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ARTICLE

A phase I, randomized, double-blind, placebo-controlled, single- and multiple dose escalation study evaluating the safety, pharmacokinetics and pharmacodynamics of VX-128, a highly selective $Na_v1.8$ inhibitor, in healthy adults

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Abstract

Selective inhibition of certain voltage-gated sodium channels (Na_vs), such as $Na_v1.8$, is of primary interest for pharmacological pain research and widely studied as a pharmacological target due to its contribution to repetitive firing, neuronal excitability, and pain chronification. VX-128 is a highly potent and selective $Na_v1.8$ inhibitor that was being developed as a treatment for pain. We evaluated the safety, tolerability, and pharmacokinetics of VX-128 in healthy subjects in a single- and multiple-ascending dose (MAD) first-in-human study. Pharmacodynamics were evaluated in the MAD part using a battery of evoked pain tests. Overall, single doses of VX-128 up to 300 mg were well-tolerated, although adverse effect (AE) incidence was higher in subjects receiving VX-128 (41.7%) compared with placebo (25.0%). After multiple dosing of up to 10 days, skin rash events were observed at all dose levels (up to 100 mg once daily [q.d.]), in five of 26 (19.2%) subjects, including one subject receiving VX-128 (100 mg q.d.) who had a serious AE of angioedema. A trend in pain tolerance were observed for cold pressor- and pressure pain, which was dose-dependent for the latter. VX-128 was rapidly absorbed (median time to maximum plasma concentration between 1 and 2 h) with a half-life of ~80 h at 10 mg q.d., and approximately two-fold accumulation ratio after 10 and 30 mg q.d. Although VX-128, when given in a multiple dose fashion, resulted in early study termination due to tolerability issues, effects were observed on multiple pain tests that may support further investigation of $Na_v1.8$ inhibitors as pain treatments.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

Selective sodium channel (Na_v) inhibitors have been proposed as an alternative to opioids for pain management. Their potential, however, has yet to be confirmed,

as none of the multiple selective Na_v inhibitors that have been investigated for pain management has reached the market.

WHAT QUESTION DID THIS STUDY ADDRESS?

We investigated the safety, tolerability, and initial analgesic effects of VX-128, a novel and highly selective $Na_v1.8$ inhibitor, in healthy volunteers.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

This is the first study to describe clinical data obtained on the highly selective $Na_v1.8$ inhibitor VX-128, and the first to report analgesic effects of this selective Na_v inhibitor in humans. VX-128 administered as a single dose was well-tolerated, but dose-limiting skin rashes occurred after multiple doses resulting in a premature study halt. Although the study had a parallel design and was not necessarily powered to detect pharmacodynamic effects, nociceptive test results suggest that VX-128 leads to dose-dependent analgesic effects.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

Our findings substantiate research that is performed on evaluating selective $Na_v1.8$ inhibitors as treatment for pain, and suggests that the cold pressor- and pressure pain models are suitable to evaluate selective $Na_v1.8$ inhibitors.

INTRODUCTION

Voltage-gated sodium channels (Na_vs)–and inhibition of these channels specifically–have been a main area of interest for pharmacological pain research in the last decades. Currently, Na_v inhibitors are among the most investigated drugs classes in early phases of the trajectory (i.e., up to clinical trial phase IIa)—only surpassed by the opioid, and non-steroidal anti-inflammatory drug classes.[1] Pain relief by Na_v inhibitors has been indicated through blocking of the $Na_v1.3$, $Na_v1.7$, $Na_v1.8$, and $Na_v1.9$ subtypes, whereas blocking of other Na_v subtypes (e.g., $Na_v1.5$, which is predominantly present in cardiac muscle) leads to unwanted (cardiac) side effects. For example, the first-generation nonselective Na_v inhibitor lidocaine is effective in reducing pain and widely used as a topical agent; however, its systemic use is limited given the high risk of cardiac adverse effects (AEs) at doses required for alleviating pain.[2–4]

To reduce side effects associated with broad inhibition of Na_v subtypes while increasing long-term efficacy, pharmacological research shifted to selectively inhibiting pain-facilitating channels, such as $Na_v1.8$: a sensory neuron-specific channel preferentially expressed on the dorsal root ganglion (DRG) and trigeminal ganglion neurons that has been found to play a critical role in pain signaling.[5,6] Specifically, gain-of-function mutations in the $Na_v1.8$ gene—which alter $Na_v1.8$ channel properties in a proexcitatory manner and so increase DRG neuron excitability—have been reported to cause chronic pain in patients with painful small fiber neuropathy.[7–9] Furthermore, $Na_v1.8$ contributes to repetitive firing and neuronal excitability, as $Na_v1.8$ rapidly recovers from inactivation and has a more depolarized voltage-dependency of (in)activation when compared with other Na_vs. Evidence from in vitro studies indicate excitation of $Na_v1.8$ is therefore involved in the development of peripheral sensitization, eventually leading to central sensitization and pain chronification,[6,10] whereas inhibition of $Na_v1.8$ was shown to block this activity leading to analgesia in vitro.[11,12] These findings combined demonstrate the potential of $Na_v1.8$ as a pharmacological target for the treatment of pain, specifically when related to nociceptor hyperexcitability.

Based on the above, VX-128, an orally bioavailable, highly potent, and selective $Na_v1.8$ inhibitor was developed. We evaluated the safety, tolerability, and pharmacokinetics (PKs) of VX-128 in healthy subjects in a single- and multiple-ascending-dose (SAD, MAD) first-in-human (FIH) study. Pharmacodynamics (PDs) were additionally evaluated in the MAD part using an integrated battery of evoked pain tests.[13–16]

MATERIALS AND METHODS

Overall study design

This was a two-part FIH study to evaluate the safety and tolerability, PKs, and PDs of VX-128 in healthy adults. Both parts (A and B) had a randomized, double-blind, placebo-controlled parallel-group design; part A evaluated VX-128 in SADs, and part B in MADs. Dose escalation was

based on a review of the available safety, tolerability, and PK data from (the) preceding cohort(s).

The study was performed at the Centre For Human Drug Research (CHDR, Leiden, The Netherlands), in accordance with the Declaration of Helsinki of 1975, its amendments, and the Guideline for Good Clinical Practice. Approval was received from Medical Review and Ethics Committee Stichting Beoordeling Ethiek Biomedisch Onderzoek (Stichting BEBO, Assen, The Netherlands) before study start. The study was registered under ToetsingOnline number NL63609.056.17 and EudraCT 2017-003557-42.

Design part A–SAD

Four cohorts of eight subjects each were randomized in a 3:1 ratio to receive VX-128 or placebo as oral suspension under fasted conditions on day 1. Subjects were admitted to the clinical research unit (CRU) on day–1, received a single dose of VX-128 or placebo on day 1, and were discharged on day 5. Safety assessments (12-lead and continuous electrocardiograms [ECGs], vital signs, safety laboratory testing, and physical examinations [Pes]) and PK blood sampling were conducted throughout the study. Each subject completed his or her study participation with a safety follow-up visit 7–10 days after study drug dosing.

Design part B–MAD

Three cohorts (B1–B3) of 12 subjects, each randomized in a 5:1 ratio to receive VX-128 or placebo as an oral suspension, were admitted to the CRU on day –1, dosed with VX-128 or placebo on days 1 up to and including day 10, and discharged from the clinic on day 14. Pain thresholds were measured using a panel of evoked pain tests (section Study procedures–pharmacodynamic) on day 1 (all cohorts) and on day 10 (only cohort B2). Safety assessments (12-lead ECG, safety laboratory testing, PE, and vital signs), and the Columbia-Suicide Severity Rating Scale (C-SSRS) were carried out throughout the study and evaluated for any trends or abnormalities. Plasma PKs was sampled throughout the study (section Study procedures-PK). Subjects completed study participation with a safety follow-up visit 7–10 days after the last study drug administration.

Participants

Healthy men (parts A and B) and women of non-childbearing potential (only part A) aged 18–55 years, inclusive, underwent screening procedures prior to enrollment. Key criteria that were evaluated for eligibility were overt healthiness and that subjects had no present or past medical conditions that could put the subject's safety in jeopardy, or influence study outcomes (e.g., history of or current cardiovascular, mental or neurological disorders, [chronic] pain, significant allergies, malignancies, or any conditions affecting drug absorption). Written informed consent was obtained from all study participants prior to any assessment taking place. Subjects were allowed to participate in only one cohort of one study part.

A training session with the pain test battery (section Study procedures–pharmacodynamic) was part of screening procedures, to minimize learning effects, as well as to exclude any subjects indicating to be too sensitive or tolerable to the included tests. The latter was defined as being tolerant to more than 80% of the maximum input intensity for the pressure, electrical, or cold pressor pain test.

Study drug VX-128 and study drug administration procedures

VX-128 is a potent and selective orally bioavailable molecule that targets the $Na_v1.8$ sodium channel (details on the potency and selectivity of VX-128 undisclosed by sponsor request).

In the morning of dosing days, a single dose of VX-128 was administered as an oral suspension with 240 ml of water in the fasted state. A taste-masking agent was provided prior and after dosing. Doses administered in part A were 10, 40, 120, or 300 mg; and in part B were 10, 30, or 100 mg based on the maximum recommended starting dose determined from preclinical toxicity studies performed in monkeys, being the most sensitive species (not published). No dose above 100 mg once daily (q.d.) was tested in part B due to the study being terminated prematurely (section Multiple-ascending dose).

Study procedures–safety

Subject safety was evaluated on an ongoing basis by AE monitoring, clinical laboratory assessments, clinical evaluation of vital signs, standard 12-lead ECGs, and physical examinations.

Study procedures–PKs

Blood plasma was sampled to evaluate VX-128 concentration time profiles. Samples in part A (SAD) were collected predose on day 1 (0 h), and at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 12,

and 24 (day 2), 36 (day 2), 48 (day 3), 72 (day 4), and 96 h (day 5) postdose. Samples in part B (MAD) were collected predose on day 1, (0 h), and at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, and 12 h postdose. Samples were collected before the next administered dose on days 2, 5, 6, 7, 8, and 9. On day 10, samples were collected predose and at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, and 24 (day 11), 36 (day 11), 48 (day 12), 72 (day 13), and 96 h (day 14) after the final dose (that was given on day 10).

Study procedures–PDs

Pain test procedures

A detailed description of all pain test procedures is provided in a related article.[17]

In brief, analgesic effects were measured twice predose, at baseline, and at 1, 2, 4, 7, and 10 h postdose using an evoked pain tests battery in a fixed sequence: electrical stair pain test,[1] pressure pain test, cold pressor pain test, electrical stair pain test,[2] heat pain test on untreated skin, and heat pain test on capsaicin-treated skin. The latter two tests (heat pain on capsaicin and heat pain on untreated skin) were switched predose, ensuring that the predose heat pain test on capsaicin-treated skin was performed 30 min after application of the capsaicin, and whereas keeping the remainder of the test sequence intact (details on the capsaicin application hereunder, section Application of capsaicin 1% cream [MAD part only]).

For all assessments except the heat pain tests, subjects were asked to hold an electronic visual analogue scale slider (eVAS slider), to indicate their current perceived pain intensity. The eVAS ranged from 0–100. The eVAS at 0 was defined as "no pain," eVAS greater than 0 as the pain detection threshold (PDT), and eVAS = 100 as the pain tolerance threshold (PTT): "worst pain tolerable." When PTT was reached, the test automatically stopped, thereby immediately relieving the subject from their pain.

Heat PDTs were determined on the capsaicin-treated skin (on the dominant volar forearm), as well as on normal (nonstimulated) skin (on the nondominant volar forearm), and recorded by the subject pushing a button on the handheld feedback control. The average of a triplicate measurement was used for further analysis of heat PDTs.

Application of capsaicin 1% cream (MAD part only)

Capsaicin 1% cream was used to evoke thermal allodynia, by selectively sensitizing the transient receptor potential cation channel subfamily V member 1 channel.[18,19] Capsaicin 1% cream was applied during screening to confirm subjects were not hyper-responsive to the cream, and was applied for 30 min, starting 60 min prior to study drug administration on a 3 × 3 cm area on the dominant volar arm. The nondominant volar forearm served as a nonstimulated control. Further details of the capsaicin model used may be found in our related article.[17]

Statistical considerations and analysis

Randomization

Both study parts were double-blind; subjects were randomly assigned to treatments. The randomization code was produced by a qualified randomization vendor (Cytel), and approved by a designated unblinded biostatistician who was not part of the study execution team.

Sample size

No formal sample size calculations were performed. Parts A and B enrolled eight and 12 subjects per ascending dose, respectively. This is a typical sample size for an FIH study in healthy subjects.

PK and PD analysis

Safety, demographic, and PK data are presented as mean ± SD unless stated otherwise. PK parameters for VX-128 were determined using standard noncompartmental methods.

For PD results, the baseline value was defined as (the average of) the non-missing pretreatment measurements for all pain tests. Only descriptive statistics were reported. Numbers represent mean (±SD), unless stated otherwise.

RESULTS

Baseline characteristics

In part A, 80 individuals were screened so that 32 male subjects were randomized. Eight subjects received placebo; and six subjects per dose level received VX-128 10, 40, 120, or 300 mg. Subjects not enrolled were mostly excluded based on hypertension, illicit drug use, abnormal clinical chemistry results, or logistical or personal reasons (e.g., change in personal or clinical planning). In Part B, 93 individuals were screened resulting in 31 male subjects that were randomized. Five subjects

received placebo, 10 subjects received VX-128 10 mg q.d., 10 subjects 30 mg q.d., and six subjects received VX-128 100 mg q.d. Primary reasons for exclusion of subjects in part B were reporting to have too high tolerance to pain tasks at screening, hypertension, abnormal clinical chemistry results, illicit drug use, or logistical reasons.

Demographics and other subject characteristics were generally similar in both parts (i.e., SAD and MAD) and in the study cohorts (Table 1). Mean subject age for SAD and MAD was 28.6 (±8.9) years and 32.1 (±10.5) years, respectively. In both study parts, ~87% were White.

Safety and tolerability

Single-ascending dose

VX-128 administered as a single dose was generally well-tolerated up to the highest evaluated dose (300 mg). AEs in subjects who received VX-128 were generally mild; mild AEs occurred in eight subjects (33.3% of those dosed with VX-128). Moderate AEs occurred in two subjects (8.3%). The most common AE was headache and only occurred in subjects who received VX-128 (37.5%; Table 2). AE incidence was higher in subjects receiving VX-128 compared with those receiving placebo ($n = 10$, 41.7% vs. $n = 2$, 25%, respectively). One subject had a minimally prolonged QT interval 4.5 h post-VX-128 300 mg administration (447 to 460 ms), which was mild in severity and resolved without intervention or sequelae. Overall, there were no clinically meaningful changes in laboratory results, vital signs, or ECGs.

Of the subjects that were administered VX-128, three received paracetamol orally post-study drug administration to treat malaise (~36 h post-VX-128 10 mg administration), myalgia (~87 h post-VX-128 40 mg administration), or influenza (~152 h post-VX-128 40 mg administration). These AEs occurred in one individual each.

Multiple-ascending dose

VX-128 administered as multiple doses was generally well-tolerated, with the exception of the occurrence of rash events in 5 of 26 (19%) subjects who received VX-128. The occurrence of rash led to treatment discontinuation in two subjects who received 100 mg q.d. of VX-128. The clinical study was subsequently terminated early due to tolerability issues. AEs in subjects that received VX-128 were generally mild and occurred in 18 subjects (69.2% of those receiving VX-128; Table 3). The most common AEs reported were headache (in $n = 9$ subjects, 34.6%), and somnolence and dizziness ($n = 4$, 15.4% each). AE incidence in the VX-128 group was lower than in the placebo group (VX-128: $n = 18$, 69.2%, placebo: $n = 4$, 80%). There were no clinically meaningful changes in laboratory results, vital signs, ECGs, or evidence of suicidal thoughts based on the C-SSRS.

Five subjects (19.2%), after q.d. dosing of a week or more with VX-128 (all dose levels) had rash-related AEs: rash papular ($n = 2$), toxic skin eruption ($n = 2$), and rash maculo-papular ($n = 1$), and resulted in discontinuation of two subjects receiving the highest tested dose (100 mg) on day 8. Refer to Table S1 for details on these AEs. One subject discontinued the study due to toxic skin eruption, the other due to toxic skin eruption and dyspnea which was followed by a serious AE (SAE) of angioedema on day 9. The SAE resolved the following day; while the subject continued to receive oral cetirizine until 13 days after the last study drug dose. Biopsies of this subject's skin eruptions were taken on days 8 and 9 and both showed superficial dermatitis with eosinophilic granulocytes. Another subject in part B had an episode of hyperventilation and was hospitalized, which was therefore classified as an SAE. This subject, however, was found to have been administered with placebo after randomization code release.

Skin and subcutaneous tissue disorders of two subjects that received 10 mg VX-128 were treated with topical cooling cream on day 12; triamcinolone was additionally administered topically on the skin of to one of these subjects on day 13 to treat eczema. Topical cooling cream was applied to one subject dosed with 100 mg VX-128 q.d. to treat skin and subcutaneous tissue disorders on day 8; whom also received paracetamol for pain around the biopsy site that day, and for headache on day 11. The same subject received intravenous clemastine to treat angioedema on day 9, and oral cetirizine to treat allergic symptoms on days 10–19. A different subject receiving 100 mg VX-128 received intravenous clemastine as treatment for skin and subcutaneous tissue disorders on day 9, and oral paracetamol-caffeine to treat headache on day 11.

PK results

PK parameters of VX-128 in the SAD part were evaluated on day 1, and in the MAD part on day 1 and day 10. Mean plasma concentration-time profiles of VX-128 in plasma after single and multiple oral doses are displayed in Figure S1. PK parameters are found in Table 4. The PKs of VX-128 after multiple oral doses on day 10 were similar to the profile observed after single doses of VX-128 in the SAD part.

As a single dose, VX-128 was rapidly absorbed: peak plasma concentrations (median T_{max}) ranged from 1 to 2 h and

TABLE 1 Subject baseline characteristics, both study parts

	SAD Placebo *N* = 8	SAD 10 mg *N* = 6	SAD 40 mg *N* = 6	SAD 120 mg *N* = 6	SAD 300 mg *N* = 6	MAD Placebo *N* = 5	MAD 10 mg q.d. *N* = 10	MAD 30 mg q.d. *N* = 10	MAD 100 mg q.d. *N* = 6
Sex, *n* (%)									
Male	8 (100)	6 (100)	6 (100)	6 (100)	6 (100)	5 (100)	10 (100)	10 (100)	6 (100)
Age, years									
Mean (SD)	32.1 (11.4)	25.7 (2.3)	31.7 (9.8)	29.8 (10.6)	22.7 (2.4)	30.2 (8.7)	30.7 (9.9)	33.7 (11.7)	33.3 (12.7)
Race, *n*, %									
White	7 (87.5)	5 (83.3)	5 (83.3)	5 (83.3)	6 (100.0)	5 (100.0)	8 (80.0)	9 (90.0)	5 (83.3)
Black or African American	1 (12.5)	0	0	1 (16.7)	0	0	2 (20.0)	0	0
Asian	0	1 (16.7)	0	0	0	0	0	0	1 (16.7)
Other	0	0	1 (16.7)	0	0	0	0	1 (10.0)	0
Weight, kg									
Mean (SD)	73.3 (10.2)	84.8 (16.6)	85.5 (8.8)	77.7 (4.9)	85.3 (14.6)	76.5 (16.5)	77.8 (14.6)	76.7 (13.3)	77.0 (13.4)
Height, cm									
Mean (SD)	180.5 (8.4)	184.3 (9.7)	180.4 (8.0)	179.8 (4.2)	180.5 (9.8)	175.1 (6.4)	178.1 (8.3)	177.7 (5.6)	180.5 (9.0)
BMI, kg/m^2									
Mean (SD)	22.42 (2.34)	24.91 (3.97)	26.43 (3.74)	24.03 (1.26)	26.11 (3.91)	24.98 (5.32)	24.39 (3.27)	24.46 (5.29)	23.65 (3.97)

Abbreviations: BMI, body mass index; MAD, multiple-ascending dose; n, number of subjects; SAD, single-ascending dose; SD, standard deviation.

TABLE 2 AEs in at least two subjects, part A (SAD)

	Placebo[a] *N* = 8 *n* (%)	10 mg *N* = 6 *n* (%)	40 mg *N* = 6 *n* (%)	120 mg *N* = 6 *n* (%)	300 mg *N* = 6 *n* (%)	VX−128 total *N* = 24 *n* (%)	Total *N* = 32 *n* (%)
Number of AEs, total	3	19	4	8	3	34	37
Subjects with any AEs	2 (25.0)	4 (66.7)	2 (33.3)	2 (33.3)	2 (33.3)	10 (41.7)	12 (37.5)
Subjects with AEs by relationship							
Not related	1 (12.5)	0	0	1 (16.7)	0	1 (4.2)	2 (6.3)
Unlikely related	1 (12.5)	0	0	0	1 (16.7)	1 (4.2)	2 (6.3)
Possibly related	0	4 (66.7)	2 (33.3)	1 (16.7)	1 (16.7)	8 (33.3)	8 (25.0)
Related	0	0	0	0	0	0	0
Subjects with AEs by severity							
Mild	2 (25.0)	3 (50.0)	1 (16.7)	2 (33.3)	2 (33.3)	8 (33.3)	10 (31.3)
Moderate	0	1 (16.7)	1 (16.7)	0	0	2 (8.3)	2 (6.3)
Severe	0	0	0	0	0	0	0
Life threatening	0	0	0	0	0	0	0
Subjects with SAEs	0	0	0	0	0	0	0
Subjects with AEs leading to death	0	0	0	0	0	0	0
System organ class[b] preferred term							
Nervous system disorders	0	4 (66.7)	2 (33.3)	1 (16.7)	2 (33.3)	9 (37.5)	9 (28.1)
Headache	0	2 (33.3)	0	1 (16.7)	2 (33.3)	5 (20.8)	5 (15.6)
Tension headache	0	2 (33.3)	2 (33.3)	0	0	4 (16.7)	4 (12.5)
General disorders and administration site conditions	1 (12.5)	3 (50.0)	1 (16.7)	0	0	4 (16.7)	5 (15.6)
Fatigue	0	2 (33.3)	0	0	0	2 (8.3)	2 (6.3)
Musculoskeletal and connective tissue disorder	1 (12.5)	0	1 (16.7)	1 (16.7)	0	2 (8.3)	3 (9.4)
Myalgia	1 (12.5)	0	1 (16.7)	0	0	1 (4.2)	2 (6.3)

Note: When summarizing number of events, a subject with multiple events within a category was counted multiple times in that category. When summarizing number and percentage of subjects, a subject with multiple events within a category was counted only once in that category.

Abbreviations: AE, adverse event; *N*, number of subjects in the analysis set; *n*, number of subjects with data; PT, preferred term; SAD, single-ascending dose; SAE, serious adverse event.

[a]Placebo was the pooled placebo from each cohort.

[b]PTs were provided only for AEs that occurred in greater than two subjects from any treatment group. A subject with multiple events within a standard of care (SOC) or PT was counted only once within the SOC or PT.

increased with higher doses. The highest exposure of VX-128 was observed at the 300 mg dose, which resulted in a mean peak plasma concentration (i.e., C_{max}) of 1020 ng/ml. C_{max} of VX-128 following a single dose appeared to increase dose proportionally over the 10 to 300 mg dose range. The mean exposure (i.e., area under the concentration versus time curve from the time of dosing to the last measurable concentration [AUC_{0-last}]) ranged between 756 and 23,800 ng h/ml; the mean terminal half-life ($t_{1/2}$) ranged between 52 and 71 h—both which also increased with higher doses.

In the MAD part, PK parameters of the highest dose level (100 mg) were not evaluable on day 10 due to premature study termination (section Multiple-ascending dose). The highest exposure was observed in the 100 mg q.d. dose level on day 1, yielding a mean C_{max} of 531 ng/ml and mean $AUC_{0-24\ h}$ of 5030 ng h/ml. Mean $t_{1/2}$ after 10 days of VX-128 10 mg q.d. was ~80 h, and after 30 mg q.d. 87 h. The mean accumulation ratio for $AUC_{0-24\ h}$ of VX-128 on day 10 was 2.3-fold after 10 and 30 mg q.d. dosing.

TABLE 3 AEs in at least twp subjects, part B (MAD)

	Placebo[a] *N* = 5 *n* (%)	10 mg q.d. *N* = 10 *n* (%)	30 mg q.d. *N* = 10 *n* (%)	100 mg q.d. *N* = 6 *n* (%)	VX−128 total *N* = 26 *n* (%)	Total *N* = 31 *n* (%)
Number of AEs, total	21	22	12	40	74	95
Subjects with any AEs	4 (80.0)	6 (60.0)	6 (60.0)	6 (100.0)	18 (69.2)	22 (71.0)
Subjects with AEs by relationship						
Not related	2 (40.0)	1 (10.0)	0	0	1 (3.8)	3 (9.7)
Unlikely related	0	0	5 (50.0)	2 (33.3)	7 (26.9)	7 (22.6)
Possibly related	2 (40.0)	5 (50.0)	1 (10.0)	2 (33.3)	8 (30.8)	10 (32.3)
Related	0	0	0	2 (33.3)	2 (7.7)	2 (6.5)
Subjects with AEs by severity						
Mild	4 (80.0)	6 (60.0)	6 (60.0)	5 (83.3)	17 (65.4)	21 (67.7)
Moderate	0	0	0	1 (16.7)	1 (3.8)	1 (3.2)
Severe	0	0	0	0	0	0
Life threatening	0	0	0	0	0	0
AEs leading to treatment discontinuation	0	0	0	2 (33.3)	2 (7.7)	2 (6.5)
Subjects with SAEs	1 (20.0)	0	0	1 (16.7)	1 (3.8)	2 (6.5)
Subjects with AEs leading to death	0	0	0	0	0	0
System organ class[b] preferred term						
Nervous system disorders	2 (40.0)	5 (50.0)	3 (30.0)	4 (66.7)	12 (46.2)	14 (45.2)
Headache	1 (20.0)	4 (40.0)	2 (20.0)	3 (50.0)	9 (34.6)	10 (32.3)
Somnolence	1 (20.0)	1 (10.0)	1 (10.0)	2 (33.3)	4 (15.4)	5 (16.1)
Dizziness	0	3 (30.0)	0	1 (16.7)	4 (15.4)	4 (12.9)
Gastrointestinal disorders	2 (40.0)	1 (10.0)	1 (10.0)	4 (66.7)	6 (23.1)	8 (25.8)
Nausea	0	1 (10.0)	0	2 (33.3)	3 (11.5)	3 (9.7)
Abdominal discomfort	2 (40.0)	0	0	0	0	2 (6.5)
Injury, poisoning, and procedural complications	1 (20.0)	2 (20.0)	1 (10.0)	3 (50.0)	6 (23.1)	7 (22.6)
Procedural pain	1 (20.0)	1 (10.0)	0	2 (33.3)	3 (11.5)	4 (12.9)
Skin and subcutaneous tissue disorders	1 (20.0)	2 (20.0)	2 (20.0)	2 (33.3)	6 (23.1)	7 (22.6)
Skin rash (maculo-) papular	0	2 (20.0)	1 (10.0)	0	3 (11.5)	3 (9.7)
Toxic skin eruption	0	0	0	2 (33.3)	2 (7.7)	2 (6.5)
General disorders and administration site conditions	1 (20.0)	2 (20.0)	0	3 (50.0)	5 (19.2)	6 (19.4)
Fatigue	0	1 (10.0)	0	1 (16.7)	2 (7.7)	2 (6.5)
Medical device site dermatitis	0	1 (10.0)	0	1 (16.7)	2 (7.7)	2 (6.5)
Musculoskeletal and connective tissue disorders	1 (20.0)	2 (20.0)	1 (10.0)	2 (33.3)	5 (19.2)	6 (19.4)
Back pain	0	2 (20.0)	1 (10.0)	0	3 (11.5)	3 (9.7)
Myalgia	1 (20.0)	0	1 (10.0)	1 (16.7)	2 (7.7)	3 (9.7)

Note: When summarizing number of events, a subject with multiple events within a category was counted multiple times in that category. When summarizing number and percentage of subjects, a subject with multiple events within a category was counted only once in that category.

Abbreviations: AE, adverse event; MAD, multiple-ascending dose; *N*, number of subjects in the analysis set; *n*, number of subjects with data; PT, preferred term; qd, daily; SAE, serious adverse event.

[a]Placebo was the pooled placebo from each cohort.

[b]PTs were provided only for AEs that occurred in greater than or equal to two subjects from any treatment group. A subject with multiple events within a standard of care (SOC) or PT was counted only once within the SOC or PT.

TABLE 4 PK results part A (SAD) and B (MAD)

Parameter	VX-128 Dose						
	SAD 10 mg (*N* = 6)	**SAD 40 mg (*N* = 6)**	**SAD 120 mg (*N* = 6)**	**SAD 300 mg (*N* = 6)**	**MAD 10 mg q.d. (*N* = 10)**	**MAD 30 mg q.d. (*N* = 10)**	**MAD 100 mg q.d. (*N* = 6)**
Day 1							
T_{max}, h[a]	1.00 (0.50, 2.00)	1.50 (1.00, 2.00)	1.75 (1.00, 4.00)	2.00 (1.50, 3.00)	1.00 (1.00, 3.00)	1.00 (1.00, 2.00)	1.50 (1.00, 3.00)
C_{max}, ng/ml	57.4 (47)	189 (29)	545(29)	1020 (21)	67.2 (27)	221 (23)	531 (29)
$AUC_{0–24\ h}$, ng h/ml	756 (33)	3350 (24)	10400 (33)	23800 (24)	522 (15)	1630 (21)	5030 (17)
$t_{1/2}$, h	52.0 (36)	70.5 (36)	60.0 (23)	70.7 (42)	NA	NA	NA
Day 10							
T_{max}, h[a]	NA				1.25 (1.00, 2.10)	1.00 (1.00, 2.02)	ND
C_{max}, ng/ml					95.4 (27)	316 (26)	
$AUC_{0–24\ h}$, ng h/ml					1210 (31)	3870 (27)	
$t_{1/2}$, h					80.8 (41)	87.1 (65)	

Note: Mean (CV%) is presented unless stated otherwise.

Abbreviations: $AUC_{0–24\ h}$, area under the concentration versus time curve from the time of dosing to 24 h; $C_{3\ h}$, concentration determined at 3 h after dosing on day 1; C_{max}, maximum observed plasma concentration; CV%, coefficient of variation; MAD, multiple-ascending dose; *N*, number of subjects in the analysis set; NA, not applicable; NCA, non-compartmental analysis; ND, not determined; PK, pharmacokinetic; q.d., daily; SAD, single-ascending dose; $t_{1/2}$, terminal half-life; T_{max}, time of maximum plasma concentration.

Note for plasma PK: Noncompartmental analysis was not done for cohort at 100 mg q.d. on day 10, as subjects did not complete dosing as planned due to premature study termination.

[a]Median (minimum, maximum) is presented for T_{max}.

PD results (MAD part only)

On day 1, cold pressor PTT and pressure PTT increased at all doses compared with placebo, at each timepoint (i.e., up until 10 h postdose; Figure 1, Table S2). The trend of effect observed on pressure PTT was dose-dependent. On day 10, a similar trend towards an effect of VX-128 30 mg versus placebo was observed for cold pressor PTT and pressure PTT.

No effect of VX-128 was observed on the PDT end points for the cold pressor, electrical stimulation, pressure pain, conditioned pain modulation CPM, capsaicin-induced and thermal pain tests, or on the PTT end points for the electrical stimulation pain test and CPM (Figure 1, Table S2).

DISCUSSION

This study evaluated the safety, tolerability, PK, and PD effects of VX-128 in healthy subjects. VX-128 was rapidly absorbed and its PKs after multiple oral doses on day 10 were similar to that after single oral doses in part A. C_{max} of VX-128 following a single dose appeared to increase dose proportionally. After multiple dosing of up to 10 days, skin rash events were observed, at all dose levels (up to 100 mg q.d.), in five of 26 (19.2%) of subjects, including one subject receiving VX-128 (100 mg q.d.) who had an SAE of angioedema. The clinical study was subsequently terminated early due to tolerability issues. Although only descriptive statistics were performed, the PD results suggest VX-128 may be a potent analgesic, as there were dose-dependent increases in pressure pain and increases in cold pressor pain thresholds.

The occurrence of skin rash observed after multiple dosing may represent an allergic reaction to the administered compound(s) or to one or more of its (unknown) metabolites, however, there is no evident link with $Na_v1.8$ or to Na_v inhibition. No reports are available providing an exact frequency of nonselective Na_v inhibitors inducing skin rash, although certain cases are known. Specifically, mild skin rash has been reported following administration of nonselective Na_v inhibitors phenytoin and mexiletine, and after multiple dosing of selective $Na_v1.7$ inhibitor PF-05089771 at higher dose levels.[20–22] The comparable incidence of skin rash between all evaluated multiple dose levels of VX-128 suggests that the occurrence is not exposure-related. Although the structural characteristics of VX-128 are not publicly available, we were not able to find an evident link between the $Na_v1.8$ class and rash AEs, suggesting it may be a compound-related rather than a class effect.

Although not statistically tested, we observed VX-128-related effects on nociceptive thresholds. No test was

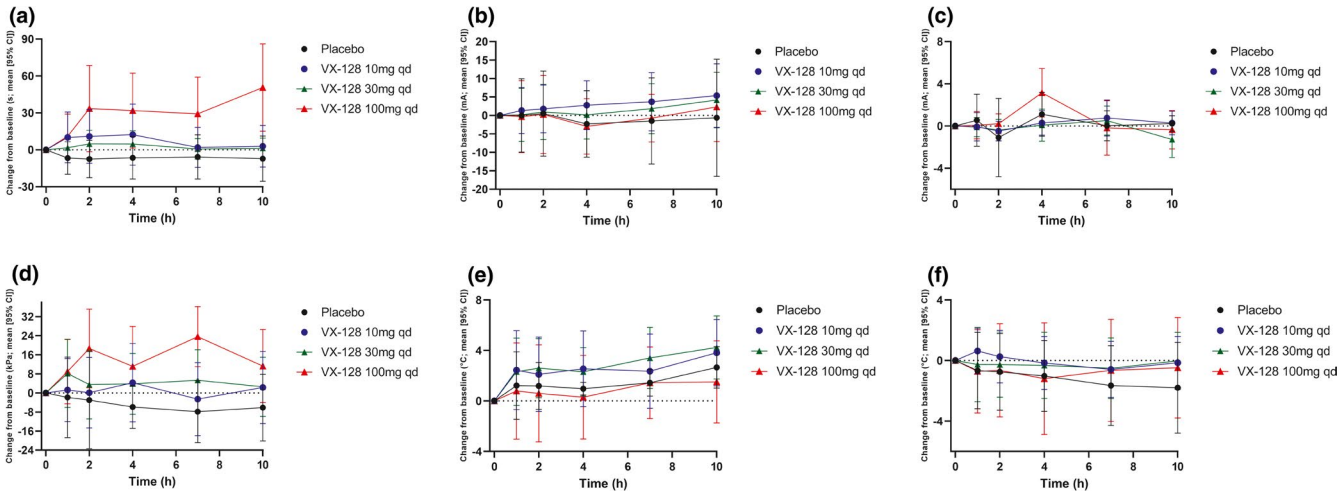

FIGURE 1 Selection of evoked pain test results–change from baseline. Effects of placebo ($n = 5$), VX-128 10 mg q.d. ($n = 10$), VX-128 30 mg q.d. ($n = 10$) and VX-128 100 mg q.d. ($n = 10$) on selected evoked pain test end points determined on day 1 of study part B. Descriptive statistical analysis was performed; data are represented as means with 95% CI. Effects of VX-128 were noted for cold pressor PTT at the highest tested dose (100 mg q.d.) and suggestive dose-dependent effects of VX-128 for pressure pain PTT. (a) Cold pressor PTT. (b) Electrical stimulation PTT. (c) Conditioned pain modulation PTT. (d) Pressure PTT. (e) Capsaicin-induced PDT. (f) Thermal PDT (on control/untreated skin). Abbreviations: ℃, degrees Celsius; CI, confidence interval; h, hour(s); kPa, kilopascal; mA, milliamperes; *n*, sample size; PDT, pain detection threshold; PTT, pain tolerance threshold; s, seconds; SD, standard deviation. (a) Mean (95% CI) cold pressor pain test results: pain tolerance threshold on day 1. (b) Mean (95% CI) electrical stimulation pain test: pain tolerance threshold on day 1. (c) Mean (95% CI) conditioned pain modulation: pain tolerance threshold on day 1. (d) Mean (95% CI) pressure pain test: pain tolerance threshold on day 1. (e) Mean (95% CI) capsaicin-induced pain test: pain detection threshold on day 1. (f) Mean (95% CI) Thermal pain test (on control/untreated skin): pain detection threshold on day 1

primarily targetted a priori; the study was exploratory in nature. In addition, little evidence is available on effects of Na_v inhibitors on experimental pain tests: in studies with registered drugs, such as lidocaine, mexiletine, and lacosamide limited and variable analgesic effects were observed.[23–25] We therefore used a multimodal test battery to evaluate the effects of VX-128 on distinctive types of evoked pain. Increases in PDT and PTT from baseline are indicative of analgesic effects, which we observed in cold pressor PTT and pressure PTT following VX-128 treatment on day 1 (10, 30, and 100 mg q.d.) and day 10 (30 mg q.d.). The analgesic effects of VX-128 were most evident at the 100 mg dose. Effects on the cold pressor and pressure pain models link to the mechanism of action of VX-128. In vitro studies showed that $Na_v1.8$ is able to rapidly recover from inactivation, demonstrating its involvement in repetitive firing, neuronal excitability, and in neuropathic pain conditions where nociceptor hyperexcitability is the underlying mechanism.[6,10,26] The cold pressor task interplays, among others, with $Na_v1.8$ via the transient receptor potential subfamily member 8 channel.[17] We previously reported significant effects on cold pressor PTT of a different $Na_v1.8$ blocker, VX-150, in a similar study in healthy men.[17] Suggestive effects on pressure PTT of VX-128 correlates to results of a preclinical study with $Na_v1.8$-deficient mice—both mechanical and thermal pain were reduced in that model.[27] Interestingly, the $Na_v1.8$ blocker VX-150 affected cold pressor PTT and heat PDT, but not pressure PTT in the previous study. Although this discrepancy is not fully understood, it is of interest to note that VX-150 is a prodrug, distinct from VX-128, with a different level of selectivity for $Na_v1.8$.

Previously, we demonstrated statistically significant analgesic effects with VX-150 on the same pain test battery.[17] That study was performed with an adequately powered two-way crossover design, in contrast to the MAD part of current study, in which analgesic effects were evaluated in parallel and not powered for determination of statistically significant differences. In any proof-of-concept/pharmacology study, but especially in (evoked) pain studies with healthy volunteers where the outcome measure is based on personal perception, crossover designs are deemed superior given the low intersubject variability.[28,29] However, in this study, it may be appreciated that VX-128 seemed to influence pressure PTT in a dose-dependent manner, and cold pressor PTT consistently (Figure 1). In a parallel-designed SAD/MAD trial primarily assessing a drug's safety and tolerability profile, pain test results may display the first signs of analgesic activity based on a dose-dependent increase of pain thresholds; as reported here. Alternatively, a stand-alone crossover pain study, such as the VX-150 study,[17] can statistically assess the analgesic potential with a dose selected for this purpose. Including evoked pain tasks in early phase studies with healthy volunteers thus may serve two distinct goals of equal importance and interest.

Although there is evident interest in developing selective Na_v inhibitors as non-opioid alternative pain treatment, preclinical findings have not often been confirmed in the clinic.[30,31] Both this study and that of VX-150, highlight the importance of proof-of-pharmacology studies in early phase clinical research. Repetitively performing fixed sequences of distinctive pain tests over time provides valuable data on the analgesic profile and the active dose range, as presented here (Figure 1) and previously for various compounds with distinctive mechanisms of action.[14,16,17] Experimental pain studies also support dose selection and patient selection for a subsequent proof-of-concept trial.[1,32] Even when deciding not to proceed with a particular compound, results may help in designing future studies testing drugs with a similar mechanism of action.

The current study has several limitations. The MAD part only included men in order to reduce test variability, and, as suggested in literature, that pain perception of women changes throughout the menstrual phase.[33–35] The conclusions therefore are limited to men, while noting that nociceptive functioning of $Na_v1.8$ is identical in men and women and therefore plausible that VX-128 would induce similar effects in women. As the study focused on safety and tolerability, the design was not powered to detect analgesic effects. The trial was also halted prematurely resulting in an incomplete dataset, therefore, the analgesic effects discussed are not statistically tested and only suggestive. The (second) electrical stair pain task, which followed after the cold pressor pain task, was included to quantify the CPM response. Heat PDTs were evaluated after this second electrical test, to allow for two baseline (i.e., predose) pain test battery sequences to be performed in combination with 30 min of capsaicin application. Therefore, heat PDTs plausibly were influenced through a persistent CPM response. However, we expect that the bias on study results—if present at all—is limited as (1) pain tasks were performed in the same sequence throughout the study and (2) the duration of a CPM response is generally only brief.[36–40]

CONCLUSION

The $Na_v1.8$ inhibitor VX-128, despite having led to skin rash and one subject with angioedema after multiple dosing and thereby halting the reported study for tolerability issues, induced analgesic effects on cold pressor and pressure pain thresholds, warranting further investigation of $Na_v1.8$ inhibitors for the treatment of pain.

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CONFLICT OF INTEREST

The authors declared no competing interests for this work.

AUTHOR CONTRIBUTIONS

H.J.H. wrote the manuscript. H.J.H., P.S.S., and G.J.G. designed the research. H.J.H., E.M.J.vB., P.S.S., and G.J.G. performed the research. H.J.H., E.M.J.vB., P.S.S., and G.J.G. analyzed the results.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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