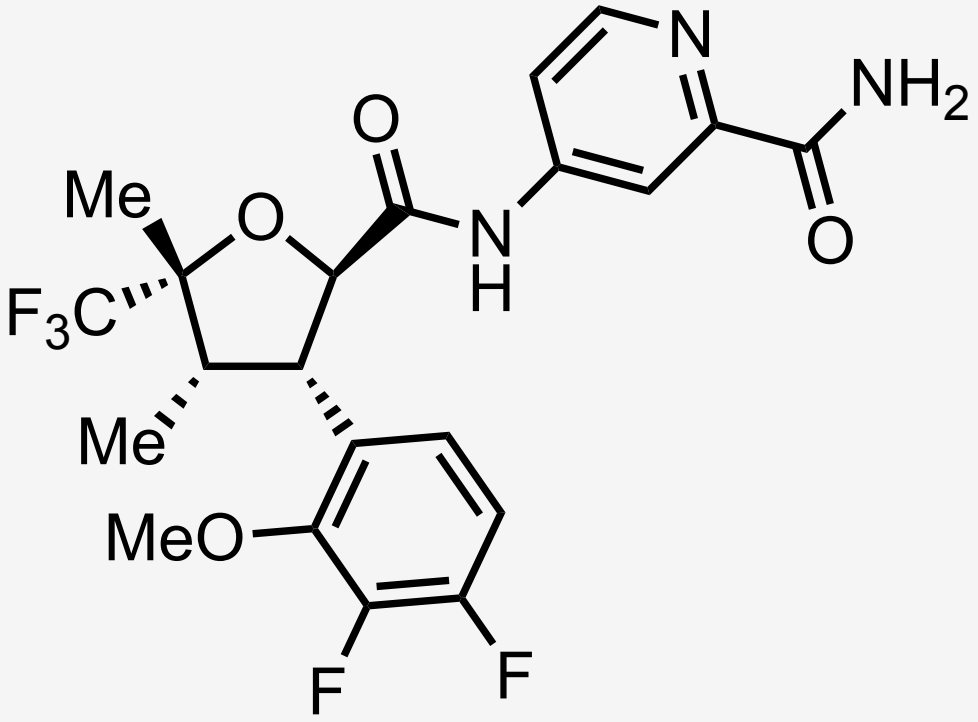
VX-548 (Nav1.8 inhibitor)

Vertex Pharmaceuticals



VX-548

VX-548 is currently in phase 3 trials as a non-opioid treatment for acute pain.

The first trial posted to trials.gov was on July 19, 2021.

Row	Saved	Status	Study Title	Conditions	Interventions	Phase	NCT Number	Study Start	Study Completion
1	☐	Not yet recruiting NEW	Evaluation of the Pharmacokinetics and Safety of VX 548 in Participants With Severe Renal Impairment	• Pain	• Drug: VX-548	Phase 1	NCT05704556	February 2023	September 2023
2	☐	Recruiting	A Single-arm Study to Evaluate Safety and Effectiveness of VX-548 for Acute Pain	• Pain	• Drug: VX-548	Phase 3	NCT05661734	January 9, 2023	March 2024
3	☐	Completed	A Study to Evaluate the Relative Bioavailability and Food Effect of a New Tablet Formulation of VX-548	• Pain	• Drug: VX-548	Phase 1	NCT05455502	July 13, 2022	September 17, 2022
4	☐	Recruiting	Evaluation of Efficacy and Safety of VX-548 for Painful Diabetic Peripheral Neuropathy (DPN)	• Diabetic Peripheral Neuropathy	• Drug: VX-548 • Drug: Pregabalin • Drug: Placebo (matched to VX-548)	Phase 2	NCT05660538	December 20, 2022	April 2024
5	☐	Completed	A Study Evaluating Efficacy and Safety of VX-548 for Acute Pain After a Bunionectomy	• Acute Pain	• Drug: VX-548 • Drug: HB/APAP • Drug: Placebo (matched to VX-548) • Drug: Placebo (matched to HB/APAP)	Phase 2	NCT04977336	July 19, 2021	March 4, 2022
6	☐	Recruiting	A Study to Evaluate the Pharmacokinetic Drug-drug Interactions Between VX-548, Midazolam, and Digoxin	• Pain	• Drug: VX-548 • Drug: Midazolam • Drug: Digoxin	Phase 1	NCT05541471	September 22, 2022	April 2023
7	☐	Recruiting	Evaluation of the Effects of Omeprazole and Rifampin on the Pharmacokinetics of VX-548 in Healthy Participants	• Pain	• Drug: VX-548 • Drug: Omeprazole • Drug: Rifampin	Phase 1	NCT05635110	December 15, 2022	March 2023
8	☐	Recruiting	Evaluation of Efficacy and Safety of VX-548 for Acute Pain After an Abdominoplasty	• Acute Pain	• Drug: VX-548 • Drug: HB/APAP • Drug: Placebo (matched to VX-548) • Drug: Placebo (matched to HB/APAP)	Phase 3	NCT05558410	October 10, 2022	March 2024
9	☐	Recruiting	Evaluation of Efficacy and Safety of VX-548 for Acute Pain After a Bunionectomy	• Acute Pain	• Drug: VX-548 • Drug: HB/APAP • Drug: Placebo (matched to VX-548) • Drug: Placebo (matched to HB/APAP)	Phase 3	NCT05553366	October 3, 2022	March 2024
10	☐	Completed	A Study Evaluating Efficacy and Safety of VX-548 for Acute Pain After an Abdominoplasty	• Acute Pain	• Drug: VX-548 • Drug: HB/APAP • Drug: Placebo (matched to VX-548) • Drug: Placebo (matched to HB/APAP)	Phase 2	NCT05034952	August 30, 2021	December 21, 2021
11	☐	Recruiting	Evaluation of the Pharmacokinetics and Safety of VX-548 in Participants With Mild or Moderate Hepatic Impairment	• Pain	• Drug: VX-548	Phase 1	NCT05560464	October 14, 2022	May 2023

Seven patents were all published by Vertex on Dec. 8, 2022 on the same series of the inhibitors.

These all have the same priority/filing/publish dates.

For these 7 patents, the earliest priority traces back to June 4, 2021.

Earliest registration date for VX-548 on trials registry is July 19, 2021.

2. SOLID DOSAGE FORMS AND DOSING REGIMENS COMPRISI...
WO2022256708A1 • 2022-12-08 • VERTEX PHARMA
Earliest priority: 2021-06-04 · Earliest publication: 2022-12-08
... salt thereof and a tablet containing the solid dispersion for treating pain. Also disclosed herein is Compound 1 or a pharmaceutically acceptable salt thereof for use in a method of treating pain. ...

3. N-(HYDROXYALKYL (HETERO)ARYL) TETRAHYDROFURAN C...
WO2022256622A1 • 2022-12-08 • VERTEX PHARMA
Earliest priority: 2021-06-04 · Earliest publication: 2022-12-08
... compositions in the treatment of various disorders, including pain.

4. HYDROXY AND (HALO)ALKOXY SUBSTITUTED TETRAHYDRO...
WO2022256842A1 • 2022-12-08 • VERTEX PHARMA
Earliest priority: 2021-06-04 · Earliest publication: 2022-12-08
... compositions in the treatment of various disorders, including pain.

5. SUBSTITUTED TETRAHYDROFURAN-2-CARBOXAMIDES AS ...
WO2022256702A1 • 2022-12-08 • VERTEX PHARMA
Earliest priority: 2021-06-04 · Earliest publication: 2022-12-08
... compositions in the treatment of various disorders, including pain.

6. N-(HYDROXYALKYL (HETERO)ARYL) TETRAHYDROFURAN C...
WO2022256679A1 • 2022-12-08 • VERTEX PHARMA
Earliest priority: 2021-06-04 · Earliest publication: 2022-12-08
... compositions in the treatment of various disorders, including pain.

7. SUBSTITUTED TETRAHYDROFURAN ANALOGS AS MODULA...
WO2022256676A1 • 2022-12-08 • VERTEX PHARMA
Earliest priority: 2021-06-04 · Earliest publication: 2022-12-08
... compositions in the treatment of various disorders, including pain.

8. PROCESS FOR THE SYNTHESIS OF SUBSTITUTED TETRAHY...
WO2022256660A1 • 2022-12-08 • VERTEX PHARMA
Earliest priority: 2021-06-04 · Earliest publication: 2022-12-08
Provided in this application is a process for making Compound I (I) and pharmaceutically acceptable salts thereof, useful as inhibitors of sodium channels. Processes for making various intermediate products, and suitable salts thereof, are

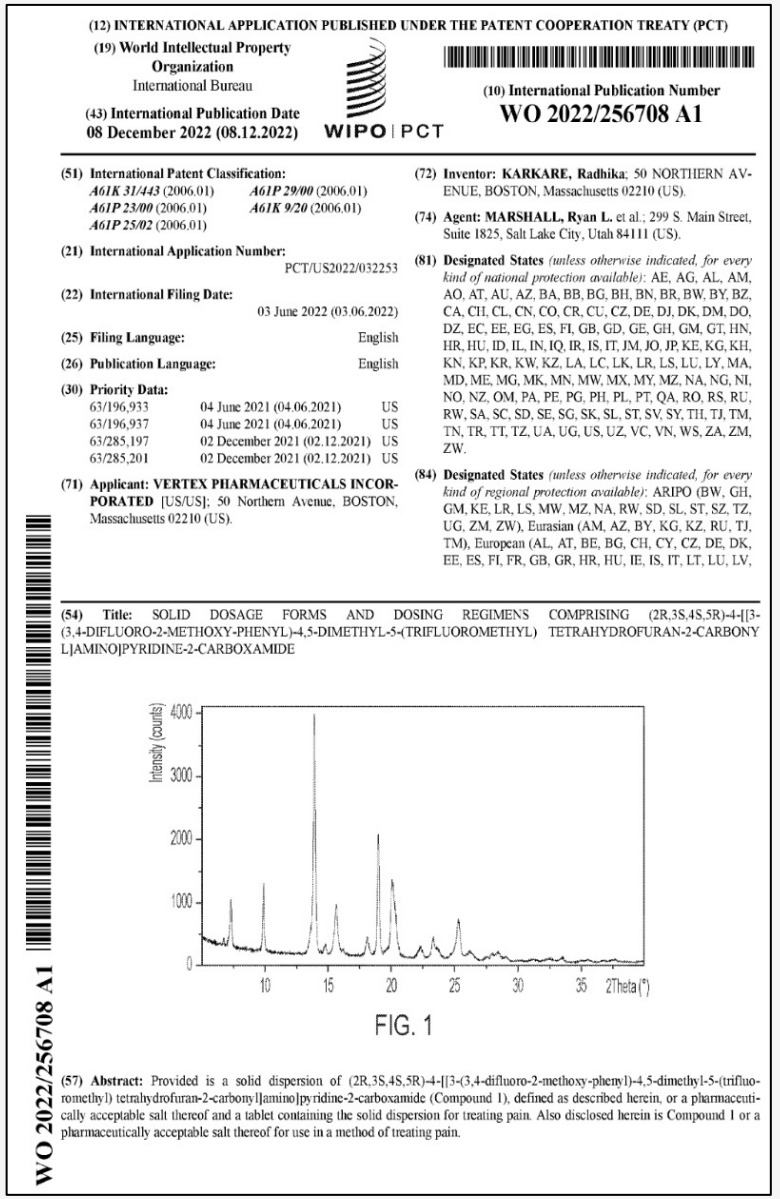
The most revealing of this set of patents relate to:

Solid dosage forms & dosing regimens (WO 2022/256708 A1)

and

Process chemistry (WO 2022/256660 A1)

Both these patents describe the same molecule.



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(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
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WIPO | PCT

(10) International Publication Number
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A61P 23/00 (2006.01) *A61K 9/20* (2006.01)
A61P 25/02 (2006.01)

(21) International Application Number:
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03 June 2022 (03.06.2022)

(25) Filing Language: English

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63/285,197	02 December 2021 (02.12.2021)	US
63/285,201	02 December 2021 (02.12.2021)	US

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IQ, IR, IS, IT, JM, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, WS, ZA, ZM, ZW.

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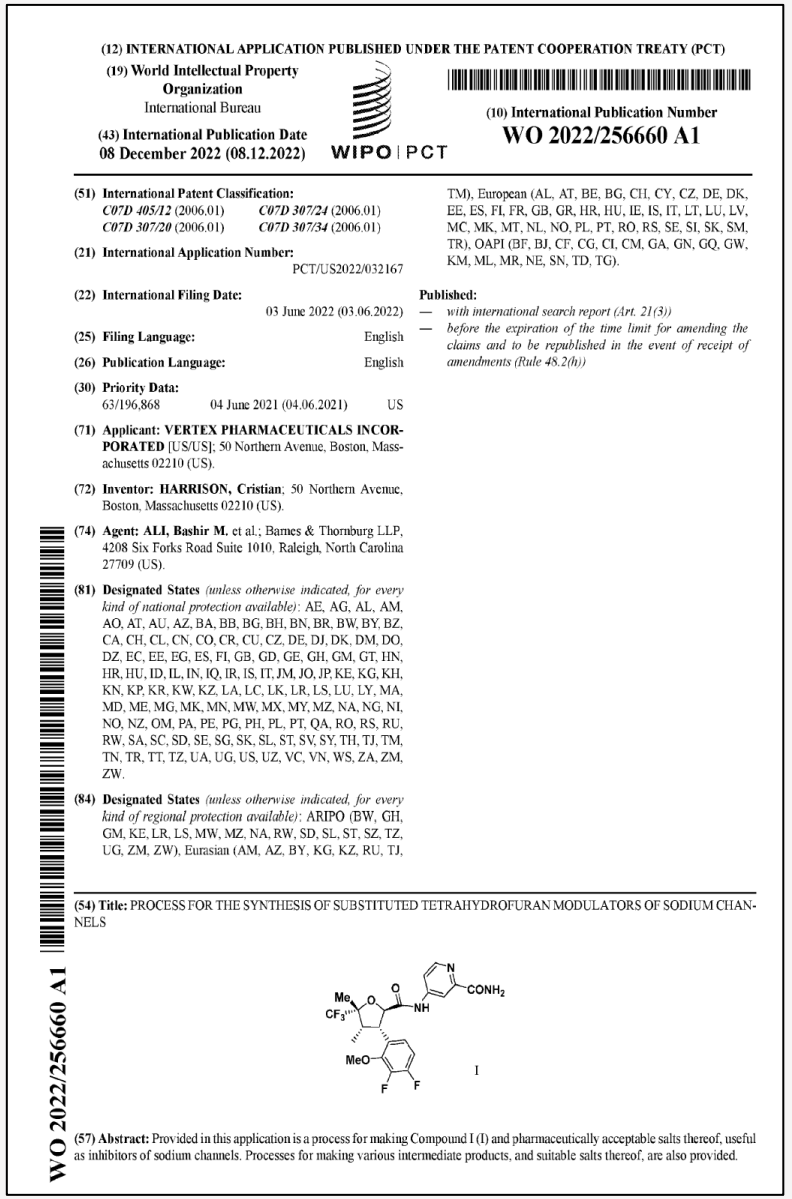
(54) Title: SOLID DOSAGE FORMS AND DOSING REGIMENS COMPRISING (2R,3S,4S,5R)-4-[[3-(3,4-DIFLUORO-2-METHOXY-PHENYL)-4,5-DIMETHYL-5-(TRIFLUOROMETHYL) TETRAHYDROFURAN-2-CARBONYL]AMINO]PYRIDINE-2-CARBOXAMIDE

FIG. 1

(57) Abstract: Provided is a solid dispersion of (2R,3S,4S,5R)-4-[[3-(3,4-difluoro-2-methoxy-phenyl)-4,5-dimethyl-5-(trifluoromethyl) tetrahydrofuran-2-carbonyl]amino]pyridine-2-carboxamide (Compound 1), defined as described herein, or a pharmaceutically acceptable salt thereof and a tablet containing the solid dispersion for treating pain. Also disclosed herein is Compound I or a pharmaceutically acceptable salt thereof for use in a method of treating pain.

WO 2022/256708 A1



(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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08 December 2022 (08.12.2022)

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(51) International Patent Classification:
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C07D 307/20 (2006.01) *C07D 307/34* (2006.01)

(21) International Application Number:
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(22) International Filing Date:
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(71) Applicant: **VERTEX PHARMACEUTICALS INCORPORATED** [US/US]; 50 Northern Avenue, Boston, Massachusetts 02210 (US).

(72) Inventor: **HARRISON, Cristian**; 50 Northern Avenue, Boston, Massachusetts 02210 (US).

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IQ, IR, IS, IT, JM, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, WS, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report (Art. 21(3))*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*

(54) Title: PROCESS FOR THE SYNTHESIS OF SUBSTITUTED TETRAHYDROFURAN MODULATORS OF SODIUM CHANNELS

I

(57) Abstract: Provided in this application is a process for making Compound I (I) and pharmaceutically acceptable salts thereof, useful as inhibitors of sodium channels. Processes for making various intermediate products, and suitable salts thereof, are also provided.

WO 2022/256660 A1

The most revealing of this set of patents relate to:

Solid dosage forms & dosing regimens (WO 2022/256708 A1)

and

Process chemistry (WO 2022/256660 A1)

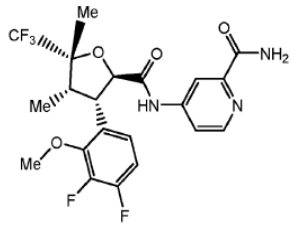
Both these patents describe the same molecule.

Solid dosage forms & dosing patent

CLAIMS

What is claimed is:

1. A method of treating or lessening the severity of pain in a subject, comprising administering to the subject Compound **1**,



(Compound **1**)

or a pharmaceutically acceptable salt thereof, in an amount of about 10 mg to about 300 mg per day, optionally in an amount of about 20 mg to 200 mg per day.

2. The method of claim 1, wherein Compound **1**, or a pharmaceutically acceptable salt thereof, is administered in an amount of about 10 mg to about 300 mg on a first day, optionally in an amount of about 20 mg to about 200 mg on a first day, optionally in an amount of about 20 mg to about 30 mg on a first day, optionally in an amount of about 60 mg to about 90 mg on a first day, optionally in an amount of about 100 mg to about 150 mg on a first day, optionally in an amount of about 5 mg to about 200 mg per day after the first day.

3. The method of any one of claims 1 to 2, wherein Compound **1**, or a pharmaceutically acceptable salt thereof, is administered in two doses per day, or is administered in a first dose and a subsequent dose on the first day, wherein the first dose is larger than the subsequent dose, optionally wherein the subsequent dose is administered 12 hours after the first dose.

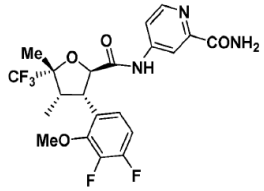
4. The method of claim 3, wherein the first dose is between about 20 mg and about 100 mg optionally the first dose is about 20 mg or optionally wherein the first dose is about 60 mg, or wherein the first dose is about 100 mg.

Process chemistry patent

CLAIMS

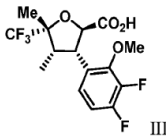
What is claimed is:

1. A method of preparing a compound of formula I, or a salt thereof:



I,

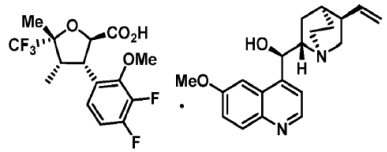
comprising converting a compound of formula III, or a salt thereof:



III

to the compound of formula I.

2. The method of claim 1, wherein said converting the compound of formula III to the compound of formula I comprises preparing a compound of formula IV:



IV.

3. The method of claim 1 or 2, wherein said converting the compound of formula III to the compound of formula I comprises reacting the compound of formula III or the compound of formula IV with a chlorinating agent to afford a compound of formula V:

The BIG CLUE from solid dosage forms & dosing patent...

Example 5: Prophetic

A Study of the Efficacy and Safety of Compound 1 in Subjects with painful diabetic peripheral neuropathy

[00691] A randomized, double-blind, active-controlled, dose-ranging, 4-arm, parallel-design study to evaluate the safety and efficacy of Compound 1 in treating subjects with painful diabetic peripheral neuropathy is conducted. A randomized, double-blind study design is selected to avoid observer bias and reduce symptoms or outcomes arising from the subjects' knowledge of treatment. A pregabalin reference arm assessing a standard-of-care treatment (100 mg tid) is included to establish the ability of the study to successfully observe a treatment effect for Compound 1.

Study Subjects

[00692] Subjects who meet eligibility criteria during Screening Visits 1 and 2 enter a 7 day Run-in Period to establish their baseline Numeric Pain Rating Scale (NPRS) pain score. Male and female patients between the ages of 18 and 75 years (inclusive) with pain that is ≥ 4 on an 11-point NPRS are included in the study. A total of approximately 150 subjects are randomized 2:1:1:2 to 4 treatment arms: Compound 1 (high, mid, or low dose) or pregabalin (reference arm) (Table 3). Randomization is stratified by sex (female and male) and body mass index (≥30 and <30 kg/m^2). To maintain the blind, all subjects receive the same number of pharmaceutical composition once daily (qd) in the morning and the same dose form 3 times per day in a double dummy design. After the Treatment Period, subjects taper off capsule (pregabalin reference or matched placebo) study drug for 7 days (4 days of dosing every 12 hours, then 3 days of dosing qd), and the safety follow up visit occurs an additional 7 (± 2) days later.

Table 12 Treatment Arms

Treatment	Active Dose	Number of Subjects (Planned)
Compound 1 (high dose)	69 mg qd	50
Compound 1 (mid dose)	46 mg qd	25
Compound 1 (low dose)	23 mg qd	25
Pregabalin	100 mg tid	50

qd: once daily; tid: 3 times per day
Note: To maintain the blind, all subjects receive the same number of tablets and the same number of capsules at the same respective frequency (i.e., qd for tablets and tid for capsules during the Treatment Period) in a double-dummy design.

150 patients + 25 on PBO = 175

[00694] Reference Drug: Pregabalin. The reference drug is administered orally in a 100 mg capsule tid. The doses and dose frequency are summarized in Table 4 below.

Table 13 Study Drug

Drug Name	Dosing Form/ Route	Dosage	How Supplied
Compound 1	Tablet/oral	23, 46, or 69 mg qd	Supplied as 23-mg tablet
Placebo	Tablet/oral	0 mg qd	Supplied as tablets
Pregabalin	Capsule/oral	100 mg tid	Supplied as 100-mg capsules
Pregabalin placebo	Capsule/oral	0 mg tid	Supplied as capsules

Trial record **3 of 10** for: vx-548

◂ Previous Study | Return to List | Next Study ▸

Evaluation of Efficacy and Safety of VX-548 for Painful Diabetic Peripheral Neuropathy (DPN)

⚠ The safety and scientific validity of this study is the responsibility of the study sponsor and investigators. Listing a study does not mean it has been evaluated by the U.S. Federal Government. Know the risks and potential benefits of clinical studies and talk to your health care provider before participating. Read our disclaimer for details.

ClinicalTrials.gov Identifier: NCT05660538

Recruitment Status : Recruiting
First Posted : December 21, 2022
Last Update Posted : January 12, 2023
See Contacts and Locations

View this study on Beta.ClinicalTrials.gov

Sponsor:
Vertex Pharmaceuticals Incorporated

Information provided by (Responsible Party):
Vertex Pharmaceuticals Incorporated

Study Details | Tabular View | No Results Posted | Disclaimer | How to Read a Study Record

Study Description Go to

Brief Summary:
The purpose of this study is to evaluate the efficacy and safety of **VX-548** doses in treating Painful DPN.

Condition or disease	Intervention/treatment	Phase
Diabetic Peripheral Neuropathy	Drug: **VX-548** Drug: Pregabalin Drug: Placebo (matched to **VX-548**)	Phase 2

Study Design Go to

Study Type : Interventional (Clinical Trial)
Estimated Enrollment : 175 participants
Allocation: Randomized
Intervention Model: Parallel Assignment
Masking: Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor)
Primary Purpose: Treatment
Official Title: A Phase 2, Randomized, Double-blind, Active-controlled, Dose-ranging, Parallel-design Study of the Efficacy and Safety of **VX-548** in Subjects With Painful Diabetic Peripheral Neuropathy
Estimated Study Start Date : January 2023
Estimated Primary Completion Date : March 2024
Estimated Study Completion Date : April 2024

Same interventions in the same condition

March 31, 2022 press release (NCT04977336)

Press Release Details

<< Back

PDF Version
Mar 31, 2022

Vertex Announces Statistically Significant and Clinically Meaningful Results From Two Phase 2 Proof-of-Concept Studies of VX-548 for the Treatment of Acute Pain

Primary Efficacy Outcomes:

Treatment groups:	**Placebo** n=59	**High-dose VX-548** (100 mg first dose/50 mg every 12 hours) n=60	**Mid-dose VX-548** (60 mg first dose/30 mg every 12 hours) n=62	**Low-dose VX-548** (20 mg first dose/10 mg every 12 hours) n=33	**Hydrocodone bitartrate /acetaminophen reference arm** (5 mg/325 mg every six hours) n=60
Mean SPID48	101.0	137.8	86.9	112.9	115.6
Mean SPID48 difference from placebo	N/A	36.8	-14.1	11.9	14.7
p-value vs. placebo		p = 0.0251	p = 0.3859	p = 0.5379	p = 0.3706

The sig fig match!

274 patients were enrolled
All p-values are based on comparison to placebo

WO 2022/256708 A1 (solid dosage forms & dosing regimens)

Example 4: A Study of the Efficacy and Safety of Compound 1 in Subjects with Pain Following Bunionectomy

[00674] A randomized, double-blind, placebo-controlled, 5-arm, parallel-design study to evaluate the efficacy and safety of Compound 1 on acute surgical pain is conducted. Bunionectomy is a well-established, multi-dose, surgical, acute pain model. A randomized, double-blind study design was used to avoid observer bias and reduce symptoms or outcomes arising from the subjects' knowledge of treatment. An opioid reference arm assessing a standard-of-care treatment (hydrocodone bitartrate (5 mg)/acetaminophen (325 mg) (HB/APAP)) was included to establish the ability of the study to successfully observe a treatment effect for Compound 1.

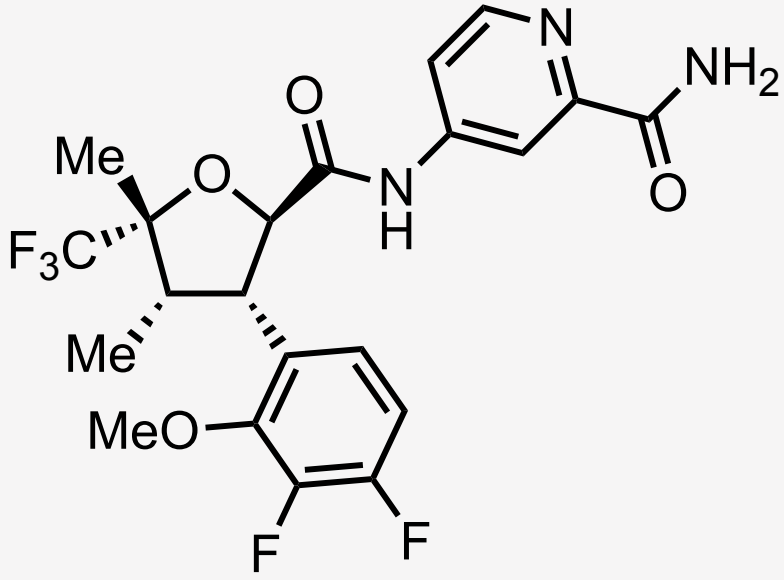
Table 10. Compound 1 Treatment Groups

Treatment	Active Dose	Number of Subjects
Compound 1 (high dose)	100 mg first dose, then 50 mg q12h	60
Compound 1 (mid dose)	60 mg first dose, then 30 mg q12h	62
Compound 1 (low dose)	20 mg first dose, then 10 mg q12h	33
HB/APAP	5 mg/325 mg q6h	60
Placebo		59

Table 11. Bunionectomy Efficacy Results

Treatment Group:	**Placebo** n=59	**High-dose Compound 1** (100 mg first dose/50 mg every 12 hours) n=60	**Mid-dose Compound 1** (60 mg first dose/30 mg every 12 hours) n=62	**Low-dose Compound 1** (20 mg first dose/10 mg every 12 hours) n=33	**Hydrocodone bitartrate /acetaminophen reference arm** (5 mg/325 mg every six hours) n=60
Mean SPID48	101.0	137.8	86.9	112.9	115.6
MeanSPID48 difference from placebo	N/A	36.8	-14.1	11.9	14.7
p-value vs. placebo	N/A	p = 0.0251	p = 0.3859	p = 0.5379	p = 0.3706

Therefore, Compound 1 = VX-548



Questions?

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