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

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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 (t_{1/2}), 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.

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

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root and trigeminal ganglia in the orofacial region, together with sympathetic neurons and olfactory epithelia. Nav1.8 is a tetrodotoxin-resistant subtype, expressed in nociceptive sensory neurons. Nav1.9, the most recently identified Nav subtype, is a marker of primary nociceptors, also expressed in the enteric nervous system. Carbamazepine, which is known to target Nav channels, is used to treat neuropathic pain, in particular trigeminal neuralgia (TN), although use is limited due to poor tolerability, need for titration, and potential pharmacological interactions. 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 currently under investigation for neuropathic pain conditions, including painful small fiber neuropathy and TN. 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 14C-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
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**Vixotrigine**

| Dose (mg) | 10 | 25 | 75 | 125 | 175 | 350 | 600 | 725 | 750 | 825 |
|----------|----|----|----|-----|-----|-----|-----|-----|-----|-----|
| PK parameter | | | | | | | | | | |
| AUC<sub>0–t</sub> | mg·h·ng/mL | 474.4 (20.8) | 1,507 (21.4) | 3,592 (20.6) | 5,958.6 (17.1) | 12,582.6 (17.3) | 24,729.0 (17.1) | 50,707.5 (5.9) | 63,234.8 | 63,550.5 |
| AUC<sub>0–inf</sub> | mg·h·ng/mL | 633.7 (17.1) | 1,653.4 (20.6) | 5,592.8 (17.1) | 9,731.7 (17.1) | 12,802.8 (17.1) | 24,953.5 (10.1) | 47,022.5 (12.4) | 64,583.6 | 66,200.4 |
| C<sub>max</sub> | ng/mL | 38.4 (27.6) | 121.1 (18.4) | 522.0 (20.6) | 1,225.2 (26.1) | 2,503.3 (17.1) | 4,878.8 (15.8) | 9,731.7 (18.4) | 12,802.8 | 17,503.1 |
| T<sub>max</sub> | hours | 17.1 (19.1) | 17.2 (15.8) | 12.6 (14.7) | 11.9 (19.1) | 11.8 (8.1) | 10.8 (9.9) | 11.4 (7.7) | 10.4 | 9.8 |

**Median (min–max)**

- AUC<sub>0–t</sub>, area under the concentration-time curve from predose to the last quantifiable concentration;
- AUC<sub>0–inf</sub>, area under the concentration-time curve from predose extrapolated to infinite time;
- C<sub>max</sub>, maximum observed concentration;
- max, maximum;
- min, minimum;
- PK, pharmacokinetic;
- 1/2, terminal half-life;
- T<sub>max</sub>, time to maximum observed concentration.

*One volunteer received 725 mg.
*One volunteer received 750 mg.
*One volunteer received 825 mg.

**Median PK parameters**: area under the concentration-time curve from predose extrapolated to infinite time (AUC<sub>0–inf</sub>), maximum observed concentration (C<sub>max</sub>), and time to maximum observed concentration (T<sub>max</sub>). Dose proportionality of AUC<sub>0–inf</sub>, C<sub>max</sub>, and T<sub>max</sub> across doses was investigated by a power model 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.

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<sub>0–inf</sub>), AUC from predose to last time of quantifiable concentration (AUC<sub>0–t</sub>), maximum observed concentration (C<sub>max</sub>), and time to C<sub>max</sub> (T<sub>max</sub>). Dose proportionality of AUC<sub>0–inf</sub>, C<sub>max</sub>, and T<sub>max</sub> was assessed through a power model 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) | Geometric mean (% CVb) Cmax, ng/mL | Geometric mean (% CVb) AUC0–24, h*ng/mL | Geometric mean (% CVb) AUC0–12, h*ng/mL | Geometric mean (% CVb) AUC, h*ng/mL | Geometric mean (% CVb) t1/2, hours |
|---------------------|-----|-----------------|-----------------------------------|----------------------------------------|----------------------------------------|-----------------------------------|----------------------------------|
| 150 mg q.d.         | 1a  | 1.50 (1.00–1.50) | 1,017 (20.0)                      | 8,789 (18.4)                           | 10,442 (20.5)                         | 9.2 (10.0)                        | 9.2 (10.0)                      |
|                     | 7a  | 1.03 (0.50–3.00) | 1,216 (19.4)                      | 11,633 (15.1)                         | 11,842 (20.5)                         | 8.6 (12.6)                        | 11.7 (6.7)                      |
|                     | 14a | 1.02 (0.52–2.03) | 1,238 (27.7)                      | 11,184 (20.5)                         | 11,842 (20.5)                         | 8.6 (12.6)                        | 11.7 (6.7)                      |
| 400 mg q.d.         | 1a  | 1.50 (0.50–2.03) | 3,310 (23.3)                      | 27,993 (16.6)                         | 34,195 (18.1)                         | 10.0 (11.1)                       | 10.0 (11.1)                     |
|                     | 7a  | 1.03 (0.50–2.00) | 3,772 (22.2)                      | 34,850 (18.7)                         | 37,033 (25.2)                         | 10.5 (12.8)                       | 10.5 (12.8)                     |
|                     | 14a | 1.50 (0.50–2.03) | 3,590 (14.7)                      | 33,265 (16.6)                         | 37,033 (25.2)                         | 9.9 (10.2)                        | 9.9 (10.2)                      |
| 300–400 mg b.i.d.   | 1   | 1.02 (1.00–2.10) | 3,799 (20.0)                      | 22,629 (14.4)                         | 37,342 (14.9)                         | 12.7 (15.4)                       | 12.7 (15.4)                     |
|                     | 7a  | 1.48 (1.00–1.57) | 4,660 (8.4)                       | 33,061 (9.7)                          | 34,052 (8.8)                          | 7.2 (19.7)                        | 7.2 (19.7)                      |
|                     | 14a | 1.50 (1.00–2.08) | 4,760 (10.9)                      | 34,052 (8.8)                          | 34,052 (8.8)                          | 7.2 (19.7)                        | 7.2 (19.7)                      |
|                     | 28a | 1.02 (1.00–2.00) | 4,846 (16.2)                      | 34,193 (10.7)                         | 34,193 (10.7)                         | 9.1 (9.2)                         | 9.1 (9.2)                       |
| 350–450 mg b.i.d.   | 1   | 1.50 (1.00–2.10) | 3,723 (23.9)                      | 23,156 (22.0)                         | 37,033 (25.2)                         | 11.7 (6.7)                        | 11.7 (6.7)                      |
|                     | 7a  | 1.50 (1.00–2.02) | 5,221 (17.7)                      | 38,345 (16.7)                         | 38,345 (16.7)                         | 7.3 (15.7)                        | 7.3 (15.7)                      |
|                     | 14a | 1.00 (0.50–2.00) | 5,546 (14.0)                      | 38,589 (15.6)                         | 38,589 (15.6)                         | 7.3 (10.4)                        | 7.3 (10.4)                      |

AUC, area under the concentration-time curve; AUC0–24, area under the concentration-time curve from time 0 (predose) to 24 hours; Cmax, maximum observed concentration; CVb, coefficient of biological variation; max, maximum; min, minimum; PK, pharmacokinetic; t1/2, terminal half-life; Tmax, time to maximum observed concentration.

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/m² and ≤ 29 kg/m². 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 treatment and a follow-up visit was conducted 1–4 days after the last dose. Cohort 1 received a 14-day repeat-dose phase (vixotrigine 150 mg q.d. or placebo). Cohort 2 received a 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 14-day repeat-dose phase (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 Cmax 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 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, 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: Cmax, Tmax, and AUC from time 0 (predose) to 24 hours after dosing (AUC0–24; q.d. dose), AUC from time 0 (predose) to 12 hours after dosing (b.i.d. dose), and terminal half-life (t1/2).

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). 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

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**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

| Dosage Level | Total AE (n = 29) | Most frequent AEs (n = 29) |
|--------------|------------------|----------------------------|
| 10 mg        | 8 (28)           | Dizziness                   |
| 25 mg        | 5 (50)           | Fatigue                     |
| 75 mg        | 2 (10)           | Headache                    |
| 125 mg       | 2 (10)           | Dizziness                   |
| 175 mg       | 3 (10)           | Fatigue                     |
| 250 mg       | 3 (10)           | Dizziness                   |
| 350 mg       | 5 (50)           | Fatigue                     |
| 600 mg       | 2 (10)           | Dizziness                   |
| 750 mg       | 1 (10)           | Fatigue                     |
| 725 mg       | 1 (10)           | Dizziness                   |
| 825 mg       | 0                |                             |
| 950 mg       | 0                |                             |

Any AE, adverse event. 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.

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 t1/2 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. 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. 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. 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.

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.

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.
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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.

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

| Most frequent AEs, n (%) | Placebo (n = 12) | 150 mg q.d. (n = 12) | 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)          | 2 (17)              | 1 (11)              | 0                        | 1 (11)                   |
| 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.

*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.
1. Colloca, L. et al. Neuropathic pain. *Nat. Rev. Dis. Primers* 3, 17002 (2017).
2. Ales, S.R.A. & Smith, P.A. Etiology and pharmacology of neuropathic pain. *Pharmacol. Rev.* 70, 315–347 (2018).
3. van Hecke, O., Austin, S.K., Khan, R.A., Smith, B.H. & Torrance, N. Neuropathic pain in the general population: a systematic review of epidemiological studies. *Pain* 155, 654–662 (2014).
4. Meisler, M.H. & Kearney, J.A. Sodium channel mutations in epilepsy and other neurological disorders. *J. Clin. Invest.* 115, 2010–2017 (2005).
5. Emery, E.C., Luiz, A.P. & Wood, J.N. Nav1.7 and other voltage-gated sodium channels as drug targets for pain relief. *Expert Opin. Ther. Targets* 20, 975–983 (2016).
6. Waxman, S.G. et al. Sodium channel genes in pain-related disorders: phenotype-genotype associations and recommendations for clinical use. *Lancet Neurol.* 13, 1152–1160 (2014).
7. Cox, J.J. et al. An SCN9A channelopathy causes congenital inability to experience pain. *Nature* 444, 894–898 (2006).
8. Eijkelkamp, N. et al. Neurological perspectives on voltage-gated sodium channels. *Brain* 135(pt 9), 2585–2612 (2012).
9. Zakrzewska, J.M. et al. Safety and efficacy of a Nav1.7 selective sodium channel blocker in patients with trigeminal neuralgia: a double-blind, placebo-controlled, randomised withdrawal phase 2a trial. *Lancet Neurol.* 16, 291–300 (2017).
10. Fong, R., Ballow, C.H., Naik, H., Steiner, D., Palmer, J. & White, W.B. Effects of a state- and use-dependent Nav1.7 channel blocker on ambulatory blood pressure: a randomized, controlled crossover study. *J. Clin. Pharmacol.* 59, 90–97 (2019).
11. Di Stefano, G., Truini, A. & Cuccu, G. Current and innovative pharmacological options to treat typical and atypical trigeminal neuralgia. *Drugs* 78, 1433–1442 (2018).
12. Shinobu, L.A. et al. CONVEY, a phase 2 placebo-controlled, double-blind, enriched enrollment randomized withdrawal study design of vixotrigine for the treatment of pain in participants with confirmed small fiber neuropathy (P2.6-068). *Neurology* 92 (suppl. 15), P2.6-068 (2018).
13. Shen, J., Swift, B., Mamellok, R., Pine, S., Sinclair, J. & Attar, M. Design and conduct considerations for first-in-human trials. *Clin. Transl. Sci.* 12, 6–19 (2019).
14. U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER). Guidance for industry: estimating the maximum safe starting dose in initial clinical trials for therapeutics in adult healthy volunteers <https://www.fda.gov/media/72309/download> (2005). Accessed February 25, 2020.
15. Hummel, J., McKendrick, S., Brindle, C. & French, R. Exploratory assessment of dose proportionality: review of current approaches and proposal for a practical criterion. *Pharm. Stat.* 8, 38–49 (2009).
16. Sheng, Y., He, Y., Huang, X., Yang, J., Wang, K. & Zheng, Q. Systematic evaluation of dose proportionality studies in clinical pharmacokinetics. *Curr. Drug Metab.* 11, 526–537 (2010).
17. Dunbar, J. et al. Evaluation of the pharmacokinetic interaction between the voltage- and use-dependent Nav1.7 channel blocker vixotrigine and carbamazepine in healthy volunteers. *Clin. Pharmacol. Drug Dev.* 9, 62–73 (2020).
18. Tolou-Ghamari, Z., Zare, M., Habibabadi, J.M. & Najafi, M.R. A quick review of carbamazepine pharmacokinetics in epilepsy from 1953 to 2012. *J. Res. Med. Sci.* 16 (suppl. 1), S81–S85 (2013).