

A Review of the Therapeutic Targeting of SCN9A and Nav1.7 for Pain Relief in Current Human Clinical Trials

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Introduction: There is a great need to find alternative treatments for chronic pain which have become a healthcare problem. We discuss current therapeutic targeting Nav1.7.

Areas Covered: Nav1.7 is a sodium ion channel protein that is associated with several human pain genetic syndromes. It has been found that mutations associated with Nav1.7 lead to the loss of the ability to perceive pain in individuals that are otherwise normal. Several therapeutic interventions are presently undergoing preclinical and research using the methodology of damping Nav1.7 expressions as a methodology to decrease the sensation of pain leading to analgesia.

Expert Opinion: It is our strong belief that there is a viable future in the targeting of protein of Nav1.7 for the relief of chronic pain in humans. The review will look at the genomics associated with SCN1A and proteomic of Nav1.7 as a foundation to explain the mechanism of the therapeutic interventions targeting Nav1.7, the human disease that are associated with Nav1.7, and the current development of treatment for chronic pain whether in preclinical or clinical trials targeting Nav1.7 expressions. The development of therapeutic antagonists targeting Nav1.7 could be a viable alternative to the current treatments which have led to the opioid crisis. Therefore, Nav1.7 targeted treatment has a major clinical significance that will have positive consequences as it relates to chronic pain interventions.

Keywords: SCN9A, Nav1.7, chronic pain, opioid crisis

Introduction

Neuronal sodium channels are coding by a family of genes, one of which is called sodium voltage-gated channel alpha subunit 9 (*SCN9A*).¹ This gene encodes for sodium channels that are designed to assist in the transportation of positively charged sodium atoms (Na⁺ ions) into the cell. This action plays a vital role in the generation and the propagation of electrical signals along the neuron.² A study which included 95 individuals was conducted of which from these persons 27 different tissues were examined to determine the SCN9A expression. The determination of SCN9A protein coding gene tissue-specificity was analyzed using RNA-seq. It was found that SCN9A was expressed in all 27 different tissues at variant degree. The highest expression of SCN9A in non-neuronal tissues was in testis, placenta, and colon.^{3–5} *SCN9A* consists of 180,803 nucleotides which encodes a 1988 amino acid Nav1.7 protein.⁶

Nav1.7 is the sodium channel expression protein of the *SCN9A* gene.⁷ The pain signals that are transmitted to the brain are facilitated by Nav1.7 nociceptors preferentially expressed on the neurons that are part of the peripheral nervous system.⁸ The peripheral nervous system (PNS) is connected to the central nervous system (CNS) which consists of the brain and the spinal cord.⁹ Nociceptors, which are part of the PNS, consist of cells that have the ability to detect many different types of sensation including pain, smell, and taste.¹⁰ Neuronal

structures consisting of nociceptors are designed primarily in the transmission of pain signals.¹¹ It is within the cell bodies that the centers of nociceptors are found. Those centers are located within the dorsal root ganglion of the spinal cord.¹² The nerve fibers that extend from those cells' bodies come from all over the human body receiving sensory information from the periphery that will be transmitted to the brain.¹² *SCN9A* which is the gene that encodes for the voltage-gated Nav1.7 sodium channel have a major role in the proper functioning of the nociceptive signaling.¹³ Mutations within *SCN9A* gene have been associated with several diseases including congenital insensitivity to pain,¹⁴ erythromelalgia,¹⁵ paroxysmal extreme pain disorder,¹⁶ and small fiber neuropathy.¹⁷

Health Conditions Related to Genetic Changes

Congenital Insensitivity to Pain

The inability of an individual from birth to have a perception of physician pain is a condition called congenital insensitivity to pain.¹⁸ Those individuals that are suffering from this condition when injured anywhere in and on their body will never feel the pain.¹⁹ Persons who have congenital insensitivity to pain do have their ability to distinguish between temperature differences and between dull and sharp stimuli. Many individuals show injuries such as lip and tongue injuries due to the individuals biting those areas during their first 4 years of life. These patients have many bruises and cuts that go unnoticed. They even have fractures that go undiagnosed, leading to additional health challenges.²⁰ The lack of awareness of pain does lead to bruises, bones that are broken, wounds, and many other health issues will not be checked.²¹ Other notable challenges include children self-biting their lips and their fingers (Klein, CJ et al, 2012). Also, many experience multiple injuries related to burns due to their insensitivity to pain (Klein et al, 2012). The life expectancy of those with congenital insensitivity to pain is severely reduced in comparison to the normal population.²¹ The condition of congenital insensitivity to pain is one that is extremely rare. Only 80 cases have been documented, with approximately 300 cases reported worldwide within the medical literature.²²

This condition can be considered a form of peripheral neuropathy since it affects the peripheral nervous system²³ due to the disconnection of the transmission of touch, small, and pain sensations through the spinal cord to the brain.²⁴ The cause of this disease is the production of an *SCN9A* gene that has undergone a nonsense mutation.²⁵ This leads to the *SCN9A* gene product to produce nonfunctional alpha subunits that cannot be incorporated in the proper Nav1.7 sodium channel configuration. The formation of sodium channels that are needed for the proper propagation of pain sensory information from the peripheral nervous system to the spinal cord towards the brain.⁶ In the absence of Nav1.7 sodium channels, there is an insensitivity to pain that is caused since there is an impairment of pain signal transmission from the periphery through the spinal cord to the brain.⁶ Congenital insensitivity to pain is a genetic disease that follows an autosomal recessive pattern. The parents are not affected by the condition but are carriers of the mutated gene which they both pass on to their child.¹⁸

Erythromelalgia

Another disease condition that can arise from *SCN9A* genetic abnormalities is erythromelalgia. One of the key characteristics of this condition is the consistent pain, swelling throughout the body mostly within the hands and feet, and redness.^{26,27} The condition is episodic and is, in many cases, triggered when there is an increase in body temperature. There are many different reasons that could lead to a spike in temperature including exercise and even entering a warm room.²⁸ A triggering episode can also occur with the ingesting alcohol or with spicy foods.²⁹ Simple activities such as walking and the wearing of shoes can stimulate pain episodes when patients wear warm socks³⁰ and shoes³¹ that are tight. Gloves can cause pain episodes in those with this condition.³¹ These painful episodes prevent individuals suffering with this condition from being able to go to school or to have regular employment.³²

In many cases, the condition will begin to show signs and symptoms during childhood. Those with a milder manifestation of the condition may have their first painful episode later in their life.³³ The hands and feet of those

with erythromelalgia become adults; the disease progresses to the point that their hands and feet are constantly red. The affected area could be extended to cover their entire arms and legs, face and shoulders.²⁶ Like congenital insensitivity to pain, erythromelalgia is a form of peripheral neuropathy.³¹ The prevalence of erythromelalgia is estimated to be approximately 1 to 2 individuals per 100,000 individuals in the general population have either moderate or severe erythromelalgia.³⁴ The mutations of the *SCN9A* gene which causes erythromelalgia codes for the protein Nav1.7 sodium channels which open more easily when stimulated and then stays open longer than a normal Nav1.7. Thus, there is an increase into the Nav1.7 nociceptor of sodium ions. The increase in the flow of the sodium ion allows for the increase in pain signal transmission that leads to erythromelalgia signs and symptoms.³⁵⁻⁴⁰

The reasons for why the pain episodes occur mostly within the hands and feet with this condition is not known.¹ A mutation of the *SCN9A* gene is estimated to be the cause of 15% of the erythromelalgia cases. The other 85% of the cases is thought to be caused due to non-genetic means or may be caused by yet unidentified mutation in one or more genes.⁴¹ Autosomal dominant patterns seem to be the genetic pattern associated with this condition. It takes only one copy of the gene which is altered from an affected parent to lead to the disorder.³¹

Paroxysmal Extreme Pain Disorder

Flushing (warmth), skin redness, and severe pain attacks in different parts of the body represent the characteristic manifestation of paroxysmal extreme pain disorder.⁴² The pain site is associated with the flushing that is found manifested with infants.⁴² Pain attacks can last for hours in some cases, but in this consideration, the pain episode usually lasts for a few seconds to a few minutes.¹⁶ Pain attacks can occur during infancy. The pain is usually triggered during infancy beginning with a movement of the bowel, and the pain is concentrated mostly around the rectum.⁴³ Children with this condition may develop constipation in an attempt to prevent pain attack.⁴⁴ The attacks of pain that occur with these young children may be also associated with seizures,⁴⁵ slowed heartbeat² and apnea.⁴⁶ As the children get older, the pain location seems to change, switching from the lower portion of the body to affecting mostly the face and the head with the pain being focused on the eyes and the jaws.

As a person with paroxysmal extreme pain disorder ages, the location of pain changes. Pain attacks switch from affecting the lower body to affecting the head and face, especially the eyes and jaw.⁴⁶ There are many different triggers to the pain attacks that occur with this condition. This includes changes in temperature,⁴⁴ emotional distress⁴⁷ and spicy food.⁴⁸ Paroxysmal extreme pain, as with the other *SCN9A* genetic mutation, leads to a peripheral neuropathy that affects the peripheral nervous system, affecting the pain sensation transmission to the brain.⁴⁹ The data available associated with the *SCN9A* worldwide prevalence are not accurate. The medical literature using available medical data identified approximately 500 individuals with paroxysmal extreme pain disorder caused by *SCN9A*. This is a very rare disease.^{50,51} Due to the physiological nature of paroxysmal extreme pain disorder, it is usually misdiagnosed or underdiagnosed.¹⁷ It is an autosomal dominant disease where the mutated gene is inherited by both parents.¹⁶

The condition is associated with a missense mutation that occurs with the *SCN9A* gene associated with the Nav1.7 potential-dependent sodium channels potential dependent alpha subunits.¹⁶ The mutational change that occurs prevents the Nav1.7 sodium channels from completely turning off which allows for the flow of sodium into the nociceptor to be abnormal. The increased flow of the sodium ions allows for the pain signals to be exaggerated. The excitation rapid phase extension due to the interference of the inactivation process causing neuronal excitability.¹⁶

Small Fiber Neuropathy

Small fiber neuropathy is one of the other syndromes that is worth mentioning that is associated with a mutation of the *SCN9A* gene.⁵² The disease sequence consists of an attack of severe pain beginning at the feet and the hand.⁵³ Even though the pain attack begins with the hand and feet as the person ages and in the more severe disease areas affected include the arm, ear, face, legs and legs.⁵³ Patients with this condition may experience a whole body pain that is generalized. There are several different presentations of pain for this condition including stabbing and burning pain and itchiness and/or tingling.⁵⁴ The pain, in some individuals, may be more severe with the patient resting or during the night.⁴⁴ For this disease, the signs and symptoms during the teen years.⁵⁵

In some individuals, the lack of being able to feel pain is concentrated in the extremely small area of the skin such as a pin prick.⁵⁶ These individuals have an increased hyperalgesia (increased sensitivity to pain) and suffer from allodynia (pain to stimulation that does not typically cause pain).⁵⁷ Individuals with this condition can have a reduced ability to differentiate between cold and hot. Even so, the pain attacks can be triggered by both cold and warm.⁵⁸

There are several associated problems that are manifested outside the challenges with pain. They include bowel⁵⁴ and urine problems,⁵⁹ palpitation (rapid heartbeats),^{17,23} xerostomia (dry mouth),⁶⁰ keratoconjunctivitis sicca (dry eyes)⁶¹, and (hyperhidrosis) abnormal sweating.⁵⁴ Individuals with this condition suffer from orthostatic hypotension (when blood pressure drops suddenly upon standing) which can cause symptoms such as blurred vision, dizziness, and fainting.^{62,63} Peripheral neuropathy is one of the challenges associated with small fiber neuropathy as with the other conditions that are caused by mutations with SCN9A which prevents the proper transmission to the brain.¹⁷ The incidence of small fiber neuropathy is estimated to be 12 in every 100,000 individuals and the prevalence is 53 patients with every 100,000 individuals without the condition.⁶⁴ Mutations in the genes *SCN9A*, *SCN10A* and *SCN11A* can be the cause of small fiber neuropathy (SFN).⁶⁵ *SCN9A* codes for Nav1.7 which is presented as a type IX α subunit, voltage-gated sodium-channel¹ *SCN10A* codes for Nav1.8 type IX α subunit, voltage-gated sodium-channel. *SCN10A* is encoded for the Nav1.9 subunits alpha voltage-gated sodium channel.⁶⁶

Due to the *SCN9A* genetic mutation the malfunctioning Nav1.7 sodium channels are not completely turned off leading to increased sodium inflow.⁶⁷ The same occurs with mutations of *SCN10A* which lead to the more easily opening of the Nav1.8 sodium channels.⁶⁸ Both genes lead to altered channels that will allow for the abnormal flow of sodium ions in the nociceptors. The individuals with this condition have an increased insensitivity to stimuli that would not normally cause pain.⁶⁹ There is an unknown cause of the degeneration that occurs in small fiber neuropathy. The neuronal degeneration that occurs could be a major factor for the temperature differentiation loss and the loss of pinprick discrimination.⁷⁰ Thirty percent of the cases associated with idiopathic small fiber neuropathy is due to a mutation of *SCN9A*.^{65,71,72} *SCN10A* gene mutations are responsible for about 5% of the cases (drbonnie360.com, 2022).⁷³ Small fiber neuropathy is found to be part of other diseases sequela but will not be highlighted within this review including diabetes mellitus, Fabry's disease, celiac disease, Sjogren's syndrome, sarcoidosis, and human immunodeficiency virus.⁷⁰ Mutations leading to alteration of the altered *SCN9A* gene or *SCN10A* gene are inherited in autosomal dominant manner.²³

Therapeutic Interventions Targeting SCN9A and Nav1.7

Therapeutic interventions targeting *SCN9A* and Nav1.7 review focus on PubMed publications using the terms *SCN9A* and Nav1.7 and "clinical trial" to identify past and current trends of the human clinical therapeutic development. In addition, <http://www.clinicaltrials.gov> terms *SCN9A* and Nav1.7 were queried in order to identify current and past clinical trials. One of the first publications of a clinical trial involving a therapeutic intervention targeting *SCN9A*/Nav1.7 was by.⁷⁴ The disease target was inherited erythromelalgia which is caused by a mutation of the *SCN9A*. The missense mutated gene leads to a non-functioning Nav1.7 sodium channel causing spontaneous pain in those individuals due to neuronal hyperexcitability within those peripheral nervous system neurons.⁷⁴ This condition is opposite to the *SCN9A* mutation that occurs in congenital indifference to pain where there is under stimulation of the peripheral nervous system neuron of the non-functioning Nav1.7 sodium channel.⁷⁴

The human clinical trial Phase I therapy given was XEN402 at a dose of 400mg twice daily topically.⁷⁴ XEN402 is also known as Funapide. It has a molecular formula of C₂₂H₁₄F₃NO₅ with a molecular weight of 429.3.⁷⁵ The name was changed TV-45070 from XEN-402 when it was in-licensed by Teva from Xenon Pharmaceuticals (<https://tinyurl.com/2p8nh2bk> 2022, <https://tinyurl.com/38bu3z27>). TV-45070 completed a Phase II trial (retrieved from clinicaltrials.gov 2022). However, the drug did not make it to Phase III for the treatment of inherited erythromelalgia (clinicaltrials.gov 2022).

The data associated with the results of efficacy and safety of the PF-05089771 therapeutic intervention for primary inherited erythromelalgia was published.⁷⁶ This phase II studies consisted of only five individuals (<http://>

www.clinicaltrials.gov, 2022). This is probably due to the small number of individuals that have this condition and the difficulty of obtaining patients for clinical trials. The small-molecule PF-05089771 selectively blocks the voltage-gated sodium channel Nav1.7 and Nav1.8. The therapy was developed by Pfizer. PF-05089771 completed a phase II clinical trial for the treatment of primary erythromelalgia and wisdom tooth removal.^{77–80} Even though PF-05089771 was used for other indications such as peripheral neuropathy, its efficacy was modest.⁸¹ There was another clinical trial with PF-05089771 looking at its ability to be analgesic to a battery of pain models. Those clinical trials did not show PF-05089771 to be clinically significant analgesic. The drug has not made it into clinical trial phase III for any indications.⁸²

Jones et al (2016)⁸³ published the results of the clinical trial that focused testing of PF-05089771, PF-05150122, PF-05186462 and PF-05241328. These compounds based on their pharmacokinetics were chosen due to their ability to selectively target the Nav1.7 sodium channels. This phase I study found compounds PF-05089771 based on the human clinical trial pharmacokinetic microdose and subsequent modeling, PF-05150122, PF-05186462 and PF-05241328.⁸³ There were 13 different studies that were conducted using the molecules PF-05089771 to test their efficacy of different pain indications. None lead to the therapeutic reaching human clinical trial phase III (<http://www.clinicaltrials.gov> 2022).

Carbamazepine and vixotrigine are used as voltage-dependent Nav1.7 sodium channel blockers that underwent a human clinical phase I study. Both drugs were investigated for their ability to treat peripheral neuropathic pain conditions including the condition of trigeminal neuralgia.⁸⁴ According to [clinicaltrials.gov](http://www.clinicaltrials.gov) (2022), there are presently 21 clinical trials investigating Vixotrigine as a treatment intervention for different pain indications. Of the 21 trials mentioned on [clinicaltrials.gov](http://www.clinicaltrials.gov) (2022), two are recruiting to use vixotrigine as a treatment for trigeminal neuralgia initiated by Convergence Pharmaceuticals. Carbamazepine has been approved by the FDA from treatment of acute manic disorder, bipolar I disorder, epilepsy, and trigeminal neuralgia, but none of the diseases that have been highlighted within this review specifically associated with SCN9A mutation.⁸⁵ There have been other small molecules that have been used to target Nav1.7 expressions for the control of pain including lacosamide.

Lacosamide is an FDA-approved antiepileptic drug which has a mechanism of action of stabilizing the slow-inactivated state of Nav1.1 and Nav1.7 sodium channels found within neurons.⁸⁶ Chronic pain can be associated with painful peripheral neuropathy and is presently a more health burden and a clinical need that is unmet. The Phase 3 study conclusion was mixed for the treatment of small fiber neuropathy due to a gain in function associated with Nav1.7 mutations. The possible determining factors of the variant outcomes are that in some patients, there was a hyperpolarizing shift associated with both of the fast and the slow voltage-dependent inactivation and thereby a use-dependent inhibition enhancement. In contrast, in some patient lacosamide enhanced the fast inactivation selectively.⁸⁷

Conclusion

As one looks at the past and present human clinical trials targeting SCN9A and Nav1.7 a challenge picture emerges. Small molecules seem not to be very effective in the management of pain associated with mutation of the *SCN9A* gene leading to the malfunction of the Nav1.7 sodium channel ([clinicaltrials.gov](http://www.clinicaltrials.gov)). Gene therapy could be a more targeted way of engaging the SCN9A therapeutically.

For example, the CRISPR/Cas9 system has been used successfully in the area of genomic editing and genomic regulation.⁸⁸ The CRISPR/Cas9 system was utilized to cause a down regulation of SCN9A leading to the repression of Nav1.7 within the dorsal root ganglia located within the lumbar region. The studied mouse models using this intervention did show decreased tactile allodynia when the mouse was in a neuropathic state. Also, there was the indication of thermal hyperalgesia that had been reduced, while there was no reduction in the motor function of the mice.⁸⁹ Even with the preliminary results, there may be challenges associated with the use of adenovirus vector to deliver the CRISPR/Cas9 system therapeutics targeted intervention for the treatment of chronic pain via the down regulations of SCN9A.

There are several disadvantages for using an adenovirus vector in the area of gene therapy including immunogenicity,⁹⁰ non-integration,⁹¹ and replication competence.⁹² The AAV vector packaging capacity is small.

The adeno-associated virus (AAV) needs a genomic helper for replication. In addition, manufacturing to produce a stock can be very challenging.⁹³ There is an alternative technology that could be utilized that could target SCN9A.

PepVax, Inc. has a drug delivery system called SMARTmid^(tm) is a DNA plasmid vector drug delivery platform that has been configured to target and down regulated SCN9A gene to be used in the treatment of chronic pain. Preliminary data showed that there was a 50% reduction of the *SCN9A* gene expression which also coincided with the similar decrease in Nav1.7 protein expression in the cell line in vitro (data not shown). Using SMARTmid^(tm) instead of an AAV delivery has many more advantages including increased insert packaging capability, replication competence, and lack of permanent integration. In addition, AAV cannot be used more than once due to its immunogenicity which can make it a limiting platform for gene therapy.⁹⁴

Based on the review of the information (Tables 1–3), a conclusion can be reached that small molecules may not be effective in the treatment of consideration of mutations associated with SCN9A. The best treatment could be the use of DNA plasmid vectors which can be used over and over again without having to be reconfigured. Further

Table 1 List of Publications Found in PubMed That are Associated with Human Clinical Trial Targeting the Pain Gene SCN9A and Its Protein Expression Nav1.7 as of December 2022

Publication Date	Study Title	Conditions	Interventions	Phase	Lead Sponsor
March 2020	Differential effect of lacosamide on Nav1.7 variants from responsive and non-responsive patients with small fiber neuropathy	Small fiber neuropathy	Lacosamide	I	Yale University School of Medicine, New Haven, CT
March 2020	Lack of detection of the analgesic properties of PF-05089771, a selective Na v 1.7 inhibitor, using a battery of pain models in healthy subjects	Battery of human evoked pain models	PF-05089771 alone and PF-05089771 concomitantly with pregabalin as treatment arms with pregabalin, ibuprofen, and placebo as control arms	I	Centre for Human Drug Research, Leiden, The Netherlands
January 2020	Evaluation of the pharmacokinetic interaction between the voltage- and use-dependent Nav1.7 channel blocker vixotrigine and carbamazepine in healthy volunteers	Peripheral neuropathic pain conditions, including trigeminal neuralgia	Vixotrigine Carbamazepine	I	Biogen, Cambridge, Massachusetts, USA
September 2019	Safety, tolerability, and pharmacokinetics of GDC-0276, a novel Na V 1.7 inhibitor, in a first-in-human, single- and multiple-dose study in healthy volunteers	Pain relief	GDC-0276 as powder-in-capsule (PIC) or cyclodextrin solution (CD) single doses	I	Genentech, Inc.
February 2019	Lacosamide in patients with Nav1.7 mutations-related small fiber neuropathy: a randomized controlled trial	Nav1.7 mutations-related small fiber neuropathy	Lacosamide	I	Department of Neurology, School of Mental Health and Neuroscience, Maastricht University Medical Center, Maastricht, The Netherlands
January 2019	Effects of a state- and use-dependent Nav1.7 channel blocker on ambulatory blood pressure: a randomized, controlled crossover study	Neuropathic pain conditions	Vixotrigine	I	Immunovant, Inc., Durham, NC, USA.
December 2018	Challenges recruiting to a proof-of-concept pharmaceutical trial for a rare disease: the trigeminal neuralgia experience	Trigeminal neuralgia	Vixotrigine	Ila	Facial Pain Unit, Division of Diagnostic, Surgical and Medical Sciences, Eastman Dental Hospital, University College London Hospitals NHS Foundation Trust/University College London, London, UK
August 2018	Efficacy of the Nav1.7 blocker PF-05089771 in a randomized, placebo-controlled, double-blind clinical study in subjects with painful diabetic peripheral neuropathy.	Diabetic peripheral neuropathy	PF-05089771	I	Pfizer WRD, Pain and Neuroscience Research Unit, Cambridge, UK

(Continued)

Table 1 (Continued).

Publication Date	Study Title	Conditions	Interventions	Phase	Lead Sponsor
April 2017	Safety and efficacy of a topical sodium channel inhibitor (TV-45070) in patients with postherpetic neuralgia (PHN): a randomized, controlled, proof-of-concept, crossover study, with a subgroup analysis of the Nav1.7 R1150V genotype	Postherpetic neuralgia	Topical sodium channel inhibitor (TV-45070)	I	Xenon Pharmaceuticals Inc.
April 2017	Safety and efficacy of a Nav1.7 selective sodium channel blocker in patients with trigeminal neuralgia: a double-blind, placebo-controlled, randomised withdrawal phase 2a trial	Trigeminal neuralgia	BIB074	Ila	Facial Pain Unit, Division of Diagnostic, Surgical and Medical Sciences, Eastman Dental Hospital, University College London Hospitals NHS Foundation Trust/University College London, London, UK
July 2016	Clinical micro-dose studies to explore the human pharmacokinetics of four selective inhibitors of human Nav1.7 voltage-dependent sodium channels	Chronic pain through inhibition of Nav1.7 channels	Intravenous and oral PK of four compounds (PF-05089771, PF-05150122, PF-05186462 and PF-05241328)	I	Department of Pharmacokinetics, Dynamics and Metabolism, Pfizer Worldwide R&D, Sandwich, Kent, UK
June 2016	Efficacy, safety, and tolerability of lacosamide in patients with gain-of-function Nav1.7 mutation-related small fiber neuropathy: study protocol of a randomized controlled trial-The LENSS study	Gain-of-function Nav1.7 mutation-related small fiber neuropathy	Lacosamide	I	Department of Neurology, School of Mental Health and Neuroscience, Maastricht University Medical Center
April 2016	Pharmacological reversal of a pain phenotype in iPSC-derived sensory neurons and patients with inherited erythromelalgia	Inherited erythromelalgia	PF-05089771	I	Pfizer Neuroscience and Pain Research Unit, The Portway Building, Granta Park, Cambridge CB21 6GS, UK.
October 2011	Treatment of Na(v)1.7-mediated pain in inherited erythromelalgia using a novel sodium channel blocker	Inherited erythromelalgia	XEN402	I	Xenon Pharmaceuticals Inc., Burnaby, British Columbia, Canada

Table 2 The SCN9A is a Gene Which Belongs to a Gene Family That is Involved in the Development of Sodium Channels

Status	Study Title	Conditions	Interventions	Phase	Sponsor/ Collaborators	Locations
Completed Has results	The impact of SCN9A gene polymorphism on individual pain perception in the general population	Pain Surgery			Xianwei Zhang Huazhong University of Science and Technology	Department of Anesthesiology, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology Wuhan, Hubei, China
Recruiting	fMRI-study in patients with small fiber neuropathy	Small fiber neuropathy	Diagnostic test: functional MRI		● Academisch Ziekenhuis Maastricht Harvard University	Maastricht University Medical Center Maastricht, Netherlands
Completed	The impact of the SCN9A gene polymorphism on postoperative pain	● Pain, postoperative Pregnancy	● Procedure: cesarean section Drug: Opioid Tramadol		Tokat Gaziosmanpasa University	Gaziosmanpasa University Medical School Hospital Tokat, Turkey
Completed	Safety and tolerability of lacosamide in patients with gain-of-function Nav1.7 mutations related small fiber neuropathy	Small fiber neuropathy	● Drug: Lacosamide Drug: Placebo	Phase 3	Academisch Ziekenhuis Maastricht	Maastricht University Medical Center Maastricht, Netherlands
Active, not recruiting	Evaluation and risk assessment for persistent postsurgical pain after breast surgery	● Breast cancer ● Chronic pain ● Acute pain Depression, anxiety	● Other: Questionnaires ● Other: Mechanical temporal summation assessment Other: Pain threshold assessment		● KK Women's and Children's Hospital Duke University	● Duke University Medical Center ● Durham, North Carolina, United States KK Women's and Children's Hospital Singapore, Singapore

(Continued)

Table 2 (Continued).

Status	Study Title	Conditions	Interventions	Phase	Sponsor/ Collaborators	Locations
Unknown †	Painful channelopathies study	<ul style="list-style-type: none"> Erythromelalgia Pain insensitivity, congenital Hereditary sensory and autonomic neuropathies Chronic pain 	Other: Observation		<ul style="list-style-type: none"> King's College London University of Oxford Neuroscience Technologies S.L.P 	Nuffield Department of Clinical Neurosciences Oxford, Oxfordshire, United Kingdom

Notes: The positively charged sodium ions are transmitted through these channels generating and transmitting electrical signals. The *SCN9A* gene is involved in the making of the alpha subunit of its protein expression which assembles into the sodium channel called Nav1.7. Nav1.7 is found in key locations within the peripheral nervous system and is involved in the transmission of pain signals. There is presently six human clinical trials studies that are associated with the understanding of *SCN9A* that are listed on <http://www.clinicaltrials.gov> as of December 2022. Of the several studies listed, only one indicated a human clinical phase III study completion. That study looked at small fiber neuropathy treated by the therapeutics lacosamide. Lacosamide is a therapeutic that is used to control seizure, namely partial onset seizures, in both adults and children from the age of one month and older. The results were in conclusion. Therefore, there is a presently no Food and Drug Administration (FDA) approval of a small molecule that can be used to treat chronic pain no matter the source of pain. The small lack of therapeutic studies could indicate the challenges of a moving a small molecule through human clinical trials targeting *SCN9A*. Yet, there is significant evidence that the targeting of the gene has the potential bring to bear hope to millions that suffering from chronic pain. A success treatment targeting *SCN9A* could be the answer to the opioid crisis by presenting a viable therapeutic alternative.

Table 3 Nav1.7 is the Gene Expression of the *SCN9A* in Humans

Status	Study Title	Conditions	Interventions	Phase	Sponsor/Collaborators	Locations
Completed	Safety and Tolerability of Lacosamide in Patients With Gain-of-function Nav1.7 Mutations Related Small Fiber Neuropathy	Small Fiber Neuropathy	<ul style="list-style-type: none"> Drug: Lacosamide Drug: Placebo 	Phase 3	Academisch Ziekenhuis Maastricht	<ul style="list-style-type: none"> Maastricht University Medical Center Maastricht, Netherlands
Completed Has Results	Carbamazepine for Inherited Erythromelalgia Patients With Nav1.7 Mutations	Erythromelalgia	<ul style="list-style-type: none"> Drug: Carbamazepine Drug: Placebo 	Phase 4	VA Connecticut Healthcare System	<ul style="list-style-type: none"> Yale University New Haven, Connecticut, United States VA Connecticut Healthcare System West Haven, Connecticut, United States
Completed	The Impact of the <i>SCN9A</i> Gene Polymorphism on Postoperative Pain	<ul style="list-style-type: none"> Pain, Postoperative Pregnancy 	<ul style="list-style-type: none"> Procedure: cesarean section Drug: Opioid Tramadol 		Tokat Gaziosmanpasa University	<ul style="list-style-type: none"> Gaziosmanpasa University Medical School Hospital Tokat, Turkey
Completed Has Results	The Impact of <i>SCN9A</i> Gene Polymorphism on Individual Pain Perception in the General Population	<ul style="list-style-type: none"> Pain Surgery 			<ul style="list-style-type: none"> Xianwei Zhang Huazhong University of Science and Technology 	<ul style="list-style-type: none"> Department of Anesthesiology, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology Wuhan, Hubei, China
Unknown †	Probing the Role of Sodium Channels in Painful Neuropathies	<ul style="list-style-type: none"> Painful Peripheral Neuropathy Painless Peripheral Neuropathy 			<ul style="list-style-type: none"> Fondazione I.R.C.C.S. Istituto Neurologico Carlo Besta Maastricht University Yale University (and 4 more.) 	
Recruiting	Depolarising Electrical Skin Stimulation in Neuropathic and Postoperative Pain	Neuropathy; Peripheral	Diagnostic Test: neurophysiology		Swiss Paraplegic Centre Nottwil	<ul style="list-style-type: none"> Centre for Pain Medicine Nottwil, Switzerland
Completed Has Results	Use of Topical Lidocaine to Reduce Pain in Patients With Diabetic Neuropathy	Diabetic Peripheral Neuropathy	<ul style="list-style-type: none"> Procedure: Skin biopsy Drug: Lidocaine 5% patches 	Phase 2 Phase 3	<ul style="list-style-type: none"> Albany Medical College Endo Pharmaceuticals 	<ul style="list-style-type: none"> Albany Medical College Albany, New York, United States
Recruiting	fMRI-study in Patients With Small Fiber Neuropathy	Small Fiber Neuropathy	<ul style="list-style-type: none"> Diagnostic Test: functional MRI 		<ul style="list-style-type: none"> Academisch Ziekenhuis Maastricht Harvard University 	Maastricht University Medical Center Maastricht, Netherlands
Completed Has Results	A Clinical Trial To Evaluate PF-05089771 On Its Own And As An Add-On Therapy To Pregabalin (Lyrica) For The Treatment Of Pain Due To Diabetic Peripheral Neuropathy (DPN)	Diabetic Neuropathy, Painful	<ul style="list-style-type: none"> Drug: PF-05089771 150 mg Drug: Matched placebo for PF-05089771 150 mg and pregabalin 300 mg Drug: Pregabalin 300 mg Drug: PF-05089771 150 mg + Pregabalin 300 mg 	Phase 2	Pfizer	<ul style="list-style-type: none"> Clinical Research Consortium Arizona Phoenix, Arizona, United States Arizona Research Center Phoenix, Arizona, United States Neuro-Pain Medical Center Fresno, California, United States (and 29 more.)
Completed	Classical Trigeminal Neuralgia and Sodium Channel Mutations	Trigeminal Neuralgia	Other: Observational		<ul style="list-style-type: none"> Danish Headache Center Maastricht University Medical Center 	
Recruiting	A SAD Study to Evaluate the Safety, Tolerability and PK/PD of iN1011-N17 in Healthy Volunteers	<ul style="list-style-type: none"> Osteoarthritis Pain 	<ul style="list-style-type: none"> Drug: iN1011-N17 Drug: Placebo 	Phase 1	iN Therapeutics Co., Ltd.	Nucleus Network, Melbourne, Victoria, Australia

(Continued)

Table 3 (Continued).

Status	Study Title	Conditions	Interventions	Phase	Sponsor/Collaborators	Locations
Active, not recruiting	Evaluation And Risk Assessment For Persistent Postsurgical Pain After Breast Surgery	<ul style="list-style-type: none"> ● Breast Cancer ● Chronic Pain ● Acute Pain ● Depression, Anxiety 	<ul style="list-style-type: none"> ● Other: Questionnaires ● Other: Mechanical Temporal Summation assessment ● Other: Pain threshold assessment 		<ul style="list-style-type: none"> ● KK Women's and Children's Hospital ● Duke University 	<ul style="list-style-type: none"> ● Duke University Medical Center, Durham, North Carolina, United States ● KK Women's and Children's Hospital, Singapore, Singapore

Notes: This I15 amino acid protein sodium ion channel is found within neurons at high levels. It is specifically nociceptive (pain) neurons located within the dorsal root ganglia, trigeminal ganglia, and the sympathetic ganglia neurons. The table information from the <http://www.clinicaltrials.gov> dated December 18, 2022 indicate the records of 12 human clinical studies targeting Nav1.7. The above clinical trials that have results is again showing the inconclusively of the effectiveness of small molecules in the treatment of pain via the targeting of Nav1.7. Therefore, it is the conclusion based on the human clinical trial that continue pursuit of the treatment of chronic in using the target of Nav1.7 by small molecule has not been successful. Therefore, there is a need for other approaches, such as focus gene therapy, which could target Nav1.7 more succinctly and thereby bring the relief of many patients that are suffering from chronic pain. Both the gene *SCN9A* and its protein expression Nav1.7 are vital targets which could be helpful in the development of alternative opioid treated chronic pain.

studies on the development of treatments targeting the *SCN9A* gene as a substitute for opioid for the treatment of chronic pain should continue.

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