixotrigine 150 mg q.d., 400 mg q.d., 300–400 mg b.i.d., and 350–450 mg b.i.d., respectively. Headache was the most commonly reported AE, with a similar incidence in vixotrigine-treated and placebo-treated volunteers. Any drug-related AE was reported by 6 (50%), 3 (25%), 4 (44%), 8 (89%), and 6 (67%) volunteers across the placebo and vixotrigine 150 mg q.d., 400 mg q.d., 300–400 mg b.i.d., and 350–450 mg b.i.d. treatment groups, respectively. Dizziness was the most frequent drug-related AE, reported by 1 (8%), 0, 2 (22%), 3 (33%), and 3 (33%) of the placebo

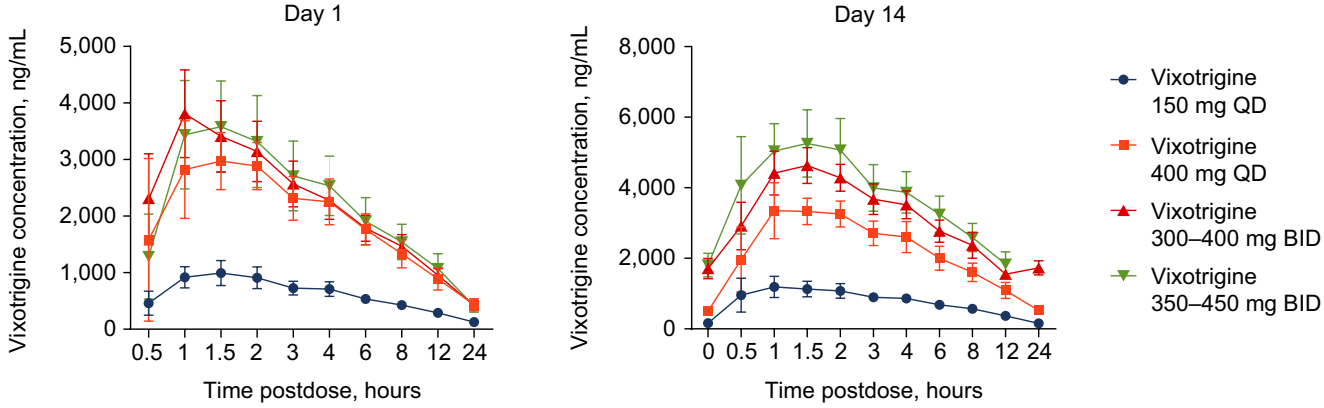

Figure 3 Mean (SD) plasma vixotrigine linear concentration-time plots in the repeat-dose study.

Table 3 AEs and drug-related AEs occurring in at least 1 volunteer in the single-dose study

		Vixotrigine									
Most frequent AEs, *n* (%)	**Placebo (*n* = 29)**	**10 mg (*n* = 10)**	**25 mg (*n* = 10)**	**75 mg (*n* = 10)**	**125 mg (*n* = 20)**	**175 mg (*n* = 20)**	**350 mg (*n* = 10)**	**600 mg (*n* = 10)**	**725 mg[a] (*n* = 1)**	**750 mg (*n* = 1)**	**825 mg (*n* = 7)**	**Total[a] (*n* = 30)**
Any AE	8 (28)	5 (50)	5 (50)	4 (40)	4 (20)	4 (20)	1 (10)	5 (50)	1 (100)	0	6 (86)	23 (77)
Most common AEs												
Dizziness	0	1 (10)	1 (10)	0	1 (5)	1 (5)	1 (10)	4 (40)	0	0	5 (71)	11 (37)
Somnolence	1 (3)	0	0	1 (10)	0	2 (10)	0	1 (10)	0	0	0	5 (17)
Fatigue	2 (7)	0	0	0	0	0	0	0	1 (100)	0	0	3 (10)
Headache	0	1 (10)	1 (10)	1 (10)	0	0	0	1 (10)	0	0	0	3 (10)
Abnormal dreams	1 (3)	0	0	1 (10)	0	0	0	0	0	0	0	2 (7)
Back pain	1 (3)	0	0	0	0	0	0	0	0	0	1 (14)	2 (7)
Diarrhea	2 (7)	0	0	0	0	0	0	0	0	0	0	2 (7)
Dyspepsia	0	0	0	0	0	0	0	2 (20)	0	0	0	2 (7)
Any drug-related AE	3 (10)	0	2 (20)	2 (20)	3 (15)	2 (10)	1 (10)	5 (50)	1 (100)	0	5 (71)	14 (47)
Most common drug-related AEs												
Dizziness	0	0	0	0	1 (5)	1 (5)	1 (10)	4 (40)	0	0	5 (71)	9 (30)
Somnolence	1 (3)	0	0	0	0	2 (10)	0	1 (10)	0	0	0	4 (13)
Fatigue	2 (7)	0	0	0	0	0	0	0	1 (100)	0	0	3 (10)
Headache	0	0	1 (10)	0	0	0	0	1 (10)	0	0	0	2 (7)
Dyspepsia	0	0	0	0	0	0	0	2 (20)	0	0	0	2 (7)

AE, adverse event.
[a]Represents the total number of volunteers with an event, irrespective of the treatment being received. Any volunteers who experienced the same event in at least 1 dosing session were counted in the total column once.

and vixotrigine 150 mg q.d., 400 mg q.d., 300–400 mg b.i.d., and 350–450 mg b.i.d. treatment groups, respectively.

All AEs were mild in nature, with the exception of 2 volunteers with vomiting of moderate intensity following placebo, and 2 volunteers with vomiting of moderate intensity following vixotrigine (1 for each of the 400 mg q.d. and 300–400 mg b.i.d. groups) treatment. No deaths, severe AEs, serious drug-related AEs, clinically significant abnormalities in ECG values or clinical laboratory evaluations, or withdrawals due to an AE were reported in the repeat-dose study.

DISCUSSION

We have described phase I studies evaluating the PK, safety, and tolerability of vixotrigine in healthy volunteers. In the SAD study, vixotrigine oral doses up to 825 mg were well-tolerated in healthy male volunteers, with PK characterized by rapid and extensive absorption, moderate to extensive tissue distribution, and low to moderate plasma clearance. The vixotrigine dose range evaluated (10–825 mg) showed an approximate dose proportionality. Dizziness was the most commonly reported AE, with the incidence appearing to increase with an increasing dose of vixotrigine.

In the repeat-dose study, vixotrigine was also well-tolerated following multiple dose administrations up to 450 mg b.i.d. in healthy volunteers. An approximate dose-proportional increase in exposure was observed, and steady-state was achieved by day 5 for all doses investigated. Accumulation of vixotrigine was higher after b.i.d. compared with q.d. dosing. The overall bioavailability of vixotrigine was unaffected by food. Headache was the most commonly reported AE, although the incidence was similar between the vixotrigine and placebo groups.

From these data, vixotrigine can be described as a compound with linear PK and dose proportionality. As expected, accumulation occurred and was faster when b.i.d. dosing was used. The short $t_{1/2}$ of vixotrigine suggests that b.i.d. dosing is needed. The PKs were similar after single and multiple doses, suggesting that there is no autoinduction as there is with carbamazepine, another compound that is used to treat neuropathic pain.[18] The PK of vixotrigine in the double-blind, multicenter, placebo-controlled, randomized-withdrawal phase II study mirrored the findings of the SAD and MAD studies described.[9] Treatment was well-tolerated, with no new safety trends reported.

The safety profiles described here were similar to those described in the vixotrigine phase II study.[9] The most commonly occurring AE in the phase II study was headache, followed by dizziness, gastrointestinal symptoms, and fatigue. Although the primary endpoint of treatment failure was not significantly lower in the vixotrigine treatment group compared with placebo, the findings of this study provided a basis for the continued investigation of vixotrigine for the treatment of patients with TN.[9]

The need for new therapies for the treatment of neuropathic pain persists. The results from these studies have been used to develop the study design and rationale for subsequent vixotrigine clinical trials in neuropathic pain conditions. Two phase III, double-blind, randomized-withdrawal studies are planned to evaluate the efficacy and safety of vixotrigine compared with placebo in participants with TN

Table 4 AEs and drug-related AEs occurring in at least 1 volunteer in the repeat-dose study

		Vixotrigine (*n* = 39)			
Most frequent AEs, *n* (%)	**Placebo (*n* = 12)**	**150 mg q.d. (*n* = 12)[a]**	**400 mg q.d. (*n* = 9)**	**300–400 mg b.i.d. (*n* = 9)**	**350–450 mg b.i.d. (*n* = 9)**
Any AE	11 (92)	9 (75)	6 (67)	9 (100)	7 (78)
Most common AEs					
Headache	3 (25)	3 (25)	2 (22)	3 (33)	1 (11)
Dizziness	2 (17)	0	2 (22)	3 (33)	3 (33)
Application site reaction	3 (25)	2 (17)	1 (11)	0	1 (11)
Catheter site-related reaction	2 (17)	2 (17)	1 (11)	1 (11)	0
Abnormal dreams	0	0	0	1 (11)	3 (33)
Conjunctival hyperemia	1 (8)	0	0	0	3 (33)
Nausea	2 (17)	1 (8)	0	1 (11)	0
Somnolence	0	0	2 (22)	2 (22)	0
Upper respiratory tract infection	1 (8)	0	0	2 (22)	1 (11)
Vomiting	2 (17)	0	1 (11)	1 (11)	0
Dizziness postural	1 (8)	1 (8)	0	1 (11)	0
Myalgia	0	0	1 (11)	2 (22)	0
Catheter site pain	0	0	0	2 (22)	0
Dry mouth	0	0	1 (11)	0	1 (11)
Epigastric discomfort	0	0	2 (22)	0	0
Ocular hyperemia	0	0	0	2 (22)	0
Blurred vision	0	0	2 (22)	0	0
Any drug-related AE	6 (50)	3 (25)	4 (44)	8 (89)	6 (67)
Most common drug-related AEs					
Dizziness	1 (8)	0	2 (22)	3 (33)	3 (33)
Headache	3 (25)	1 (8)	2 (22)	2 (22)	1 (11)
Abnormal dreams	0	0	0	1 (11)	3 (33)
Nausea	2 (17)	1 (8)	0	1 (11)	0
Somnolence	0	0	2 (22)	2 (22)	0
Dizziness postural	1 (8)	1 (8)	0	1 (11)	0
Vomiting	1 (8)	0	1 (11)	1 (11)	0
Conjunctival hyperemia	0	0	0	0	2 (22)
Dry mouth	0	0	1 (11)	0	1 (11)
Epigastric discomfort	0	0	2 (22)	0	0
Blurred vision	0	0	2 (22)	0	0

AE, adverse event.
[a]Includes 3 volunteers recruited following the withdrawal of 3 volunteers.

(NCT03070132). The ongoing phase II CONVEY study will investigate the efficacy and safety of vixotrigine in participants diagnosed with idiopathic or diabetes-related painful small fiber neuropathy.

We conclude that vixotrigine, administered as single oral doses up to 825 mg and multiple doses up to 450 mg b.i.d., was well-tolerated in healthy volunteers.

Supporting Information. Additional supporting information may be found in the online version of this article at the publisher's web site:

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Conflict of Interest. H.N. is an employee of and owns stock/stock options in Biogen. D.J.S. was previously the Biogen medical lead for vixotrigine and owns stock/stock options in Biogen. M.V. was a paid consultant to Biogen and Convergence Pharmaceuticals Ltd., a Biogen company, in relation to this study. J.P. was an employee of GlaxoSmithKline at the time of the study, and subsequently an employee of Convergence Pharmaceuticals Ltd., a Biogen company, and Biogen, and owned stock in Biogen and Convergence Pharmaceuticals Ltd. R.F. was an employee of GlaxoSmithKline at the time the study was conducted.

Author Contributions. R.F. designed the research. R.F. performed the research. D.J.S., H.N., J.P., M.V., and R.F. analyzed the data. D.J.S., H.N., J.P., M.V., and R.F. wrote the manuscript.

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