Efficacy and safety of vixotrigine in idiopathic or diabetes-associated painful small fibre neuropathy (CONVEY): a phase 2 placebo-controlled enriched-enrolment randomised withdrawal study

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Summary

Background No pharmacological treatments are specifically indicated for painful small fibre neuropathy (SFN). CONVEY, a phase 2 enriched-enrolment study, evaluated the efficacy and safety of vixotrigine, a voltage- and use-dependent sodium channel blocker, in participants with idiopathic or diabetes-associated painful SFN.

Methods CONVEY was a phase 2, multicentre, placebo-controlled, double-blind (DB), enriched-enrolment, randomised withdrawal study. The study was conducted at 68 sites in 13 countries (Europe and Canada) between May 17, 2018, and April 12, 2021. Following a 4-week open-label period in which 265 adults with painful SFN (a mixture of large and small fibre neuropathy was not exclusionary) received oral vixotrigine 350 mg twice daily (BID), 123 participants (with a ≥30% reduction from baseline in average daily pain [ADP] score during the open-label period) were randomised 1:1:1 to receive 200 mg BID, 350 mg BID or placebo for a 12-week double-blind (DB) period. Primary endpoint was change from baseline in ADP at DB Week 12. Secondary endpoints included the proportion of participants with a ≥30% reduction from baseline in ADP and the proportion of Patient Global Impression of Pain (PGIC) responders at DB Week 12. Treatment-emergent adverse events (AEs) were monitored. Statistical significance was set at 0.10 (2-sided). The trial was registered on ClinicalTrials.gov (NCT03339336) and on ClinicalTrialsregister.eu (2017-000991-27).

Findings A statistically significant difference from placebo in least squares mean reduction in ADP score from baseline to DB Week 12 was observed with vixotrigine 200 mg BID (–0.85; SE, 0.43; 95% CI, –1.71 to 0.00; p = 0.050) but not 350 mg BID (–0.17; SE, 0.43; 95% CI, –1.01 to 0.68; p = 0.70). Numerically, but not statistically significantly, more participants who received vixotrigine vs placebo experienced a ≥30% ADP reduction from baseline (68.3–72.5% vs 52.5%), and only the 350 mg BID group had significantly more PGIC responders vs placebo (48.8% vs 30.0%; odds ratio = 2.60; 95% CI, 0.97–6.99; p = 0.058) at DB Week 12. AEs were mostly mild to moderate in the vixotrigine groups. The most common AEs (≥5% of vixotrigine-treated participants) in the DB 200 mg BID and 350 mg BID vixotrigine groups were falls, nasopharyngitis, muscle spasm, and urinary tract infection.

Interpretation In our study, vixotrigine 200 mg BID, but not 350 mg BID, met the primary endpoint; more vixotrigine-treated participants experienced a ≥30% reduction from baseline in ADP at DB Week 12. Vixotrigine (at both dosages) was well tolerated in participants with SFN.

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Research in context

Evidence before this study

A PubMed search was conducted using the term "small fibre neuropathy" and filtered for English-language systematic reviews and meta-analyses published between January 1, 2000 and May 1, 2022. The search identified 22 papers, only one of which reported on treatments. An additional search using the same term but limited to randomised controlled trials identified three papers. No treatment has been approved for SFN; current standard of care includes antidepressants, anticonvulsants, opioids, and topical treatments to address symptoms, using a trial-and-error approach. These standard-of-care treatments are often poorly tolerated and/or associated with inadequate pain management.

Added value of this study

Very few clinical studies have evaluated treatments specific for painful SFN. This study suggests vixotrigine, a voltage- and use-dependent sodium channel blocker, is well tolerated and potentially efficacious in patients with painful SFN.

Implications of all the available evidence

These data support the potential for vixotrigine as a nonopioid treatment option for neuropathic pain.

Introduction

Small fibre neuropathy (SFN) is a subtype of peripheral neuropathy. Its frequency in patients with diabetic peripheral neuropathy varies (1.6–13.5%) due to the different types and number of criteria applied in diagnostic models.[1,2] SFN is caused by injury to small nerve fibres Aδ (myelinated) and C (unmyelinated).[3] It clinically presents with distal symmetric pain, numbness, or paraesthesia and is often accompanied by hyperalgesia or allodynia.[4] SFN can also impair autonomic nervous system function.[5] SFN can be diagnosed using a combination of symptomatic, clinical, quantitative sensory testing, and histological markers, with a decrease in intraepidermal nerve fibre density in skin biopsies considered the 'silver standard' (due to some limitations such as a normal skin biopsy not completely excluding SFN) for diagnosis.[6–8] Although SFN is commonly associated with diabetes, it has been considered idiopathic[6] in 23–93% of cases in recently published original research articles and systematic reviews.[4,9,10]

Current therapies for idiopathic SFN are limited to treating symptoms, but symptom management is challenging and remains unsatisfactory—responses are variable, and adverse effects are an issue for patients. No treatment is specifically approved for idiopathic pain associated with SFN; consequently, treatment approaches involve a trial-and-error process.[5] Treatments include tricyclic antidepressants, selective serotonin and norepinephrine reuptake inhibitors, gabapentinoids, opiates, and topical treatments.[5,7] Autonomic symptoms are treated as needed.

The expression or function of voltage-gated sodium channels is altered in response to peripheral system injury or disease, thereby inducing sensory neuron hyperexcitability and subsequent ectopic action potentials that ultimately result in pain.[11] Voltage-gated sodium channel $Na_v1.7$, expressed in Aδ and C nerve fibres, is the dominant sodium channel in peripheral nerves. The genes SCN9A, SCN10A, SCN11A encode Nav1.7, Nav1.8, and Nav1.9, respectively. Rare missense variants in patients with SFN have been reported for SCN9A (5.1%), SCN10A (3.7%), and SCN11A (2.9%).[12] Further research is needed to fully understand the role of rare missense variants in the aetiology of SFN.

Vixotrigine (BIIB074) is a voltage- and use-dependent sodium channel blocker that inhibits the function of the family of voltage-gated sodium channels (i.e., it is a broad-spectrum sodium channel blocker that has been shown to block sodium channels found in the CNS and PNS [including in DRG neurons]) and may have the potential to treat painful SFN.[11,13] In a previous enriched enrolment, randomised withdrawal, double-blind, placebo-controlled phase 2a study, vixotrigine was investigated in another neuropathic disease, trigeminal neuralgia.[14] While the primary endpoint was not met in that study, overall data (e.g., a significant reduction in number of paroxysms) from the study supported additional investigation of vixotrigine. Vixotrigine doses of 200 mg twice daily (BID) and 350 mg BID were selected as they were predicted to maintain mean trough plasma concentrations above 1.12 μg/mL and 1.96 μg/mL, respectively, which was predicted to

provide therapeutic effects in participants with painful SFN, based on preclinical findings. Based on clinical trial data, vixotrigine was well tolerated with repeat dosing up to 450 mg BID in healthy individuals; the BID dosing interval in the present study was determined based on a terminal half-life of 7.2–12.7 h.[15] CONVEY was designed to evaluate the efficacy and safety of vixotrigine in patients with idiopathic or diabetes-associated painful SFN.

Methods

Study design and participants

CONVEY was a phase 2, multicentre, placebo-controlled, double-blind (DB), enriched-enrolment, randomised withdrawal study (Supplemental Fig. S1). The trial was registered on November 13, 2017 on ClinicalTrials.gov (NCT03339336; https://clinicaltrials.gov/ct2/show/NCT03339336) and on October 18, 2017 on ClinicalTrialsregister.eu (2017-000991-27; https://www.clinicaltrialsregister.eu/ctr-search/trial/2017-000991-27/GB). The study was conducted at 68 sites in 13 countries (Europe and Canada) between May 17, 2018 and April 12, 2021. The protocol noted that an interim analysis may be conducted; an interim analysis was conducted by a separate unblinded team not involved in study conduct in April 2020. The prespecified futility analysis used an O'Brien and Fleming stopping rule and neither dose met the stopping criteria. The study was terminated early by the sponsor, for business reasons, not related to safety, on March 8, 2021. The decision to terminate the study was made by parties with knowledge of the results of the interim analysis. The study team remained blinded until the database was locked.

Key inclusion criteria included age ≥18 years; a diagnosis of probable or confirmed length-dependent SFN (defined by the presence of at least one of four pain symptoms and at least one of four associated clinical signs)[6] of ≥6 months and ≤10 years in duration and confirmed by the presence of an abnormality in a single skin biopsy, with intraepidermal nerve fibre density values outside of the normal ranges for age and sex; stable diabetes for ≥6 months prior to screening in participants with diabetes; and a self-reported average daily pain (ADP) score of ≥5 and ≤9 over the 7 days before screening. Participants were not required to have isolated SFN (i.e., copresence of large fibre neuropathy was not exclusionary). Full eligibility criteria are reported in the Supplemental Material.

During the 3-week screening period, participants were required to make daily entries in an eDiary to monitor their pain severity. After screening, participants tapered their use of pain medications and entered a 5-day washout period (if applicable) once they had down titrated and discontinued pain medication use; participants entered the washout period directly if no tapering was required. After washout, participants entered the open-label (OL) run-in period, during which they received vixotrigine 350 mg BID for 4 weeks, which was administered orally.

Participants with an improvement of ≥30% in mean ADP score during the last 7 days of the OL period compared with baseline (mean ADP score during the 5 days prior to the start of the OL period [i.e., the washout period]) and who met other randomisation eligibility criteria (Supplemental Material) were randomised 1:1:1 to orally receive vixotrigine 200 mg BID, vixotrigine 350 mg BID, or placebo during a 12-week DB period. There was no washout period between the OL and DB periods. During the DB period, participants self-administered the study drug in the morning and evening and continued to record their ADP, worst daily pain (WDP), and sleep interference. Follow-up consisted of a clinic visit 1 week after the last dose and a telephone call 4 weeks after the last dose.

The study was conducted in accordance with the Declaration of Helsinki, the International Conference on Harmonisation, and the Good Clinical Practice guidelines. Ethics committee approval was obtained at each participating site. All participants provided written informed consent.

Randomisation and masking

Participants were each assigned a unique identification number via an interactive voice/web response system during registration for randomisation. Investigators verified that participants were eligible per randomisation criteria. During the DB period, investigators, study personnel, and participants were blinded to the treatment assignments, which were not shared with the participants, their families, or anyone involved in conducting the study. An unblinded interim analysis was performed, but the study team remained blinded.

Study assessments

Patients self-assessed and recorded their pain in an eDiary. ADP and WDP scores were both entered daily before bed; scores were based on an 11-point numerical rating scale, with lower scores indicating less pain, and pertained to the previous 24-h period. Sleep interference score (considering only SFN causes) was entered daily after waking in the morning; scores were based on an 11-point numerical rating scale, with lower scores indicating less interference. Answers to the following self-assessments were also entered in the eDiary during clinic visits: the Neuropathic Pain Symptom Inventory (NPSI; self-assessment of 10 items corresponding to pain qualities, with a 0–10 rating scale where 0 = no pain and 10 = worst pain imaginable, and two items for assessing pain duration and number of pain paroxysms),[16] Brief Pain Inventory-Short Form (BPI-SF) interference score (assesses quality of life by calculating the mean of seven interference item scores for general activity, walking, work, mood, enjoyment of life,

relations with others, and sleep),[17] and Patient Global Impression of Change (PGIC; based on a seven-point scale reflecting the participant's perceived change in overall status relative to Day 1 [first day of OL period]).[18]

Study objectives and endpoints

The primary efficacy endpoint was change from baseline to Week 12 of the DB period (DB Week 12) in mean ADP score on the 11-point numerical rating scale (baseline was defined as the 5 days prior to the first dose of vixotrigine in the OL period); this is in accordance with numerous previously conducted chronic pain studies and enables the assessment of the therapeutic effect of an investigational drug over a sustained period.[19] Change from randomisation to DB Week 12 in mean ADP score was a secondary endpoint (randomisation was defined as the 7 days prior to the first dose of study treatment in the DB period). Other secondary endpoints included change from baseline to DB Week 12 in WDP score, sleep interference, NPSI total score and sum score of symptoms of neuropathic pain (burning and pressing), and BPI-SF interference score; the proportion of participants with at least a two-point reduction in mean ADP score from baseline to DB Week 12; the proportion of participants with at least a 30% reduction in mean ADP score from baseline to DB Week 12; the amount of rescue medication (paracetamol/acetaminophen) used for SFN pain during the DB period; and the proportion of responders (those reporting being "much improved" or "very much improved") on the PGIC questionnaire at DB Week 12. Participants completed all evaluations in the eDiary either daily at home or during clinic visits.

To investigate the safety and tolerability of vixotrigine, the incidence of adverse events (AEs) and serious adverse events (SAEs) was recorded during the DB period. Vital signs, electrocardiogram parameters, and laboratory safety test results were also monitored and recorded. AEs were coded using the Medical Dictionary for Regulatory Activities (version 24.0).

Statistical analysis

For assessment of the primary endpoint, assuming a withdrawal rate of 20% during the DB period, a sample size of 62 randomised participants per treatment group in the DB period would provide 80% power to detect a statistically significant difference in change from baseline in mean ADP scores between each dose group and the placebo group at the 2-sided 10% significance level, assuming a true difference of 1.0 with an SD of 2.0. The statistical significance level set at $p < 0.10$ was prespecified for this proof-of-concept study. No adjustments for the interim analysis or multiplicity were made.

The full analysis set included all patients randomised in the DB period who received at least one dose of DB vixotrigine or placebo and had at least one postrandomisation efficacy assessment. The safety population for the OL and DB periods included all participants who received at least one dose of OL vixotrigine and at least one dose of DB vixotrigine or placebo, respectively.

Change from baseline or from randomisation in ADP and WDP scores and change from baseline in sleep interference, BPI-SF, and NPSI were analysed using mixed-model repeated measures (MMRM) models including terms for treatment, time point, treatment-by-time point interaction, baseline score, baseline score-by-time point interaction, and SFN aetiology. Missing data were considered missing at random (MAR) and handled by the MMRM models. A similar MMRM model was used for a prespecified exploratory subgroup analysis of change from baseline in ADP scores by SFN aetiology. Logistic regression models were used to analyse the proportion of participants who achieved significant reductions (≥30%, or ≥2 points) from baseline in ADP score at DB Week 12 (including terms for treatment, baseline score and SFN aetiology) and the proportion of participants who were responders in the PGIC assessment at DB Week 12 (including terms for treatment and SFN aetiology). For the ADP endpoints, missing data at DB Week 12 were imputed using a MAR approach prior to deriving response status if the participant had completed study treatment, otherwise the participant was considered a non-responder. For PGIC, all participants with missing data at DB Week 12 were considered non-responders. Use of rescue medication (paracetamol/acetaminophen) was also analysed using logistic regression (including terms for treatment, previous use of paracetamol/acetaminophen and SFN aetiology).

Role of the funding source

The trial was designed primarily by the sponsor (Biogen) with input from external experts. Biogen provided trial oversight, collection, and analysis of the data. All the authors reviewed the data and participated in writing or reviewing the manuscript, and agreed in the decision to submit the paper for publication. The sponsor paid for medical writing assistance.

Results

Participants

Of 265 participants enrolled between May 17, 2018, and April 12, 2021, 234 completed the OL period, of whom 123 were randomised and continued to the DB period (all but one of the 123 had a ≥30% reduction in mean ADP score during the OL period compared with baseline; the participant with <30% reduction was withdrawn from the study after a single dose of DB treatment); 122 were included in the safety population, and 121 in the full analysis set (Fig. 1). The first dose of study treatment was administered on May 31, 2018. In

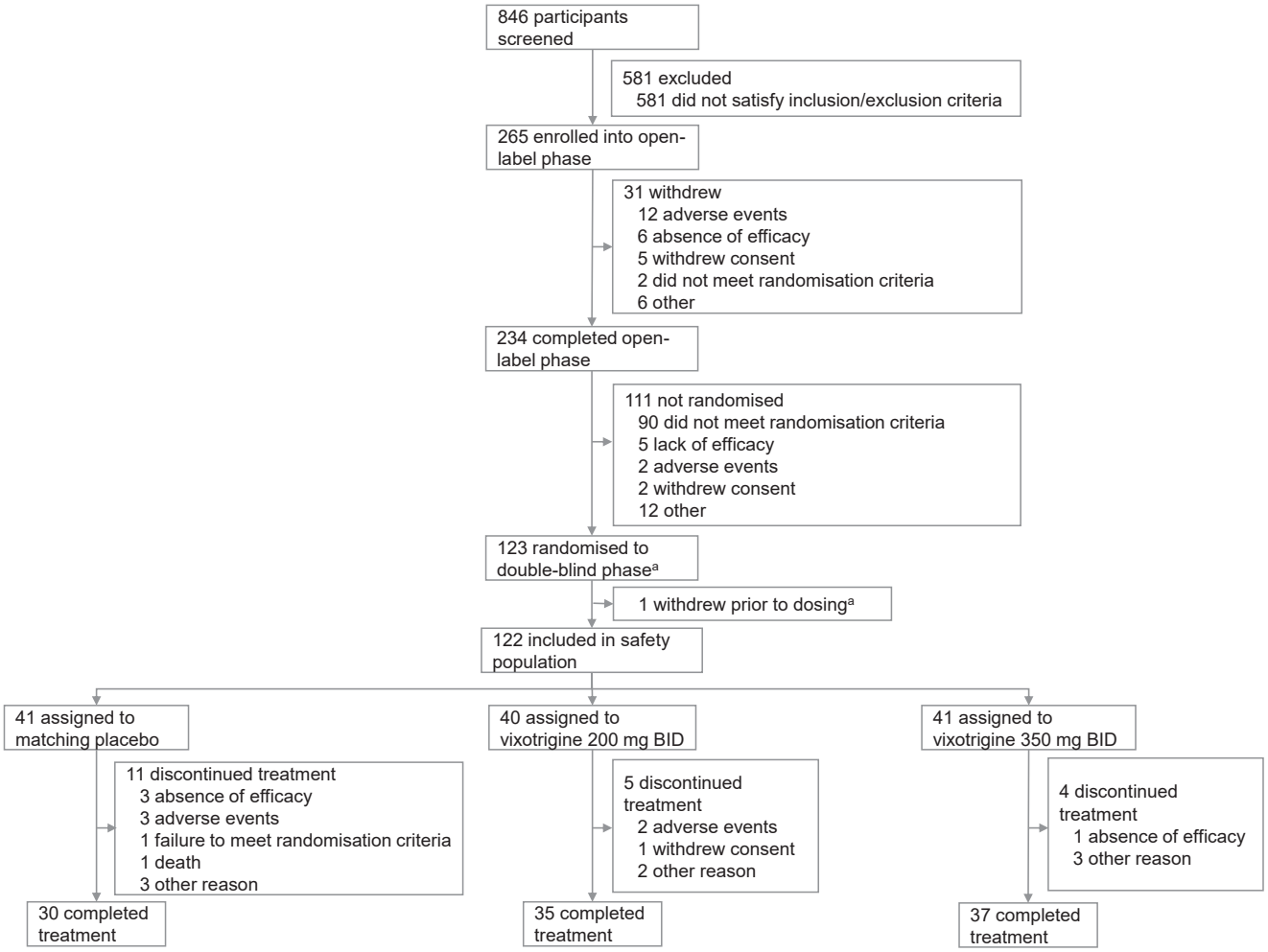

Fig. 1: **Participant Disposition.** [a]Three patients not eligible for randomisation were randomised: one withdrew prior to dosing, one received one dose of double-blind treatment, and one completed the study. BID, twice daily; FAS, full analysis set.

the placebo group, one participant with pre-existing cardiovascular abnormalities died due to cardiac arrest after approximately 12 weeks of placebo treatment; the investigator did not consider the death to be treatment related. Overall, 83.6% of treated participants completed DB treatment: 30 of 41 in the placebo group, 35 of 40 in the vixotrigine 200 mg BID group, and 37 of 41 in the vixotrigine 350 mg BID group. In the DB period, participants were mostly White (91.8%), with a mean (SD) age of 59.5 (10.4) years (Table 1). These demographics were similar across treatment arms. Overall, 73.8% of participants in the DB safety population had SFN associated with diabetes, while the remainder had idiopathic SFN (Table 2). The mean (SD) duration of SFN symptoms in DB participants was 59.8 (42.0), 74.3 (60.8), and 60.6 (43.9) months in the placebo, vixotrigine 200 mg BID, and vixotrigine 350 mg BID groups, respectively. Over 60% of DB participants took a medication for SFN prior to the OL period (Table 2). The most common medications were anticonvulsants (45.9%), tricyclic antidepressants (12.3%), antidepressants excluding tricyclic antidepressants (11.5%), and opioids/opiates (17.2%); 13.1% received medications categorised as "other," which included thioctic acid, capsaicin, cannabidiol, and lidocaine.

Changes in ADP and WDP

In the OL period (in which all participants received vixotrigine 350 mg BID), the mean (SD) change from baseline in ADP score at Week 4 was −2.7 (2.0). The change in scores ranged from +1.8 to −7.7. Over half of OL participants (50.9%) had a ≥30% reduction in ADP. A statistically significantly larger decrease in ADP from baseline to DB Week 12 was observed in the vixotrigine 200 mg BID group vs the placebo group (least squares [LS] mean difference −0.85; SE, 0.43; 95% CI, −1.71 to

	Placebo (N = 41)	Vixotrigine 200 mg BID (N = 40)	Vixotrigine 350 mg BID (N = 41)	Overall (N = 122)
Age, mean (SD), y	57.1 (11.0)	62.7 (9.8)	58.8 (9.8)	59.5 (10.4)
Sex, n (%)				
Female	20 (48.8)	20 (50.0)	16 (39.0)	56 (45.9)
Male	21 (51.2)	20 (50.0)	25 (61.0)	66 (54.1)
Ethnicity, n (%)				
Hispanic or Latino	0	0	1 (2.4)	1 (0.8)
Not Hispanic or Latino	40 (97.6)	37 (92.5)	36 (87.8)	113 (92.6)
Not reported	1 (2.4)	3 (7.5)	4 (9.8)	8 (6.6)
Race, n (%)				
American Indian or Alaska native	0	0	0	0
Asian	0	0	1 (2.4)	1 (0.8)
Black or African American	0	0	0	0
Native Hawaiian or other Pacific Islander	0	0	0	0
White	40 (97.6)	37 (92.5)	35 (85.4)	112 (91.8)
Not reported	1 (2.4)	3 (7.5)	4 (9.8)	8 (6.6)
Other	0	0	1 (2.4)	1 (0.8)
Height, mean (SD), cm	171.5 (8.1)	170.1 (8.4)	172.6 (8.6)	171.4 (8.3)
Weight, mean (SD), kg	91.5 (19.0)	89.2 (17.5)	88.4 (18.0)	89.7 (18.1)
Body mass index, mean (SD), kg/m^2	31.2 (6.3)	30.7 (5.1)	29.7 (6.0)	30.5 (5.8)

Abbreviations: BID, twice daily; DB, double blind; SD, standard deviation.

Table 1: **Baseline demographics of the DB safety population.**

0.00; p = 0.050) but not in the vixotrigine 350 mg BID group vs the placebo group (LS mean difference, –0.17; SE, 0.43; 95% CI, –1.01 to 0.68; p = 0.70) (Fig. 2). A statistically significantly larger decrease in ADP from randomisation to DB Week 12 was also observed in the vixotrigine 200 mg BID group vs the placebo group (LS mean difference, –0.85; SE, 0.44; 95% CI, –1.74 to 0.03; p = 0.058) but not in the vixotrigine 350 mg BID group vs the placebo group (LS mean difference, –0.32; SE, 0.44; 95% CI –1.19 to 0.55; p = 0.47). Over the first 9 weeks of the DB period, the change from baseline in ADP scores numerically favoured both doses of

	Placebo (N = 41)	Vixotrigine 200 mg BID (N = 40)	Vixotrigine 350 mg BID (N = 41)	Overall (N = 122)
ADP score, mean (SD)	6.70 (0.95)	6.93 (1.12)	6.39 (0.90)	6.67 (1.01)
WDP score, mean (SD)	7.32 (0.97)	7.42 (1.06)	7.28 (0.92)	7.34 (0.98)
Time since diagnosis, mean (SD), mo	29.9 (41.6)	36.6 (49.3)	25.9 (30.1)	30.8 (40.9)
Duration of SFN symptoms, mean (SD), months	59.8 (42.0)	74.3 (60.8)	60.6 (43.9)	64.8 (49.5)
SFN aetiology, n (%)				
Idiopathic	12 (29.3)	7 (17.5)	13 (31.7)	32 (26.2)
Diabetes	29 (70.7)	33 (82.5)	28 (68.3)	90 (73.8)
Type 1	1 (2.4)	4 (10.0)	2 (4.9)	7 (5.7)
Type 2	27 (65.9)	29 (72.5)	25 (61.0)	81 (66.4)
Other	1 (2.4)	0	1 (2.4)	2 (1.6)
Prior pain treatments, n (%)	29 (70.7)	22 (55.0)	25 (61.0)	76 (62.3)
Anticonvulsants	19 (46.3)	19 (47.5)	18 (43.9)	56 (45.9)
Opioids/opiates	9 (22.0)	6 (15.0)	6 (14.6)	21 (17.2)
NSAIDs	5 (12.2)	5 (12.5)	5 (12.2)	15 (12.3)
Tricyclic antidepressants	5 (12.2)	1 (2.5)	9 (22.0)	15 (12.3)
Antidepressants excluding tricyclics	4 (9.8)	4 (10.0)	6 (14.6)	14 (11.5)
Paracetamol/acetaminophen	5 (12.2)	6 (15.0)	3 (7.3)	14 (11.5)
Benzodiazepines	1 (2.4)	0	1 (2.4)	2 (1.6)
Other	9 (22.0)	2 (5.0)	5 (12.2)	16 (13.1)

Abbreviations: ADP, average daily pain; BID, twice daily; DB, double blind; NSAID, nonsteroidal anti-inflammatory drug; SD, standard deviation; SFN, small fibre neuropathy; WDP, worst daily pain.

Table 2: **Baseline clinical characteristics of the DB population.**

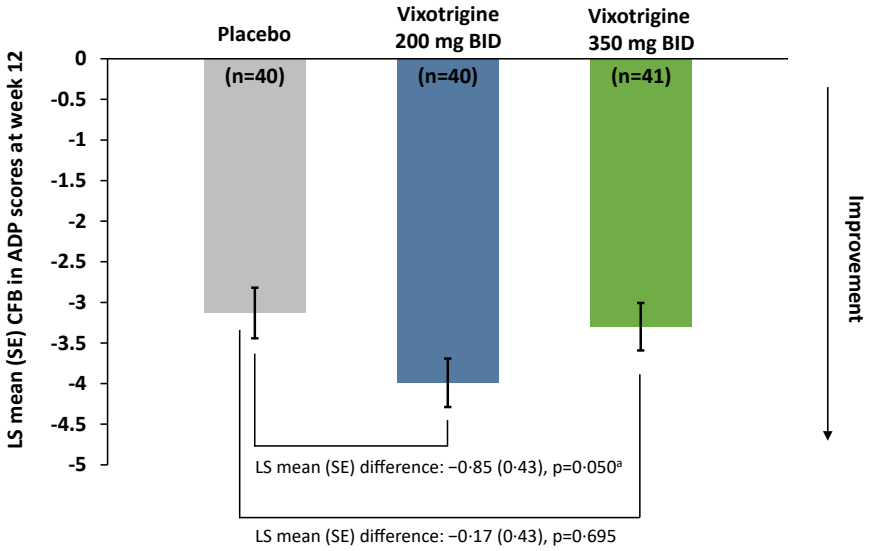

Fig. 2: **Change in ADP Scores From Baseline to DB Week 12.** [a]Statistically significant vs placebo, with a priori two-sided α = 0.10. Numbers evaluable for this analysis: n = 37 (placebo); n = 38 (200 mg BID); n = 41 (350 mg BID). ADP, average daily pain; BID, twice daily; CFB, change from baseline; DB, double blind; LS, least squares; SE, standard error.

vixotrigine, but after 9 weeks, scores in the 350 mg BID dose group were similar to those observed with placebo (Supplemental Fig. S2). The proportion of participants with a ≥30% reduction from baseline in ADP score at DB Week 12 was numerically, but not statistically significantly, greater with vixotrigine 200 mg BID (72.5%; odds ratio [OR], 2.18; 95% CI, 0.79–5.96; p = 0.13) and 350 mg BID (68.3%; OR, 2.20; 95% CI, 0.81–5.99; p = 0.12) vs placebo (52.5%) (Fig. 3). A greater number of participants in both vixotrigine groups experienced a reduction in ADP from baseline to DB Week 12 of at least two points, but compared with the placebo group, ORs were not statistically significant in either the 200 mg BID (OR, 2.15; 95% CI, 0.77–5.97; p = 0.14) or 350 mg BID (OR, 2.33; 95% CI, 0.85–6.43; p = 0.10) groups.

The SFN-aetiology subgroup analysis showed that the mean change in ADP scores from baseline to DB

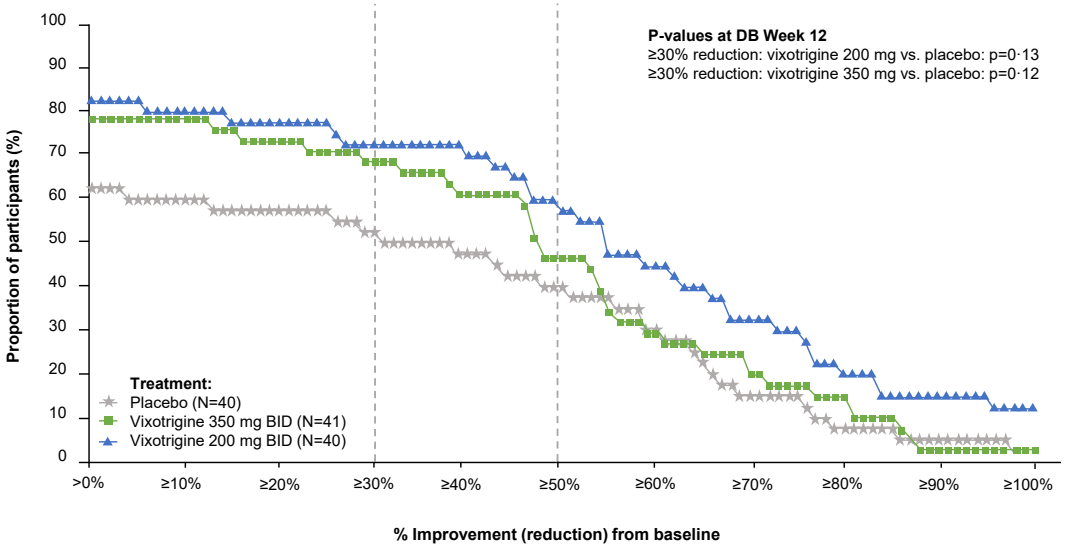

Fig. 3: **Cumulative Percent Improvement of ADP Scores From Baseline Over the DB Period.** ADP, average daily pain; BID, twice daily; DB, double blind.

Week 12 in participants with diabetes (N = 86 evaluable) favoured vixotrigine 200 mg BID, but not 350 mg BID, over placebo (200 mg: LS mean difference, –0.94; 95% CI, –1.85 to –0.03; 350 mg: LS mean difference, –0.25; 95% CI –1.18 to 0.69), while no such effect was observed in those with idiopathic SFN (N = 30 evaluable) in either vixotrigine group vs placebo (200 mg: LS mean difference, 0.13; 95% CI, –1.98 to 2.24; 350 mg: LS mean difference, 0.13, 95% CI, –1.61 to 1.86) (Supplemental Fig. S3).

At DB Week 12, a statistically significant reduction in change from baseline WDP score was observed in the vixotrigine 200 mg BID group vs the placebo group (LS mean difference, –0.93; SE, 0.46; 95% CI, –1.85 to –0.02; p = 0.046) but not in the 350 mg BID group vs the placebo group (LS mean difference, –0.25; SE, 0.46; 95% CI, –1.15 to 0.65; p = 0.58) (Supplemental Fig. S4).

PGIC

A statistically significantly larger proportion of the vixotrigine 350 mg BID group vs the placebo group reported being "improved" or "very much improved" on the PGIC questionnaire (48.8% vs 30.0%; OR, 2.60; 95% CI, 0.97–6.99; p = 0.058) at DB Week 12 (Fig. 4). The proportion of PGIC responders was similar in the vixotrigine 200 mg BID group (37.5%) and the placebo group (30.0%; OR, 1.18; 95% CI, 0.45–3.14; p = 0.74).

Other efficacy outcomes

Over the 12-week DB period, there was no statistically significant reduction (all p > 0.10) in the vixotrigine 200 mg BID group compared with the placebo group (change from baseline in LS mean differences) in sleep interference score (–0.47; 95% CI, –1.30 to 0.36), NPSI total score (–2.9; 95% CI, –13.3 to 7.6), NPSI sum score of burning and pressing (–0.47; 95% CI, –2.79 to 1.84) or mean BPI-SF interference score (0.60; 95% CI, –1.65 to 2.84; number evaluable for vixotrigine 200 mg BID group = 7; number evaluable for placebo = 16). Similarly, there was no statistically significant reduction in the vixotrigine 350 mg BID group compared with the placebo group in sleep interference score (–0.08; 95% CI, –0.89 to 0.74), NPSI total score (1.30; 95% CI, –11.20 to 8.50), NPSI sum score of burning and pressing (0.07; 95% CI, –2.11 to 2.26) or mean BPI-SF interference score (–0.65; 95% CI, –2.52 to 1.22; number evaluable for vixotrigine 350 mg BID group = 16; number evaluable for placebo = 16).

During the DB period, the proportion of participants who took rescue paracetamol/acetaminophen was numerically greater in the placebo group (30.0%) than in the vixotrigine 200 mg BID (22.5%) or 350 mg BID group (17.1%). However, the ORs vs the placebo group were not statistically significant in the vixotrigine 200 mg BID (OR, 0.73; 95% CI, 0.26–2.03; p = 0.55) or 350 mg BID groups (OR, 0.46; 95% CI, 0.16–1.34; p = 0.15).

Safety outcomes

Overall, 41.9% of participants in the OL period experienced at least one AE (Supplemental Table S1). Most participants experienced AEs that were mild (24.2% of participants) or moderate (15.1%) in severity. Severe AEs occurred in 2.6% of participants, and 5.3% of participants withdrew from the study due to an AE in the OL period. Dizziness and headache (9.4% of

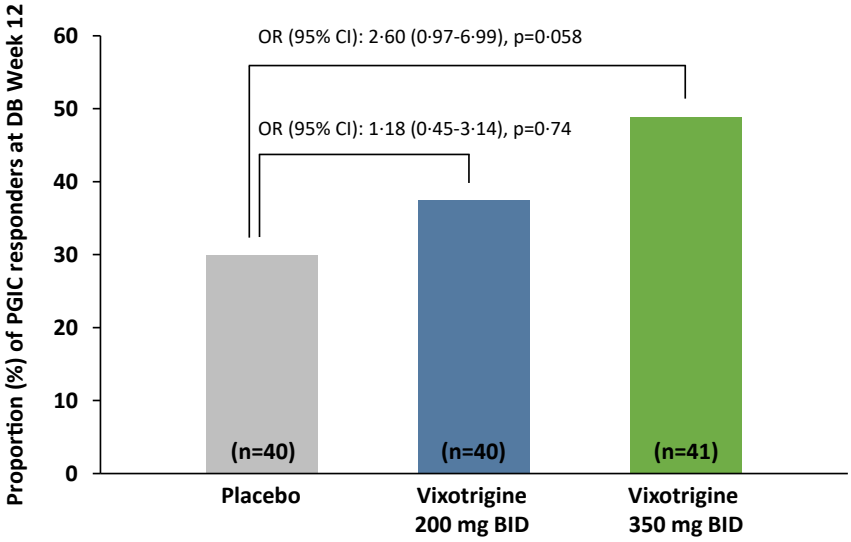

Fig. 4: **Proportion of PGIC Responders at DB Week 12.** BID, twice daily; DB, double blind; OR, odds ratio; PGIC, Patient Global Impression of Change; SFN, small fibre neuropathy.

participants each) were the most common AEs. Only one participant had an SAE, a rash, that was considered related to treatment. No participant died due to an AE during the OL period.

During the 12-week DB period, a greater percentage of placebo-treated participants (61.0%) reported an AE compared with those treated with vixotrigine 200 mg BID (47.5%) or 350 mg BID (43.9%); more placebo-treated participants (7.3%) discontinued study drug due to an AE than those receiving vixotrigine 200 mg BID (5.0%) or 350 mg BID (0%) (Table 3). Most participants in the vixotrigine treatment groups (200 mg BID and 350 mg BID) experienced AEs that were mild (25.0% and 24.4% of participants, respectively) or moderate (17.5% and 19.5%, respectively). The most common AEs (≥5% of vixotrigine-treated participants) in the vixotrigine 200 mg BID and 350 mg BID groups were fall, nasopharyngitis, muscle spasm and urinary tract infection. The three participants who experienced events of fall (two were assessed as mild and one was assessed at moderate in severity) did not report any concurrent dizziness and the events were assessed as not related to vixotrigine by the Investigator. SAEs were reported in four placebo group participants compared with one each in the vixotrigine-treated groups; none were considered treatment related. Three participants (7.3%) in the vixotrigine 350 mg BID group experienced AEs suggestive of the potential for medication misuse (one each reporting amnesia, hypoesthesia, and lethargy), while two participants (4.9%) in the placebo group experienced AEs suggestive of abuse potential (one participant each reported depressed mood and nervousness); no participants in the vixotrigine 200 mg BID group reported an AE suggestive of the potential for medication misuse. One participant with pre-existing cardiovascular abnormalities experienced ventricular arrhythmia leading to cardiac arrest in the placebo group approximately 3 months after the last dose of study treatment in the OL period; the investigator considered the event unrelated to the study treatment. No deaths occurred in the vixotrigine treatment groups.

In the 4-week follow-up period, more participants in the placebo group (26.8%) than in the vixotrigine 200 mg BID (5.0%) or 350 mg BID (12.2%) groups experienced AEs, suggesting a lack of withdrawal potential after abrupt discontinuation of vixotrigine.

No clinically significant trends in laboratory parameters, electrocardiogram or vital signs were found during either the OL or DB period; clinically relevant abnormalities in vital signs were reported infrequently (Supplemental Table S2).

Discussion

The CONVEY trial evaluated the efficacy and safety of vixotrigine, a novel voltage- and use-dependent sodium channel blocker, in participants with idiopathic or diabetes-associated painful SFN. Despite early termination of the

Preferred term, n (%)[a]	Placebo (N = 41)	Vixotrigine 200 mg BID (N = 40)	Vixotrigine 350 mg BID (N = 41)
Any AE	25 (61.0)	19 (47.5)	18 (43.9)
Severity			
Mild	13 (31.7)	10 (25.0)	10 (24.4)
Moderate	8 (19.5)	7 (17.5)	8 (19.5)
Severe	4 (9.8)	2 (5.0)	0
SAE	4 (9.8)	1 (2.5)	1 (2.4)
AE leading to study drug discontinuation	3 (7.3)	2 (5.0)	0
Common AEs (>2.5% in any treatment group)			
Headache	5 (12.2)	1 (2.5)	1 (2.4)
Diarrhoea	4 (9.8)	1 (2.5)	2 (4.9)
Fall	0	0	3 (7.3)
Nasopharyngitis	3 (7.3)	2 (5.0)	2 (4.9)
Nausea	3 (7.3)	0	0
Urinary tract infection	3 (7.3)	2 (5.0)	0
Muscle spasms	1 (2.4)	2 (5.0)	1 (2.4)
Abdominal pain	1 (2.4)	0	2 (4.9)
Arthralgia	1 (2.4)	0	2 (4.9)
Hypertension	2 (4.9)	0	0
Influenza	2 (4.9)	0	0
Pain in extremity	2 (4.9)	0	0
Peripheral swelling	2 (4.9)	0	0

Abbreviations: AE, adverse event; BID, twice daily; DB, double blind; MedDRA, Medical Dictionary for Regulatory Activities; SAE, serious adverse event. [a]MedDRA version 24.0.

Table 3: **Summary of adverse events during DB treatment.**

study, the primary efficacy endpoint was met in participants treated with vixotrigine 200 mg BID. Although the primary outcome was not met in the vixotrigine 350 mg BID group, a numerically greater proportion of participants in both vixotrigine dose groups vs the placebo group achieved a ≥30% or ≥50% decrease in ADP at DB Week 12. Both vixotrigine groups also had a larger proportion of PGIC responders compared with the placebo group; the comparison was statistically significant only for the 350-mg dose group. No statistically significant improvements were recorded for measures of neuropathic pain (NPSI total score and NPSI sum score for burning and pressing) or pain interference (BPI-SF). Although the results of some efficacy assessments of vixotrigine did not reach statistical significance, several had outcomes numerically favouring vixotrigine. Vixotrigine was generally well tolerated.

Diabetes is one of the most common causes of SFN, and neuropathic pain is commonly the first and leading symptom in patients with SFN, having the most relevant patient-reported impact on quality of life.[20,21] However, patients with painful SFN have a significant unmet need due to a lack of specifically approved treatments. Current treatments for painful SFN are those approved for diabetic peripheral neuropathy[22] and are associated with significant safety and tolerability issues: gabapentinoids have adverse effects including sleepiness, dizziness, ataxia, oedema, and tremor; tricyclic antidepressants have anticholinergic effects and duloxetine often induces nausea and abdominal pain; and opioids and opiates may cause addiction.[7] There is a need to develop safe and well tolerated nonopioid analgesics for neuropathic pain. While there have been investigational therapies in clinical studies in neuropathic pain, they mostly had low or moderate response rates owing to their failure to adequately block the underlying causes of neuropathic pain; agents with greater target specificity may result in improved responses.[11,22] The development of voltage-gated sodium channel inhibitors to address neuropathic pain is a prime example of this approach. However, many voltage-gated sodium channel inhibitors are nonselective, have a narrow therapeutic index, and are associated with multiple serious AEs.[23] A Phase 2 study of the $Na_v1.7$ blocker PF-05089771, which does not penetrate the central nervous system, in participants with painful diabetic neuropathy demonstrated a significant but modest treatment effect on NPSI burning scores, but no significant reduction was found in average pain score vs placebo in the last week of the 4-week DB period.[24]

The mechanism of action of vixotrigine is distinct from that of current treatments for painful SFN in that it inhibits a broad spectrum of Na_v subtypes in a voltage- and use-dependent manner, blocks fast-inactivated channels, and slows channel recovery from inactivated states.[13] Unlike current treatments for painful SFN and investigational therapies in neuropathic pain, vixotrigine was found to be well tolerated, with minimal signs of potential for medication misuse and no withdrawal syndrome following an abrupt discontinuation of dosing. AEs were mild in severity, and no deaths related to the study drug occurred. The safety profile in the OL period and lack of withdrawal syndrome following abrupt discontinuation of dosing were consistent with that observed in previous studies of vixotrigine.[14,15] We also observed a significant reduction in ADP scores with vixotrigine compared with placebo, despite having a smaller sample size than planned, suggesting that vixotrigine is indeed effective.

In this study, a statistically significant and clinically meaningful difference (–0.85) in favour of vixotrigine 200 mg BID over placebo was observed for the primary endpoint. The magnitude of this treatment difference, albeit small, is not uncommon when evaluating therapies for neuropathic pain. For example, in nine published opioid studies (of which eight focused on neuropathic pain) that used pain intensity as a primary outcome, the magnitude of effect on 11-point scales ranged from 0.68 to 2.0, with a median of 1.1.[25] The magnitude of a statistically significant group mean difference may bear little relation to a clinically meaningful difference in an individual.[26] One way to address this potential issue is to assess the proportion of responders between treatment arms.[26] In this study, the proportion of participants with a clinically meaningful reduction (≥30%) from baseline in ADP score at DB Week 12 was numerically, but not statistically significantly, greater with vixotrigine 200 mg BID and 350 mg BID than with placebo.

We observed that not all participants in this study responded to vixotrigine. The efficacy of vixotrigine vs placebo may depend on the aetiology of painful SFN; in participants who received vixotrigine 200 mg BID, the LS mean change from baseline to DB Week 12 in ADP was greater in those with diabetes (90.9% of whom had haemoglobin A_{1c} ≥6) than in those with idiopathic SFN (14.3% of whom had haemoglobin A_{1c} ≥6), and the OR vs placebo for a ≥30% reduction in ADP was higher in those with diabetes than in those with idiopathic SFN. Our findings emphasise the need for future studies to assess the profiles of responders to determine the patient population that may best benefit from this treatment. The subgroup findings in this study need to be interpreted with caution considering there were 86 evaluable participants in the diabetes subgroup and only 30 evaluable participants in the idiopathic aetiology subgroup.

This study employed an enriched-enrolment randomised withdrawal trial design, which may be open to criticism regarding the generalisability of the DB data.[19] However, this trial design could require fewer patients and provide a more sensitive option for proof-of-concept studies assessing new treatments for neuropathic pain.[27] The target sample size in this study was calculated using a standardised effect size of 0.5, which falls within the

range of standardised effect sizes (0.25–0.72) reported in other enriched-enrolment randomised withdrawal trials of treatment for pain.[19,27,28]

Several limitations should be considered when interpreting the results of this study. Each treatment arm included fewer participants than planned as the trial was terminated early by the sponsor for business reasons that were not related to safety. To detect a statistically significant and clinically meaningful difference between treatment arms, 62 participants per group were needed (see Methods section), but there were only 40 participants in the vixotrigine 200 mg BID group and 41 each in the placebo and vixotrigine 350 mg BID groups. Furthermore, participants with diabetes comprised the majority of the study population. The majority of participants included in the DB period were White, which may limit generalisability of the study findings to the broader population of patients with SFN. The small sample size and insufficient statistical power resulting from early study termination may also limit the generalisability of the results. The authors are unaware of the NPSI or BPI-SF being validated for longitudinal follow-up. However, these assessments are frequently used in chronic pain studies and have detected significant treatment differences in several studies.[29,30] The trial did not exclude patients with large fibre neuropathy, which may have contributed to heterogeneity of participants and their treatment response in the study. The lack of dose response observed in this study indicates that further studies are warranted to establish the efficacy of vixotrigine. The lack of dose response may be attributable to a variety of factors, including early termination of the study (limiting the total sample size) and that the study was not designed prospectively to assess induction of response by both vixotrigine doses. The enriched enrolment, randomised withdrawal design, in which all participants received 350 mg in the OL run-in period, may have contributed to the inability to discriminate between doses in what was effectively a 'maintenance' phase of the trial. A larger study or one that utilises multiple doses prospectively (e.g., a parallel design) may elucidate further the dose–response relationship. As previously alluded to, future research should assess whether particular patient characteristics (e.g., history of sodium channel blocker use, genetic variants in genes that encode sodium channels, and neuropathic pain phenotype) predict treatment response to vixotrigine.

In conclusion, vixotrigine 200 mg BID was effective in participants with painful SFN, particularly in those with diabetes. Vixotrigine was generally well tolerated in adults with painful SFN. Our findings suggest that vixotrigine is a promising nonopioid treatment option in neuropathic pain. Given the few clinical studies on the treatment of idiopathic or diabetes-associated painful SFN to date, the efficacy, safety and tolerability data from this study support the continued development of vixotrigine as a potential nonopioid treatment for painful SFN.

Contributors

C.G.F., G.L., R.F., and H.N. were involved in the conceptualization of the study. C.G.F., N.A., G.L., K.T.D., A.H., H.N., C.J.M., and M.K. were involved in the investigation process. N.A., K.T.D., and H.F. were involved in the development of methodology. N.A. was involved in study supervision. N.A. and H.F. directly accessed and verified the underlying data reported in the manuscript. R.F. was involved in data curation. R.F., K.T.D., H.F., M.S., and M.K. were involved in the formal analysis and/or interpretation of data. C.G.F., R.H.D., A.H., C.J.M., and M.K. were involved in writing the original draft. C.G.F., N.A., G.L., R.H.D., R.F., K.T.D., H.F., A.H., H.N., M.S., and M.K. reviewed and edited the manuscript. All the authors reviewed the data and participated in writing or reviewing the manuscript, and agreed in the decision to submit the paper for publication.

Data sharing statement

The authors and Biogen are fully supportive of data sharing. Biogen has established processes to share protocols, clinical study reports, study-level data, and de-identified patient-level data. Proposals should be submitted through Vivli (https://vivli.org). To gain access, data requestors will need to sign a data sharing agreement. Data are made available for 1 year on a secure platform. For general inquiries, please contact datasharing@biogen.com. Biogen's data-sharing policies and processes are detailed on the website http://clinicalresearch.biogen.com.

Declaration of interests

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2023.101971.

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