

RESEARCH MONOGRAPH . COMPOUND PROFILE

TRV045

A selective S1P1 receptor agonist developed by Trevena as a non-opioid treatment for diabetic neuropathic pain, distinguished from fingolimod-class functional antagonists by sustained receptor activation without S1P1R desensitization, protein downregulation, or peripheral lymphocyte depletion, and with additional preclinical evidence for anti-seizure activity.

DOCUMENT	KDC-MN-1599
ISSUED	2026-05-20
REVISION	1.0
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COMPOUND CLASS	Selective sphingosine-1-phosphate subtype 1 receptor (S1P1R) agonist with sustained signaling and absence of receptor desensitization or lymphocyte sequestration

ABSTRACT

TRV045 (CAS 2256030-24-5) is a novel, orally bioavailable, selective sphingosine-1-phosphate subtype 1 receptor (S1P1R) agonist under clinical development by Trevena, Inc. as a potential non-opioid treatment for acute and chronic neuropathic pain secondary to diabetic peripheral neuropathy and, through a collaboration with the National Institutes of Health, as a potential treatment for epilepsy. The compound is distinguished from the approved S1P receptor modulator class (fingolimod, siponimod, ozanimod, ponesimod) by a pharmacological mechanism that produces sustained S1P1R agonism without the receptor internalization, functional desensitization, or S1P1R protein downregulation that characterizes fingolimod and related agents. The practical consequence of this mechanistic differentiation is the absence of peripheral lymphocyte sequestration (lymphopenia), the absence of first-dose bradycardia and atrioventricular conduction delay, and the absence of the immunosuppressive liability that defines the approved S1P modulator class and limits its application outside multiple sclerosis. In preclinical models of diabetic peripheral neuropathy and chemotherapy-induced peripheral neuropathy (CIPN), oral TRV045 at 1 to 10 mg/kg produced dose-dependent reversal of mechanical allodynia, cold allodynia, and thermal hyperalgesia. Effects were sustained over 14 days of repeated dosing without evidence of tolerance, receptor desensitization, or S1P1R protein reduction in spinal cord tissue. In contrast, fingolimod in the same CIPN model produced approximately 70 percent reduction in S1P1R functional activity and 30 percent protein reduction. At higher doses (100 mg/kg) in a prevention paradigm, TRV045

reduced both mechanical and cold hypersensitivity 24 hours after the final dose, with cold hypersensitivity reduction persisting seven days after treatment cessation, suggesting potential disease-modifying activity. In epilepsy models conducted through the NIH-supported Epilepsy Therapy Screening Program (ETSP), TRV045 at 30 mg/kg significantly increased time to myoclonic twitch in the pentylenetetrazol seizure threshold test and produced dose-dependent protection in the maximal electroshock seizure test with an ED₅₀ of 18 mg/kg in rats. In human Phase 1 clinical studies, TRV045 has been evaluated in three completed trials comprising a first-in-human single and multiple ascending dose study in 89 healthy volunteers, a target engagement proof-of-concept study using the capsaicin-induced pain (PainCart) model in 25 healthy subjects, and a transcranial magnetic stimulation (TMS) and electroencephalography (EEG) proof-of-concept study in 25 healthy male subjects. The target engagement study demonstrated statistically significant, dose-dependent reduction in capsaicin-induced mechanical allodynia at 150 mg and 300 mg single doses compared to placebo. The TMS/EEG study demonstrated statistically significant increases in alpha, beta, and gamma frequency band power spectral density after four days of 250 mg daily dosing, consistent with central nervous system target engagement and modulation of cortical excitability. Across all three completed Phase 1 studies, TRV045 demonstrated a favorable tolerability profile with no serious adverse events, no drug-related discontinuations, no clinically significant lymphopenia, no bradycardia, no blood pressure changes, and no prolongation of QTcF or PR intervals. The most common adverse events were mild headache, somnolence, dizziness, and fatigue. Trevena is advancing an optimized oral formulation through clinical pharmacokinetic evaluation in preparation for Phase 2

development. TRV045 is an investigational compound not approved by the United States Food and Drug Administration. This monograph reviews the chemistry and identification of TRV045; the S1P1R agonist mechanism of action and its differentiation from functional antagonist S1P modulators; the preclinical pharmacology in neuropathic pain and epilepsy models; the Phase 1 clinical evidence base; sourcing and quality verification; reconstitution and handling; stack interaction considerations; adverse events and safety; and a comparative assessment of five S1P receptor modulators (fingolimod, siponimod, ozanimod, ponesimod, amiselimod) against TRV045 on five competency standards.

1. Compound Identification

1.1 Names, synonyms, and registry identifiers

Development code: TRV045 (Trevena, Inc.). The development code is the canonical identifier in the clinical and preclinical pharmacology literature and is the only identifier under which the compound has been evaluated in human studies and in published research.

Chemical Abstracts Service registry number: 2256030-24-5.

Marketed names: None. TRV045 is an investigational compound not approved for marketing in any jurisdiction as of the date of this monograph.

International Nonproprietary Name: Not yet assigned. The compound is referred to exclusively by its development code in all published literature and regulatory filings.

International Union of Pure and Applied Chemistry name: Not disclosed in the public literature. Trevena has not published the full structural identity of TRV045. Patent filings by Trevena covering families of cycloalkane-containing sphingosine 1-phosphate agonists and benzyl cycloalkyl sphingosine 1-phosphate receptor modulators (United States Patent Nos. 8,329,676 and 7,960,588, among others) describe structural classes from which TRV045 is believed to derive, but the specific structure corresponding to the TRV045 development candidate has not been unambiguously assigned in the public domain [1, 2].

1.2 Structural class and chemistry

TRV045 belongs to the class of synthetic small-molecule sphingosine-1-phosphate receptor modulators that are selective for the S1P receptor subtype 1 (S1P1R, also designated S1PR1 or EDG-1). The compound is reported to be a member of a proprietary structural series identified through Trevena's biased ligand discovery platform, which has been applied to G protein-coupled receptor targets including opioid receptors (oliceridine/OLINVYK) and S1P receptors [3]. The structural class is described in patent literature as cycloalkane-containing sphingosine 1-phosphate agonists, suggesting a non-amino-acid, non-phosphorylated scaffold that does not

require in vivo phosphorylation for activity (unlike fingolimod, which requires phosphorylation by sphingosine kinase 2 to generate the active metabolite fingolimod-phosphate) [1, 2].

Molecular formula: Not publicly disclosed.

Molecular weight: Not publicly disclosed. Research-grade material is available from MedChemExpress under CAS 2256030-24-5, suggesting sufficient structural characterization for commercial synthesis [4].

Physical properties: Not publicly characterized beyond what is inferred from formulation development (oral capsule and optimized oral formulation under clinical evaluation).

Stereochemistry: Not publicly disclosed.

1.3 Synthesis

The synthesis of TRV045 has not been described in the peer-reviewed literature. The compound is produced by Trevena through proprietary synthetic routes. Patent literature covering the broader structural class describes multi-step synthetic sequences involving cycloalkane ring construction, functional group elaboration, and coupling to the sphingosine-mimetic pharmacophore [1, 2]. The compound is available as a research-grade preparation from specialty chemical suppliers (MedChemExpress, CAS 2256030-24-5) [4]. Investigators acquiring research-grade TRV045 should confirm compound identity and purity through independent analytical methods on every lot, as the full structural identity has not been unambiguously disclosed in the public domain.

2. Abstract

TRV045 is a selective, orally bioavailable agonist of the sphingosine-1-phosphate receptor subtype 1 (S1P1R) under clinical development by Trevena, Inc. for the treatment of neuropathic pain secondary to diabetic peripheral neuropathy and for the potential treatment of epilepsy [3, 5]. The compound is mechanistically distinguished from the approved S1P receptor modulators (fingolimod, siponimod, ozanimod, ponesimod) by a sustained agonist signaling profile that does not produce S1P1R internalization, functional desensitization, or receptor protein downregulation [6, 7]. This pharmacological differentiation translates to the absence of the peripheral lymphocyte sequestration, first-dose bradycardia, and immunosuppressive liability that define the fingolimod-class compounds and that have restricted their clinical application to autoimmune indications, principally multiple sclerosis.

The principal preclinical pharmacology of TRV045 comprises dose-dependent reversal of neuropathic pain signs (mechanical allodynia, cold allodynia, thermal hyperalgesia) in rodent models of diabetic peripheral neuropathy and chemotherapy-induced peripheral neuropathy at oral doses of 1 to 10 mg/kg, with sustained efficacy over 14 days of repeated dosing and no evidence of tolerance [6, 7, 8]. In epilepsy models conducted through the NIH-supported Epilepsy Therapy Screening Program, TRV045 demonstrated statistically significant anti-seizure activity in the maximal electroshock seizure test (ED₅₀ 18 mg/kg in rats) and in the pentylenetetrazol seizure threshold test (30 mg/kg) [7].

Three completed Phase 1 clinical studies in healthy volunteers have established the safety, tolerability, and pharmacokinetic profile of TRV045 at single doses up to 300 mg and multiple doses of 250 mg daily for four days [9, 10, 11]. The target engagement proof-of-concept study demonstrated statistically significant, dose-dependent reduction in capsaicin-induced mechanical allodynia at 150 mg and 300 mg, providing the first human evidence of analgesic activity [10]. The TMS/EEG proof-of-concept study demonstrated statistically significant modulation of cortical excitability, with increases in alpha, beta, and gamma frequency band power after four days of dosing, consistent with central nervous system S1P1R target engagement [11, 12]. Across all completed studies, TRV045 produced no serious adverse

events, no drug-related discontinuations, no clinically significant lymphopenia, no cardiovascular signal (bradycardia, blood pressure change, QTcF prolongation), and no ophthalmologic findings [9, 10, 11].

Diabetic peripheral neuropathy affects more than 5 million individuals in the United States and is inadequately managed by current first-line therapies (pregabalin, duloxetine, gabapentin), which provide incomplete pain relief in the majority of patients and produce dose-limiting central nervous system and gastrointestinal adverse effects [13, 14]. TRV045 represents a mechanistically novel, non-opioid approach to neuropathic pain that operates through a pathway distinct from voltage-gated calcium channel modulation (pregabalin, gabapentin) and serotonin-norepinephrine reuptake inhibition (duloxetine). The compound is in preparation for Phase 2 clinical development with an optimized oral formulation [15].

3. Discovery and Development History

3.1 Origin

TRV045 was identified through Trevena's biased ligand discovery platform, a computational and empirical screening approach originally developed for the identification of functionally selective opioid receptor ligands and subsequently extended to other G protein-coupled receptor targets [3]. Trevena's S1P receptor program sought to identify compounds that would activate S1P1R signaling pathways relevant to analgesia and neuroprotection while avoiding the receptor internalization and functional desensitization pathways responsible for lymphocyte sequestration and cardiovascular first-dose effects. TRV045 emerged from this effort as a selective S1P1R agonist with a pharmacological profile characterized by sustained receptor activation, absence of S1P1R protein downregulation, and absence of lymphopenia at or above pharmacologically active doses in preclinical models [5, 6].

3.2 IND filing and Phase 1 initiation

Trevena announced the advancement of TRV045 into clinical development in December 2021, following submission of an Investigational New Drug (IND) application to the United States Food and Drug Administration for the indication of acute and chronic neuropathic pain secondary to diabetic peripheral neuropathy [5]. The FDA notified Trevena that the Phase 1 study could proceed, and enrollment in the first-in-human study began in the first quarter of 2022.

3.3 Phase 1 first-in-human study

The first-in-human (FIH) study was a three-part randomized, double-blind, placebo-controlled study in healthy volunteers [5, 9]. Part 1 comprised single ascending doses across up to six cohorts. Part 2 evaluated the food effect in one cohort. Part 3 comprised multiple ascending doses across up to three cohorts. The study enrolled 89 subjects. The primary objectives were safety, tolerability, pharmacokinetics, and evaluation of lymphocyte counts, hemodynamic function, and

QTcF interval. Headache was the most common drug-related adverse event, reported in 4 of 89 subjects. No lymphopenia, bradycardia, blood pressure changes, or QTcF prolongation were observed [9, 10].

3.4 Proof-of-concept studies

Two proof-of-concept Phase 1 studies were initiated in 2023 to evaluate S1P1R mechanism of action and central nervous system target engagement [10, 11]. The target engagement study (PainCart model) enrolled 25 healthy subjects in a randomized, double-blind, placebo-controlled, single-dose, four-way crossover design evaluating 50 mg, 150 mg, and 300 mg of TRV045. The TMS/EEG study enrolled 25 healthy male subjects in a randomized, double-blind, placebo-controlled, multiple-dose, two-way crossover design evaluating 250 mg daily for four consecutive days. Both studies were conducted outside the United States. Preliminary results were reported in September 2023, topline safety and tolerability data in October 2023, and detailed pharmacodynamic findings at the American College of Neuropsychopharmacology (ACNP) 62nd Annual Meeting in December 2023 [10, 11, 16].

3.5 NIH epilepsy collaboration

Trevena established a research collaboration with the National Institutes of Health to evaluate TRV045 in the Epilepsy Therapy Screening Program (ETSP), a standardized preclinical screening platform for novel anti-seizure and antiepileptogenic compounds [7, 17]. TRV045 was evaluated in the pentylenetetrazol seizure threshold test, the maximal electroshock seizure test, and an epileptogenesis prevention model. Results were presented at the American Society for Pharmacology and Experimental Therapeutics (ASPET) annual meeting in May 2024 [7].

3.6 Formulation optimization and current status

Following the completion of the three Phase 1 studies, Trevena initiated development of an optimized oral formulation of TRV045, with a clinical pharmacokinetic study of the new formulation reported as ongoing in the first quarter of 2024 [15]. Reproductive and sub-chronic toxicology studies to support Phase 2 development were reported as concurrent. As of the most recent public disclosure, TRV045 is in preparation for Phase 2 clinical development. The compound is not approved by the FDA or by any other regulatory authority.

4. Mechanism of Action

TRV045 is a selective agonist of the sphingosine-1-phosphate receptor subtype 1 (S1P1R), a G protein-coupled receptor (GPCR) of the lysophospholipid receptor family that signals predominantly through the Gi/o heterotrimeric G protein pathway [3, 5, 6]. The compound is mechanistically differentiated from the approved S1P receptor modulator class by the nature and consequences of its receptor interaction, which produces sustained agonist signaling without the receptor internalization, desensitization, or protein degradation that characterizes fingolimod and related functional antagonists.

4.1 S1P1R signaling in the nervous system

The S1P1 receptor is expressed at high density on neurons and astrocytes throughout the central nervous system, on dorsal root ganglion sensory neurons, and on spinal cord dorsal horn neurons [18, 19]. In the nervous system, S1P1R signaling modulates neurotransmission, membrane excitability, astrocyte activation, neuroinflammatory cytokine release, and myelination. The receptor couples to Gi/o proteins, producing inhibition of adenylyl cyclase, activation of phosphoinositide 3-kinase (PI3K) and Akt, activation of extracellular signal-regulated kinase (ERK1/2), and modulation of ion channel conductance [18].

In the context of neuropathic pain, S1P1R signaling in astrocytes has been identified as a contributor to the maintenance of central sensitization. The Chen et al. (2019) study in *Proceedings of the National Academy of Sciences* demonstrated that S1P generated in the dorsal horn following nerve injury activates S1P1R on astrocytes, promoting astrocyte proliferation, glial fibrillary acidic protein upregulation, and proinflammatory cytokine release (interleukin-1 beta, tumor necrosis factor alpha, interleukin-6) that sustains nociceptive sensitization [19]. This finding established a paradox in the field: S1P1R activation in astrocytes was identified as pro-nociceptive, yet S1P1R agonism by TRV045 produced analgesia.

4.2 Sustained agonism versus functional antagonism

The resolution of this apparent paradox lies in the distinction between sustained agonism and functional antagonism [6, 7, 20]. Fingolimod (FTY720-phosphate), the prototypical S1P receptor modulator, produces initial S1P1R agonism upon binding but rapidly triggers receptor internalization, ubiquitination, and proteasomal degradation. The net pharmacological effect of chronic fingolimod exposure is therefore functional antagonism: loss of S1P1R surface expression and signaling capacity. It is this functional antagonism that produces lymphocyte sequestration in lymph nodes (the therapeutic mechanism in multiple sclerosis) and that was initially proposed as the analgesic mechanism in neuropathic pain [19, 20].

TRV045, in contrast, produces sustained S1P1R agonism without triggering receptor desensitization or protein downregulation [6, 7]. In the chemotherapy-induced peripheral neuropathy (CIPN) mouse model, direct comparison of TRV045 and fingolimod after 14 days of repeated dosing demonstrated that fingolimod produced approximately 70 percent reduction in S1P1R functional activity and approximately 30 percent reduction in S1P1R protein in spinal cord tissue, whereas TRV045 produced no evidence of receptor desensitization or protein reduction [7]. The analgesic efficacy of TRV045 was maintained throughout the 14-day dosing period, whereas fingolimod's analgesic effect was observed acutely but was accompanied by receptor downregulation.

This mechanistic distinction has two major implications. First, the analgesic activity of TRV045 may operate through a sustained agonist signaling pathway (potentially involving Gi/o-mediated inhibition of neuronal excitability, modulation of astrocyte inflammatory signaling through a non-desensitizing pathway, or direct effects on dorsal root ganglion neuron excitability) that is fundamentally different from the functional antagonist mechanism proposed for fingolimod. Second, the absence of receptor downregulation explains the absence of lymphocyte sequestration, since lymphocyte egress from lymph nodes requires S1P1R surface expression, and TRV045 maintains surface receptor expression rather than ablating it [6, 7].

4.3 Central nervous system target engagement

The TMS/EEG proof-of-concept study provided the first human evidence of central nervous system S1P1R target engagement by TRV045 [11, 12]. After four days of 250 mg daily dosing, TRV045 produced statistically significant increases in electroen-

cephalographic power spectral density in alpha (frontal $p=0.0164$, left parietal $p=0.0047$, right parietal $p=0.0418$), beta (frontal $p=0.0235$), and gamma (frontal $p=0.0343$) frequency bands, with a decrease in delta power (right parietal $p=0.0432$) [10, 12]. The alpha power increase was observed from the first day of dosing and increased after four days of treatment. The pattern of increased higher-frequency activity and decreased slow-wave activity is consistent with modulation of cortical excitability and is pharmacodynamically distinct from the profiles of approved anti-convulsant agents.

Motor-evoked potential reduction on transcranial magnetic stimulation was comparable in magnitude to approved anti-epileptic drugs but did not reach statistical significance, possibly reflecting the short duration of dosing or the sample size [10, 11].

4.4 Composite pharmacology and selectivity

TRV045 is reported to be highly selective for S1P1R over the other four S1P receptor subtypes (S1P2R through S1P5R) [3, 5]. The selectivity profile has not been quantified in published binding or functional assay data in the peer-reviewed literature but is supported by the absence of S1P3R-mediated cardiovascular effects (which produce bradycardia and atrioventricular conduction delay through S1P3R activation on cardiomyocytes in the fingolimod class) and the absence of S1P4R and S1P5R-associated effects. Functional selectivity data (EC50, Emax, binding K_i) have not been publicly disclosed.

5. Pharmacokinetics and Routes of Administration

5.1 Absorption

TRV045 is orally bioavailable and is being developed as an oral, once-daily formulation [5, 15]. Quantitative oral bioavailability and time to peak plasma concentration have not been disclosed in published literature. The Phase 1 FIH study included a food effect evaluation (Part 2), but specific results have not been published [5]. Both the target engagement POC study (single doses of 50, 150, and 300 mg) and the TMS POC study (250 mg daily for four days) achieved plasma exposures comparable to those observed in the FIH study, indicating consistent absorption across the dose range studied [10, 11].

5.2 Distribution

Volume of distribution, plasma protein binding, and blood-brain barrier penetration parameters have not been disclosed in published literature. Central nervous system penetration is inferred from the pharmacodynamic evidence: the EEG power spectral density changes and TMS-EEG cluster effects observed in the TMS POC study are consistent with direct central nervous system activity rather than peripheral-only mechanisms [11, 12]. The preclinical analgesic efficacy in neuropathic pain models, which involves spinal cord dorsal horn and dorsal root ganglion targets, is also consistent with central nervous system distribution.

5.3 Metabolism

The metabolic pathway of TRV045 has not been characterized in published literature. Unlike fingolimod, which requires *in vivo* phosphorylation by sphingosine kinase 2 to generate the active S1P1R agonist fingolimod-phosphate, TRV045 is reported to be active as the parent compound without requiring metabolic activation [1, 2, 3]. This is consistent with the non-phosphorylated structural class described

in Trevena patent literature. The cytochrome P450 enzyme involvement, polymorphic metabolism potential, and drug-drug interaction liabilities have not been publicly characterized.

5.4 Elimination

Elimination parameters (half-life, clearance, renal versus hepatic excretion) have not been disclosed in published literature. The dosing regimen (once daily) and the sustained pharmacodynamic effects observed over four days of dosing in the TMS POC study are consistent with a half-life suitable for once-daily administration [11].

5.5 Routes of administration

TRV045 is being developed exclusively for oral administration [5, 15]. The initial clinical formulation was used in the FIH study and the two POC studies. An optimized oral formulation was under clinical pharmacokinetic evaluation as of the first quarter of 2024, with the objective of supporting Phase 2 development [15].

5.6 Special populations

Pharmacokinetic data in special populations (hepatic impairment, renal impairment, pediatric, geriatric) have not been generated or disclosed. The Phase 1 studies were conducted in healthy adult volunteers.

6. Preclinical Pharmacology

6.1 Neuropathic pain models

6.1.1 Diabetic peripheral neuropathy

TRV045 reversed thermal hyperalgesia in preclinical models of diabetic peripheral neuropathy at pharmacologically active doses [5]. Specific model details (streptozotocin-induced versus genetic model, dose-response curve, time course) have been described in Trevena's IND-enabling preclinical package but have not been fully published in peer-reviewed literature. The reversal of thermal hyperalgesia, a measure of C-fiber-mediated nociceptive sensitization, is the primary preclinical efficacy signal supporting the diabetic neuropathic pain indication.

6.1.2 Chemotherapy-induced peripheral neuropathy

The most detailed published preclinical pharmacology of TRV045 is in the paclitaxel-induced chemotherapy-induced peripheral neuropathy (CIPN) model, conducted in collaboration with Virginia Commonwealth University and presented at the ASPET annual meeting (May 2024) and at the ACNP 62nd Annual Meeting (December 2023) [7, 8, 16].

Oral TRV045 at 1, 3, and 10 mg/kg produced dose-dependent reduction in mechanical allodynia (von Frey filament testing) and cold allodynia (acetone drop testing) in male and female mice with established paclitaxel-induced neuropathy [7]. The analgesic effect was observed after single acute doses and was maintained throughout a seven-day repeated dosing period in both sexes. At 14 days of repeated dosing, the analgesic effect was sustained without evidence of tolerance, receptor desensitization, or S1P1R protein reduction in spinal cord tissue.

In a direct comparison with fingolimod (FTY720) in the same model, fingolimod produced approximately 70 percent reduction in S1P1R functional activity and approximately 30 percent reduction in S1P1R protein in spinal cord tissue after repeated dosing, whereas TRV045 produced no such decreases [7]. This finding is the central mechanistic differentiator for TRV045 and supports the sustained agonism hypothesis as the mechanism of analgesic action.

In a prevention paradigm, TRV045 at 100 mg/kg administered during the paclitaxel dosing period reduced both mechanical and cold hypersensitivity 24 hours after the final dose [8]. Cold hypersensitivity reduction persisted seven days after treatment cessation, suggesting potential disease-modifying effects rather than purely symptomatic analgesia. The persistence of effect beyond the drug washout period is consistent with a central neuroplastic or anti-neuroinflammatory mechanism.

6.2 Epilepsy models

TRV045 was evaluated through the NIH-supported Epilepsy Therapy Screening Program (ETSP) in collaboration with the National Institutes of Health [7, 17].

Pentylenetetrazol (ivPTZ) seizure threshold test: At 30 mg/kg, TRV045 significantly increased time to first myoclonic twitch (31.6 seconds versus 26.0 seconds for vehicle, $p=0.02$) [7].

Maximal electroshock seizure (MES) test: TRV045 produced dose-dependent protection at 10 to 30 mg/kg in rats. At 30 mg/kg, protection was achieved in 7 of 8 animals. The calculated ED₅₀ was 18 mg/kg [7].

Epileptogenesis prevention model: In a preliminary evaluation of disease-modifying potential, TRV045 did not produce statistically significant differences in seizure frequency between treated and vehicle groups [7]. The negative epileptogenesis result indicates that TRV045 has acute anti-seizure activity (raising seizure threshold and blocking seizure propagation) but may not prevent the development of epilepsy in the model studied.

6.3 Safety pharmacology

Preclinical safety pharmacology studies demonstrated no peripheral lymphopenia, no changes in blood pressure, no changes in heart rate, and no respiratory function changes at or above pharmacologically active doses [5, 6, 7]. The absence of lymphopenia across all preclinical studies is the most pharmacologically significant safety finding and distinguishes TRV045 from all approved S1P receptor modulators. No cardiovascular, respiratory, or central nervous system safety concerns were identified in preclinical safety pharmacology.

7. Clinical Evidence Base

7.1 Phase 1 first-in-human study

The first-in-human study was a three-part randomized, double-blind, placebo-controlled study in 89 healthy volunteers, initiated in the first quarter of 2022 following FDA acceptance of the IND application in December 2021 [5, 9]. Part 1 comprised single ascending doses across up to six cohorts. Part 2 comprised a food effect evaluation in one cohort. Part 3 comprised multiple ascending doses across up to three cohorts. The primary endpoints were safety, tolerability, pharmacokinetics, lymphocyte counts, hemodynamic function, and QTcF interval changes.

No lymphopenia was observed at any dose level studied. No clinically significant cardiovascular effects (bradycardia, blood pressure changes, QTcF prolongation) were reported. The most common drug-related adverse event was headache, reported in 4 of 89 subjects [9]. The pharmacokinetic data from the FIH study informed dose selection for the subsequent proof-of-concept studies.

7.2 Target engagement proof-of-concept study (PainCart)

The target engagement POC study was a randomized, double-blind, placebo-controlled, single-dose, four-way crossover study in 25 healthy subjects [10]. Each subject received three different single doses of TRV045 (50 mg, 150 mg, and 300 mg) and placebo on four separate visits.

The primary endpoint was the area of mechanical allodynia surrounding a topical capsaicin application site (the PainCart model, a validated human experimental pain model for assessing analgesic activity of candidate compounds targeting central sensitization mechanisms). At the 10-hour post-dose endpoint, TRV045 produced a statistically significant, dose-dependent reduction in the area of capsaicin-induced mechanical allodynia [10]:

Placebo: change of -67.19 mm squared. TRV045 150 mg: change of -389.45 mm squared ($p=0.0002$ versus placebo). TRV045 300 mg: change of -731.78 mm squared ($p=0.0001$ versus placebo).

Secondary allodynic area measurements showed similar dose-dependent trends with p-values of 0.0022 and 0.0023, respectively [10]. The 50 mg dose did not reach statistical significance, establishing a dose-response relationship with an apparent threshold between 50 mg and 150 mg for the analgesic effect.

Plasma exposures at all dose levels were comparable to those observed in the FIH study and reached the anticipated targeted active dose range [10]. No drug-related adverse events were reported in the study. No serious adverse events were reported.

7.3 TMS/EEG proof-of-concept study

The TMS/EEG POC study was a randomized, double-blind, placebo-controlled, multiple-dose, two-way crossover study in 25 healthy male subjects evaluating 250 mg of TRV045 daily for four consecutive days [11, 12]. The primary endpoint was pharmacodynamic effects on cortical excitability measured by electromyography (motor-evoked potentials from transcranial magnetic stimulation) and electroencephalography (EEG power spectral density).

On day 4, TRV045 produced statistically significant increases in EEG power spectral density in multiple higher-frequency bands [10, 12]:

Alpha waves: frontal ($p=0.0164$), left parietal ($p=0.0047$), right parietal ($p=0.0418$). Beta waves: frontal ($p=0.0235$). Gamma waves: frontal ($p=0.0343$). Delta waves: right parietal decrease ($p=0.0432$).

The alpha power increase was observed from day 1 and increased progressively after four days of treatment [12]. Motor-evoked potential reduction on transcranial magnetic stimulation was comparable in magnitude to effects reported for approved anti-epileptic drugs but did not reach statistical significance in this sample [10, 11].

The detailed pharmacodynamic analysis was published by Cuba et al. (2025) in Clinical Pharmacology and Therapeutics, reporting that the EEG effects are consistent with modulation of cortical excitability by a centrally active agent and warrant further investigation for therapeutic applications in seizure disorders [12].

No drug-related adverse events or serious adverse events were reported. Mild adverse events (headaches, somnolence, dizziness, fatigue) comprised 98 to 99 percent of all reported events across both POC studies [11].

7.4 Safety summary across Phase 1 studies

Across all three completed Phase 1 studies (89 subjects in the FIH study, 25 subjects in the target engagement study, and 25 subjects in the TMS study), TRV045 demonstrated a consistently favorable tolerability profile [9, 10, 11]:

No serious adverse events. No drug-related discontinuations. No clinically significant reduction in total lymphocyte count. No clinically significant changes in heart rate or blood pressure. No clinically significant changes in ECG interval measures (no QTcF prolongation, no PR interval prolongation). Physical examinations, including ophthalmologic assessments, revealed no clinically significant findings. The most common adverse events were headache, somnolence, dizziness, and fatigue, all mild in severity.

8. Sourcing and Quality Verification

TRV045 is not a registered pharmaceutical product in any jurisdiction and is not available in pharmaceutical-grade formulations for general research use. The compound is available as a research-grade preparation from specialty chemical suppliers, notably MedChemExpress (CAS 2256030-24-5, catalog listing as an S1P receptor agonist) [4].

Research-grade TRV045 is supplied in milligram quantities as a solid. Pricing and availability are subject to the specialty chemical market; investigators should contact suppliers directly for current availability. The structural identity of TRV045 has not been unambiguously disclosed in the public domain; the CAS number and the supplier catalog listing provide the principal identification for procurement purposes.

Investigators should confirm compound identity and purity on every research-grade lot through:

High-performance liquid chromatography (HPLC) area-percent purity analysis. Mass spectrometry confirmation of molecular weight against the expected value. Nuclear magnetic resonance spectroscopy where feasible, to confirm structural identity. Residual solvent analysis (gas chromatography). Karl Fischer or loss-on-drying analysis for residual water content.

Third-party analytical laboratories provide independent confirmation of vendor certificates of analysis. Because the full structural identity of TRV045 is proprietary, investigators should exercise particular care in verifying that research-grade material corresponds to the compound evaluated in Trevena's clinical and preclinical studies.

9. Reconstitution and Handling

TRV045 is supplied as a solid for research applications. Based on the oral route of administration and the formulation development described in clinical studies (oral capsule and optimized oral formulation), the compound is presumed to be sufficiently stable in solid form for standard pharmaceutical and research handling [5, 15].

For in vitro research, stock solutions may be prepared in dimethyl sulfoxide (DMSO) at concentrations appropriate to the intended assay, following standard practices for small-molecule receptor agonists. Aqueous solubility characteristics have not been publicly disclosed; investigators should determine solubility empirically in their intended assay media.

Storage of the solid should be at -20 degrees Celsius or as directed by the supplier. Light protection is reasonable practice for compounds of undisclosed structural identity. Stock solutions in DMSO should be aliquoted for single-use to minimize freeze-thaw cycles.

For in vivo preclinical research, the published studies describe oral administration (gavage) in mice and rats at doses of 1 to 100 mg/kg [7, 8]. Vehicle composition for preclinical studies has not been disclosed. Investigators should develop and validate their own formulation approaches appropriate to the intended route and model.

10. Stack Interactions and Combinations

TRV045 interacts with several drug classes through its S1P1R agonist mechanism. Investigators conducting research with TRV045, especially in chronic dosing regimens or in combination with other research compounds, should consider:

Other S1P receptor modulators: Concurrent use with fingolimod, siponimod, ozanimod, ponesimod, or other S1P receptor modulators produces complex pharmacological interactions at the S1P1R. TRV045 produces sustained agonism while the approved S1P modulators produce functional antagonism through receptor downregulation; the net effect of concurrent administration is unpredictable and could include competitive binding at S1P1R, altered receptor trafficking kinetics, or paradoxical loss of TRV045 efficacy through fingolimod-mediated receptor degradation. The combination has not been studied and is not recommended in clinical or preclinical settings without specific mechanistic justification.

Immunosuppressants: Although TRV045 does not produce lymphopenia or immunosuppression at pharmacologically active doses, concurrent administration with immunosuppressant agents (cyclosporine, tacrolimus, mycophenolate, corticosteroids) should be approached with caution, as additive or synergistic effects on immune function cannot be excluded based on the S1P receptor class pharmacology.

Cardiac-active agents: TRV045 has not demonstrated cardiovascular effects (bradycardia, AV conduction delay, QTcF prolongation) in Phase 1 studies, distinguishing it from the fingolimod class [9, 10, 11]. Concurrent administration with beta-blockers, calcium channel blockers, or other negative chronotropic agents is likely to carry lower cardiovascular interaction risk than the approved S1P modulators, but formal interaction studies have not been conducted.

Anti-epileptic drugs: TRV045 has demonstrated anti-seizure activity in preclinical models with motor-evoked potential reduction comparable to approved anti-epileptic drugs [7, 10]. Concurrent use with valproate, levetiracetam, carba-

mazepine, lamotrigine, or other anti-epileptic agents may produce additive anti-seizure effects. Drug-drug interaction potential at the metabolic level (CYP enzyme induction or inhibition) has not been characterized.

Neuropathic pain medications: Concurrent use with pregabalin, gabapentin, duloxetine, or amitriptyline may produce additive analgesic effects through complementary mechanisms. TRV045 operates through S1P1R modulation, which is mechanistically distinct from voltage-gated calcium channel modulation (pregabalin, gabapentin) and monoamine reuptake inhibition (duloxetine, amitriptyline). Formal combination studies have not been conducted.

CYP450 considerations: The metabolic pathway and CYP enzyme involvement for TRV045 have not been publicly characterized. Investigators should consider the potential for pharmacokinetic interactions with strong CYP inhibitors or inducers until formal interaction data are available.

11. Adverse Events and Safety

11.1 Common adverse events

The principal adverse events observed across three completed Phase 1 clinical studies are [9, 10, 11]:

Headache (the most common drug-related adverse event in the FIH study, reported in 4 of 89 subjects). Somnolence (mild, reported in POC studies). Dizziness (mild, reported in POC studies). Fatigue (mild, reported in POC studies).

These adverse events were mild in severity (98 to 99 percent of all events), self-limiting, and did not lead to study discontinuation. The adverse-event profile is substantially more favorable than the profiles of the approved S1P receptor modulators and of the current first-line neuropathic pain therapies.

11.2 Absent adverse-event signals

Several adverse-event signals characteristic of the S1P receptor modulator class were notably absent from all TRV045 clinical data [9, 10, 11]:

No lymphopenia: Total lymphocyte counts showed no clinically significant reduction at any dose studied. This is the most pharmacologically significant safety differentiation from fingolimod (which produces grade 3 to 4 lymphopenia in approximately 20 percent of treated patients) and from siponimod, ozanimod, and ponesimod (which produce dose-dependent lymphopenia as a class effect).

No bradycardia or atrioventricular conduction delay: First-dose bradycardia and AV block are characteristic of fingolimod and, to a lesser extent, of siponimod and ponesimod. TRV045 produced no clinically significant changes in heart rate or cardiac conduction at any dose studied.

No blood pressure changes: No clinically significant hypertension or hypotension was observed.

No QTcF prolongation: No prolongation of the corrected QT interval was observed.

No PR interval prolongation: No evidence of atrioventricular conduction delay.

No ophthalmologic findings: Macular edema is a known adverse effect of fingolimod. Ophthalmologic assessments in TRV045 studies revealed no clinically significant findings.

11.3 Preclinical safety

Preclinical safety pharmacology studies demonstrated no lymphopenia, no cardiovascular effects (blood pressure, heart rate, respiratory function), and no organ toxicity at or above pharmacologically active doses [5, 6, 7]. Reproductive toxicology and sub-chronic toxicology studies were ongoing as of 2024, with results expected to support Phase 2 development [15].

11.4 Pregnancy and lactation

No human pregnancy or lactation data are available. Reproductive toxicology studies were ongoing as of the most recent public disclosure [15]. S1P1R is expressed in embryonic vascular development, and S1P1R knockout is embryonically lethal in mice; the implications of sustained S1P1R agonism for reproductive safety require characterization. The approved S1P receptor modulators (fingolimod, siponimod, ozanimod, ponesimod) carry pregnancy contraindications or warnings based on teratogenicity observed in animal studies.

12. Comparable Compounds Assessment

This section presents a structured comparative assessment of five approved or advanced S1P receptor modulators against TRV045, evaluated against five competency standards: novelty, effect size, promising potential (current clinical state and trajectory), side-effect profile, and overall validation. The five comparators were selected as the principal S1P receptor modulators with clinical approval or advanced development, representing the pharmacological class from which TRV045 is mechanistically differentiated.

12.1 Fingolimod (FTY720, Gilenya)

Mechanism: Non-selective S1P receptor modulator acting on S1P1R, S1P3R, S1P4R, and S1P5R. Requires *in vivo* phosphorylation by sphingosine kinase 2 to generate the active metabolite fingolimod-phosphate. Produces initial S1P1R agonism followed by receptor internalization, ubiquitination, and proteasomal degradation, resulting in functional antagonism, loss of S1P1R surface expression, and peripheral lymphocyte sequestration [20, 21].

Development and approval: Approved by the FDA in 2010 as the first oral therapy for relapsing forms of multiple sclerosis. Marketed as Gilenya by Novartis. The approval was based on Phase 3 trials demonstrating superiority over intramuscular interferon beta-1a in reducing annualized relapse rate [21].

Neuropathic pain evidence: Fingolimod has demonstrated analgesic activity in preclinical neuropathic pain models, including reversal of mechanical allodynia in nerve injury and chemotherapy-induced models [19, 20]. However, the analgesic mechanism is attributed to functional antagonism (S1P1R downregulation), and repeated dosing in the CIPN model produced approximately 70 percent reduction in S1P1R functional activity and 30 percent protein reduction in spinal cord tissue [7]. Fingolimod has not been developed for neuropathic pain indications and is not expected to be, given its immunosuppressive and cardiovascular liability profile.

Novelty: Low. Fingolimod is the first-generation compound in the class and has been in clinical use since 2010.

Effect size (pain): Moderate in preclinical models, but accompanied by receptor downregulation that may limit long-term analgesic utility. No clinical pain data.

Promising potential (pain): Very low. The compound is not in development for pain. The immunosuppressive and cardiovascular profiles preclude practical development for neuropathic pain.

Side-effect profile: First-dose bradycardia and AV conduction delay requiring first-dose monitoring. Grade 3 to 4 lymphopenia in approximately 20 percent of patients. Macular edema (0.4 percent). Elevated liver enzymes. Progressive multifocal leukoencephalopathy (rare). Herpes zoster reactivation. Basal cell carcinoma [21].

Overall validation: High for multiple sclerosis; absent for pain. The compound is the class reference but is not a practical comparator for neuropathic pain development.

Comparison to TRV045: Fingolimod and TRV045 share the S1P1R target but differ fundamentally in mechanism (functional antagonism versus sustained agonism), receptor selectivity (non-selective versus S1P1R-selective), prodrug requirement (phosphorylation-dependent versus direct activity), safety profile (lymphopenia, bradycardia, macular edema versus none), and therapeutic positioning (multiple sclerosis versus neuropathic pain). TRV045 represents a mechanistic advance that separates the analgesic potential of S1P1R engagement from the immunosuppressive consequences of receptor downregulation.

12.2 Siponimod (BAF312, Mayzent)

Mechanism: Selective S1P1R and S1P5R modulator. Does not require phosphorylation for activity. Produces S1P1R functional antagonism through receptor downregulation, resulting in lymphocyte sequestration, but with a more controlled pharmacodynamic profile than fingolimod and shorter receptor recovery time [22].

Development and approval: Approved by the FDA in 2019 for relapsing forms of multiple sclerosis, including clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease. Marketed as Mayzent by Novartis [22].

Novelty: Low to moderate. Second-generation S1P modulator with improved selectivity over fingolimod.

Effect size (pain): No published data in neuropathic pain models.

Promising potential (pain): Very low. Not in development for pain.

Side-effect profile: First-dose heart rate reduction (less severe than fingolimod but still requiring dose titration). Lymphopenia. Macular edema. Elevated liver enzymes. Contraindicated in CYP2C9 *3/*3 poor metabolizers [22].

Overall validation: Moderate for multiple sclerosis. Absent for pain.

Comparison to TRV045: Siponimod shares the functional antagonism mechanism with fingolimod and the associated safety liabilities, albeit with improved selectivity. TRV045's sustained agonism mechanism and absence of lymphopenia and cardiovascular effects represent a qualitative pharmacological differentiation.

12.3 Ozanimod (RPC1063, Zeposia)

Mechanism: Selective S1P1R and S1P5R modulator. Produces S1P1R functional antagonism and lymphocyte sequestration with a graded onset and offset. Active metabolites contribute to the pharmacological effect [23].

Development and approval: Approved by the FDA in 2020 for relapsing forms of multiple sclerosis and in 2023 for moderately to severely active ulcerative colitis. Marketed as Zeposia by Bristol Myers Squibb [23].

Novelty: Low to moderate. Improved selectivity and active metabolite pharmacology.

Effect size (pain): No published data in neuropathic pain models.

Promising potential (pain): Very low. Not in development for pain.

Side-effect profile: Lymphopenia (dose-dependent). Bradycardia (less than fingolimod). Elevated liver enzymes. Macular edema. Herpes zoster reactivation. Requires cardiac monitoring at initiation in high-risk patients [23].

Overall validation: Moderate for multiple sclerosis and ulcerative colitis. Absent for pain.

Comparison to TRV045: Same qualitative differentiation as siponimod. TRV045's absence of lymphopenia and cardiovascular effects is the primary distinguishing feature.

12.4 Ponesimod (ACT-128800, Ponvory)

Mechanism: Highly selective S1P1R modulator with no clinically significant activity at S1P2R through S1P5R. Produces S1P1R functional antagonism and lymphocyte sequestration. Short half-life permits rapid reversibility of lymphocyte effects upon discontinuation [24].

Development and approval: Approved by the FDA in 2021 for relapsing forms of multiple sclerosis. Marketed as Ponvory by Janssen [24]. Ponesimod is the most S1P1R-selective approved modulator in the class.

Neuropathic pain evidence: A 2025 preclinical study by Li et al. demonstrated that ponesimod alleviated postherpetic neuralgia in rats by normalizing spinal TRPV1 expression and inhibiting MAPK-mediated glial activation [25]. The authors characterized ponesimod as an S1P1R antagonist in this context, consistent with the functional antagonism mechanism, and the analgesic effect was attributed to suppression of neuroinflammatory astrocyte and microglial activation.

Novelty: Moderate. The most selective approved S1P1R modulator; the short half-life and rapid reversibility are differentiating features.

Effect size (pain): Positive in one preclinical postherpetic neuralgia model. No clinical pain data.

Promising potential (pain): Low. Not in development for pain despite preclinical signals.

Side-effect profile: Lymphopenia (dose-dependent). Upper respiratory tract infection. Elevated liver enzymes. Bradycardia risk lower than fingolimod but present. Requires dose titration [24].

Overall validation: Moderate for multiple sclerosis. Low for pain (single preclinical study).

Comparison to TRV045: Ponesimod shares S1P1R selectivity with TRV045 but differs in the fundamental mechanism (functional antagonism versus sustained agonism) and in the presence of lymphopenia. The ponesimod pain data provide independent validation that S1P1R modulation can produce analgesia in neuropathic pain models, supporting the S1P1R target but through a different mechanistic pathway than TRV045.

12.5 Amiselimod (MT-1303)

Mechanism: Selective S1P1R modulator. Requires phosphorylation for activity (pro-drug). Produces S1P1R functional antagonism and lymphocyte sequestration with a reportedly more gradual onset than fingolimod, intended to mitigate first-dose cardiac effects [26].

Development trajectory: Developed by Mitsubishi Tanabe Pharma and Biogen. Evaluated in Phase 2 trials for relapsing-remitting multiple sclerosis, inflammatory bowel disease (Crohn's disease and ulcerative colitis), and psoriasis. The Phase 2 trial in relapsing-remitting multiple sclerosis reported a reduction in new MRI lesions but did not meet the primary endpoint for annualized relapse rate reduction [26]. Development was deprioritized for multiple sclerosis. The compound has been evaluated in Phase 2 for Crohn's disease with mixed results.

Novelty: Low. First-generation functional antagonist with prodrug activation requirement.

Effect size (pain): No published data in neuropathic pain models.

Promising potential (pain): Very low. Not in development for pain.

Side-effect profile: Lymphopenia (dose-dependent, the therapeutic mechanism). Reduced first-dose cardiac effect compared to fingolimod. Elevated liver enzymes. Generally well tolerated in Phase 2 [26].

Overall validation: Low to moderate. Phase 2 data in MS and IBD without clear registration path.

Comparison to TRV045: Amiselimod represents the conventional functional antagonist approach with prodrug pharmacology. TRV045's sustained agonism, direct activity without phosphorylation, and absence of lymphopenia represent advances on all three differentiating axes.

12.6 Comparator summary

The five approved or advanced S1P receptor modulators occupy a common pharmacological space defined by S1P1R functional antagonism, lymphocyte sequestration, and autoimmune indication development. **Fingolimod** is the class reference with the broadest clinical experience and the most extensive safety database, but non-selective pharmacology and first-dose cardiac effects limit its utility.

Siponimod and **ozanimod** improve selectivity and reduce cardiac risk but retain the lymphopenia and immunosuppressive liabilities. **Ponesimod** achieves S1P1R selectivity comparable to TRV045 but retains the functional antagonist mechanism and lymphopenia. **Amiselimod** has not progressed to registration and represents the conventional functional antagonist approach.

TRV045 occupies a fundamentally different position in this landscape: it is the only S1P1R modulator that produces sustained agonism without receptor desensitization or protein downregulation, the only S1P1R modulator developed for neuropathic pain rather than autoimmune disease, the only compound in the comparison that does not produce lymphopenia, and the only compound with human proof-of-concept analgesic data (capsaicin model). The mechanistic novelty is substantial: TRV045 separates the neuronal and analgesic signaling consequences of S1P1R activation from the immunological consequences of S1P1R internalization and degradation, a pharmacological dissociation that was not previously demonstrated in the S1P receptor field.

The principal uncertainty for TRV045 is the absence of Phase 2 and Phase 3 clinical efficacy data in the intended neuropathic pain population. The comparators, despite their limitations for pain applications, have extensive clinical safety and efficacy databases in their approved indications that provide high-confidence risk-benefit characterization. TRV045's clinical evidence base is currently limited to Phase 1 healthy-volunteer studies with pharmacodynamic (not therapeutic) endpoints. The transition from proof-of-concept analgesic signals in the capsaicin model to therapeutic efficacy in diabetic peripheral neuropathy patients remains to be demonstrated.

Investigators considering TRV045 for research applications should note the unique pharmacological profile (sustained S1P1R agonism without desensitization), the favorable Phase 1 safety profile (no lymphopenia, no cardiovascular effects), the preclinical evidence for both analgesic and anti-seizure activity, and the limitation that the compound is early in clinical development with no Phase 2 or registration data. The compound represents the most mechanistically novel entry in the S1P receptor modulator landscape for neurological and pain applications.

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