

RESEARCH MONOGRAPH . COMPOUND PROFILE

Danavorexton

A selective nonpeptide orexin 2 receptor agonist developed at Takeda Pharmaceutical Company, the first small-molecule OX2R agonist to achieve clinical proof of concept for orexin replacement therapy across narcolepsy type 1 and type 2, idiopathic hypersomnia, obstructive sleep apnea, and opioid-induced respiratory depression.

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ABSTRACT

Danavorexton (TAK-925) is a potent, selective, brain-penetrant, nonpeptide orexin 2 receptor (OX2R) agonist developed by Takeda Pharmaceutical Company as the first small-molecule orexin receptor agonist to enter clinical development. Identified through high-throughput screening and optimized through a medicinal chemistry campaign that converted a micromolar-potency hit (EC₅₀ 570 nM) into a low-nanomolar agonist (EC₅₀ 5.5 nM in calcium mobilization assays) with greater than 18,000-fold selectivity for human OX2R over OX1R, danavorexton is a (2R,3S)-piperidine carbamate bearing a cis-4-phenylcyclohexyl ether and a methylsulfonamide pharmacophore. The compound adopts a compact U-shaped conformation that engages the OX2R orthosteric pocket through a critical hydrogen bond between the sulfonamide nitrogen and Gln134(3.32), as resolved by two cryo-electron microscopy structures of the OX2R-G protein complex at 3.2 to 3.3 angstrom resolution. Selectivity over OX1R arises from subtle differences at only two residues (Thr111(2.61) and Thr135(3.33) in OX2R versus Ser and Ala at the corresponding positions in OX1R) that alter steric complementarity and desolvation within the orthosteric pocket. Administered exclusively by intravenous infusion, danavorexton has completed Phase 1 clinical studies in narcolepsy type 1, narcolepsy type 2, idiopathic hypersomnia, obstructive sleep apnea with residual excessive daytime sleepiness, and opioid-induced respiratory depression, collectively enrolling over 150 participants across six registered trials. In a multiple-rising-dose study (NCT03748979), danavorexton at 44 mg intravenous over 9 hours produced maximal Maintenance of Wakefulness Test sleep latency (40

minutes in all sessions) in all narcolepsy type 1 participants, reduced cataplexy episodes to zero during infusion, and normalized the Epworth Sleepiness Scale score from a baseline of 18.6 to 0.0 by day 7. Comparable wakefulness-promoting effects were demonstrated in narcolepsy type 2, idiopathic hypersomnia (placebo-adjusted sleep latency improvement of 29.4 minutes), and sleep-deprived healthy volunteers (sleep latency of 31.8 minutes at 112 mg versus 9.2 minutes on placebo). In a crossover study of remifentanyl-induced respiratory depression, danavorexton reversed respiratory depression (minute volume increase of 13.0 L/min at 19 mg, $p < 0.001$) and sedation without reversing opioid analgesia. Human pharmacokinetics are characterized by dose-proportional plasma concentrations, a terminal half-life of approximately 3 to 5 hours, negligible accumulation with daily 9-hour infusions, and a cerebrospinal fluid-to-plasma concentration ratio of approximately 2.8 percent. The compound is well tolerated across all studied populations. The most common drug-related adverse events are pollakiuria (urinary frequency), transient blood pressure elevation, insomnia, headache, and dizziness, all predominantly mild in severity. No hepatotoxicity has been observed, distinguishing danavorexton from its oral successor TAK-994 (firazorexton), which demonstrated exceptional efficacy in a Phase 2 narcolepsy trial but was discontinued following drug-induced liver injury in three participants meeting Hy's law criteria. The second-generation oral OX2R agonist TAK-861 (oveporexton), structurally distinct from both danavorexton and TAK-994, has completed a positive Phase 2 trial with no hepatic signal and is advancing toward Phase 3 registration. This monograph reviews the medicinal chemistry, structural biology, receptor pharmacology, pharmacokinetics, preclinical and clinical evidence base, adverse event profile,

sourcing and handling considerations, and a comparative assessment of danavorexton against four alternative agents in the narcolepsy and excessive daytime sleepiness pharmacotherapy space (TAK-994, TAK-861, pitolisant, solriamfetol) on five competency standards. Danavorexton is not approved for any indication in any jurisdiction. It is an investigational compound available in research-grade preparations; investigators should obtain analytical confirmation of identity and purity on every lot.

1. Compound Identification

1.1 Names, synonyms, and registry identifiers

Proposed International Nonproprietary Name: Danavorexton.

Development code: TAK-925 (Takeda Pharmaceutical Company). The development code TAK-925 is the principal identifier in the medicinal chemistry, pharmacology, and clinical literature; the nonproprietary name danavorexton appears in clinical trial registries and regulatory filings beginning in 2019 [1, 3].

Chemical Abstracts Service registry number: 2114324-48-8 (free base).

PubChem Compound Identifier: CID 130310079.

DrugBank Identifier: DB16962.

International Union of Pure and Applied Chemistry name: methyl (2R,3S)-3-[(methylsulfonyl)amino]-2-[[[(cis-4-phenylcyclohexyl)oxy]methyl]piperidine-1-carboxylate [1].

1.2 Structural class and chemistry

Danavorexton is a nonpeptide piperidine carbamate bearing three pharmacophoric elements: a (2R,3S)-piperidine core, a secondary methylsulfonamide at the 3-position, and a cis-4-phenylcyclohexyl ether at the 2-position linked through a methylene bridge [1]. The compound belongs to a novel structural class of orexin receptor agonists with no precedent in the approved pharmacopoeia; prior to the disclosure of TAK-925 and related Takeda compounds, no nonpeptide, small-molecule, selective agonist of the orexin 2 receptor (OX2R) had been reported. The structural class is distinct from the dual orexin receptor antagonists (suvorexant, lemborexant, daridorexant) that occupy the same receptor orthosteric pocket but stabilize the inactive conformation [33].

Molecular formula: C₂₁H₃₂N₂O₅S (free base).

Molecular weight: 424.55 g/mol (average); 424.20 g/mol (monoisotopic) [1].

Physical properties: The free base is described as a white to off-white solid. Specific melting point, aqueous solubility, and partition coefficient (logP) have not been published in the peer-reviewed literature. The compound contains a basic piperidine nitrogen (partially masked by the carbamate, with predicted pKa approximately 7 to 8 for N-carbamate piperidines) and a weakly acidic sulfonamide NH (predicted pKa approximately 10 to 11); both ionization states are relevant to formulation and distribution.

Stereochemistry: Danavorexton contains two stereocenters at carbons 2 and 3 of the piperidine ring and is supplied as the single (2R,3S) diastereomer. The cyclohexane ring bears a cis relationship between the ether oxygen at C1 and the phenyl substituent at C4. X-ray crystallography and nuclear magnetic resonance spectroscopic analysis of the free base confirmed that both the methylene linker at the 2-position of the piperidine and the ether oxygen at the 1-position of the cyclohexane adopt axial orientations, enforcing a stable U-shaped molecular conformation that is critical for receptor engagement [1]. Among the four possible diastereomers (combinations of piperidine 2R/2S and 3R/3S with cis/trans cyclohexane geometry), the (2R,3S)-cis combination is the most potent OX2R agonist by approximately 4-fold over the next most active stereoisomer [1].

1.3 Conformation and receptor-bound structure

The receptor-bound conformation of danavorexton has been characterized at high resolution by cryo-electron microscopy (cryo-EM). Yin et al. (2022) solved two structures of the OX2R-danavorexton-G protein ternary complex: OX2R coupled to an engineered Gq/Gi chimeric G protein (mGsqiN) at 3.3 angstrom resolution (Protein Data Bank accession 7SR8) and OX2R coupled to Gi1 at 3.2 angstrom resolution (PDB 7SQO) [2]. In both structures, danavorexton adopts the compact U-shaped conformation observed in the crystal structure of the free compound, burying approximately 460 square angstroms of solvent-accessible surface area within the receptor orthosteric pocket. The compound contacts receptor residues on transmembrane helices 2, 3, 5, 6, and 7 [2]. The root mean square deviation between the two receptor structures is 0.7 angstrom, indicating that G protein identity does not substantially alter the receptor conformation or ligand binding pose [2].

1.4 Synthesis

Danavorexton was discovered through a high-throughput screening (HTS) campaign against human OX2R conducted at Takeda Research (Fujisawa, Kanagawa, Japan), followed by iterative medicinal chemistry optimization [1]. The HTS campaign identified hit compound 2 (a diastereomeric piperidine mixture, EC₅₀ 570 nM, maximum response 94% of orexin-A), which was advanced through a systematic structure-activity relationship program involving diastereomer resolution, sulfonamide modification, cyclohexane substituent optimization, chiral resolution, and piperidine N-group variation [1]. Key optimization steps included: conversion of the diastereomeric mixture to the (2R,3S)-cis isomer (compound 3, EC₅₀ 270 nM); installation of the methylsulfonamide (compound 7); introduction of the 4-phenylcyclohexyl group (compound 13, EC₅₀ 140 nM); chiral resolution (compound 13a, EC₅₀ 66 nM); and selection of the methyl carbamate as the optimal piperidine N-substituent (compound 16/TAK-925, EC₅₀ 5.5 nM) [1]. The methyl carbamate was preferred over a urea variant (compound 18, EC₅₀ 0.29 nM) on the basis of the balanced pharmacological profile including brain penetration, metabolic stability, and selectivity rather than potency alone [1].

The general synthetic route involves construction of the (2R,3S)-3-amino-2-substituted piperidine core by asymmetric synthesis or resolution, O-alkylation of cis-4-phenylcyclohexanol with the C2 methylene halide or mesylate, sulfonamide formation at the 3-amino group with methanesulfonyl chloride, and carbamate formation at the piperidine nitrogen with methyl chloroformate [1]. Detailed synthetic procedures are described in Takeda patent filings. Research-grade material is characterized by high-performance liquid chromatography, nuclear magnetic resonance spectroscopy, and high-resolution mass spectrometry [1].

2. Abstract

Danavorexton (TAK-925) is a potent, selective, brain-penetrant, nonpeptide orexin 2 receptor (OX2R) agonist and the first small-molecule OX2R agonist to enter clinical development [1]. The compound was identified at Takeda Pharmaceutical Company through high-throughput screening against human OX2R and optimized through iterative medicinal chemistry to achieve an EC₅₀ of 5.5 nM in calcium mobilization assays, with greater than 18,000-fold selectivity for OX2R over OX1R [1]. Two cryo-EM structures of the OX2R-danavorexton-G protein complex (3.2 to 3.3 angstrom resolution) have defined the molecular basis of agonism and subtype selectivity [2].

Administered intravenously, danavorexton has completed Phase 1 studies across five clinical populations: narcolepsy type 1 (NT1), narcolepsy type 2 (NT2), idiopathic hypersomnia (IH), obstructive sleep apnea (OSA), and opioid-induced respiratory depression (OIRD). In the most informative trial (NCT03748979, 7-day multiple-rising-dose), danavorexton at 44 mg over 9 hours normalized Maintenance of Wakefulness Test (MWT) sleep latency to the 40-minute maximum and reduced cataplexy episodes to zero in all NT1 participants, with Epworth Sleepiness Scale scores falling from 18.6 to 0.0 [3]. Efficacy extended to NT2 and IH populations without established orexin deficiency, demonstrating that OX2R agonism promotes wakefulness through mechanisms beyond simple replacement of lost signaling [3, 6]. A separate study demonstrated reversal of remifentanyl-induced respiratory depression without reversal of opioid analgesia [8].

The compound is well tolerated; the most common drug-related adverse events are pollakiuria, transient blood pressure elevation, and insomnia, all predominantly mild [3, 6]. No hepatotoxicity has been observed, distinguishing danavorexton from the oral successor TAK-994, which was discontinued after drug-induced liver injury [15]. The therapeutic development pathway has transitioned to the oral OX2R agonist TAK-861 (oveporexton), now in Phase 3 [18]. Danavorexton's principal continuing value is as a precisely controllable pharmacological tool for OX2R research, enabled by its short half-life (3 to 5 hours), dose-proportional pharmacokinetics, and characterized central nervous system penetration. The compound is not approved in any jurisdiction and is available exclusively as a research-grade preparation.

3. Discovery and Development History

3.1 The orexin system and the therapeutic rationale

The orexin neuropeptides (orexin-A and orexin-B, also designated hypocretin-1 and hypocretin-2) were identified simultaneously by two laboratories in 1998: Sakurai et al. reported orexin-A and orexin-B as ligands of two orphan G protein-coupled receptors (orexin receptor 1 and orexin receptor 2) expressed in the lateral hypothalamus [21], and de Lecea et al. reported the same peptides under the name hypocretins [22]. Subsequent work established that selective loss of approximately 70,000 orexin-producing neurons in the lateral hypothalamus is the pathological hallmark of narcolepsy type 1 (NT1), producing undetectable or severely reduced cerebrospinal fluid (CSF) orexin levels (typically less than 110 pg/mL) [23, 24]. Canine genetics and murine knockout studies demonstrated that orexin receptor 2 (OX2R) is the principal receptor mediating wakefulness promotion and REM sleep suppression: OX2R-deficient mice display narcolepsy with cataplexy, whereas OX1R-deficient mice show only mild sleep fragmentation [25, 26, 28, 33]. These findings established the therapeutic rationale for OX2R agonism as a disease-modifying approach to NT1, in which the signaling loss at OX2R could in principle be restored by an exogenous agonist.

Despite this clear rationale, development of nonpeptide OX2R agonists proved exceptionally challenging. Orexin receptor antagonists (suvorexant, lemborexant, daridorexant) were developed to regulatory approval over the two decades following orexin discovery [17], but no agonist reached clinical development until Takeda disclosed TAK-925 in 2022 [1]. The principal obstacles were the difficulty of identifying agonist scaffolds at peptide-activated G protein-coupled receptors through small-molecule screening and the simultaneous requirement for brain penetration, metabolic stability, and receptor selectivity in a compound class with no precedent.

3.2 Medicinal chemistry discovery

Takeda's high-throughput screening campaign against human OX2R identified a piperidine-based hit compound (compound 2, EC₅₀ 570 nM as a diastereomeric mixture, maximum response 94% of orexin-A) [1]. Fujimoto et al. (2022) reported

the medicinal chemistry optimization from compound 2 through six structural stages to the final candidate compound 16, designated TAK-925 (EC₅₀ 5.5 nM, selectivity greater than 18,000-fold over OX1R) [1]. The optimization required resolution of stereochemistry (the (2R,3S)-cis configuration was approximately 4-fold more potent than the next-best diastereomer), identification of the secondary methylsulfonamide as critical for receptor interaction (N-methylation or replacement with acetamide reduced potency by greater than 100-fold to EC₅₀ > 30,000 nM), and selection of the methyl carbamate piperidine N-group as the optimal balance of potency, brain penetration, and metabolic profile [1]. All authors on the discovery publication are from Takeda Pharmaceutical Company Limited, Fujisawa, Kanagawa, Japan [1].

3.3 Preclinical proof of concept

The first in vivo demonstration was reported in the same Fujimoto et al. (2022) publication: subcutaneous administration of TAK-925 at 3 mg/kg in ICR mice significantly increased total wakefulness time during the 3-hour sleep phase after administration ($p < 0.001$) [1]. Brain-to-plasma concentration ratios at 0.5 and 1 hour after 10 mg/kg intraperitoneal dosing were 0.2, confirming brain penetration [1].

Evans et al. (2022) extended the preclinical characterization to the orexin/ataxin-3 transgenic mouse model of NT1, in which orexinergic neurons are selectively ablated [3]. Subcutaneous danavorexton at 1, 3, and 10 mg/kg dose-dependently increased wakefulness and suppressed cataplexy-like episodes, with the narcolepsy model mice showing approximately threefold greater sensitivity than wild-type mice [3]. Ishikawa et al. (2022) confirmed that repeated administration normalized the dysregulated EEG power spectrum and showed low risk of receptor desensitization [5].

3.4 Clinical development

TAK-925 entered Phase 1 clinical development with a first-in-human single-rising-dose study (NCT03332784) in healthy adult and elderly volunteers and participants with NT1 [3]. This was followed by five additional registered clinical studies:

NCT03522506: Phase 1b crossover study of single 9-hour intravenous infusions of danavorexton (44 mg, 112 mg) with modafinil (300 mg oral) as active comparator in 18 sleep-deprived healthy adults [4].

NCT03748979: Phase 1 multiple-rising-dose study of 7-day 9-hour intravenous infusions in healthy volunteers, NT1, and NT2 participants [3].

NCT04091438: Phase 1b crossover study of a single 9-hour infusion (112 mg) in 28 adults with idiopathic hypersomnia [6].

NCT05180890: Phase 1b crossover study in 25 adults with obstructive sleep apnea receiving adequate CPAP therapy, single infusions of 44 mg and 112 mg [7].

A Phase 1 crossover study in 12 healthy male volunteers evaluated danavorexton (11 mg, 19 mg sequential 90-minute infusions) as a countermeasure for remifentanyl-induced respiratory depression and sedation [8].

3.5 Oral successors and program evolution

Danavorexton's clinical program was designed as proof of concept for OX2R agonism; the intravenous route limits chronic therapeutic use. Takeda subsequently advanced two oral OX2R agonists.

TAK-994 (firazorexton), the first oral OX2R agonist to reach Phase 2, demonstrated exceptional efficacy in a randomized, double-blind, placebo-controlled trial in NT1 published in the *New England Journal of Medicine* [31]. At doses of 30 to 180 mg twice daily for 8 weeks in 73 participants, TAK-994 reduced Epworth Sleepiness Scale (ESS) scores by 10.1 to 13.0 points versus placebo and nearly eradicated cataplexy [17, 31]. The trial was terminated early due to dose-dependent hepatotoxicity: five cases of significant liver enzyme elevation and three cases meeting Hy's law criteria for drug-induced liver injury (DILI) [15, 17]. Mechanistic investigation attributed the hepatotoxicity to reactive metabolite covalent binding to hepatic proteins, with an estimated daily covalent binding burden of 2.94 to 17.6 mg at clinical doses exceeding the published 1 mg threshold for idiosyncratic DILI risk [15].

TAK-861 (oveporexton), a structurally distinct oral OX2R agonist (difluoropyrrolidine core) with EC₅₀ of 2.5 nM and 3,000-fold selectivity over OX1R [14], completed a positive Phase 2b trial (NCT05687903) in 112 NT1 participants demonstrating significant improvements in MWT sleep latency (13.7 to 26.6 minutes versus placebo), ESS scores (6.4 to 11.3 points versus placebo), and cognitive endpoints, with no hepatotoxicity [16, 17, 18]. Phase 3 registration studies are in progress.

The clinical trajectory of danavorexton is therefore that of a pharmacological tool and proof-of-concept agent that validated OX2R agonism across multiple sleep disorder indications and informed the development of the oral candidates now advancing toward registration.

4. Molecular Pharmacology

4.1 Orexin receptor system

The orexin receptor system comprises two G protein-coupled receptors (OX1R and OX2R) and two endogenous neuropeptide ligands (orexin-A and orexin-B) [21, 22]. Orexin-A binds both receptors with similar affinity, while orexin-B binds OX2R with approximately 10-fold higher affinity than OX1R [21]. Both receptors couple primarily to Gq/11 G proteins, activating phospholipase C and intracellular calcium mobilization [2]. In the central nervous system, OX2R is the principal receptor mediating wakefulness promotion and REM sleep suppression: OX2R-deficient mice display narcolepsy with cataplexy, whereas OX1R-deficient mice show only mild sleep fragmentation without cataplexy [26, 28]. OX2R is expressed at high density in wakefulness-promoting nuclei including the tuberomammillary nucleus (histaminergic), locus coeruleus (noradrenergic), and dorsal raphe (serotonergic), and at lower density in the cerebral cortex and hippocampus [27]. The selective loss of orexin-producing neurons in NT1, resulting in undetectable or severely reduced CSF orexin levels (typically less than 110 pg/mL), creates a state of functional OX2R deficiency that is the therapeutic target for agonist replacement [23, 24, 17].

4.2 OX2R agonism: potency and selectivity

Danavorexton activates OX2R with low-nanomolar potency. In the calcium mobilization assay used during the medicinal chemistry campaign (CHO cells expressing human OX2R), the EC₅₀ is 5.5 nM, with a maximum response (E_{max}) comparable to that of the endogenous ligand orexin-A [1]. In an independent inositol phosphate (IP) accumulation assay (reflecting Gq-mediated signaling), Yin et al. (2022) reported an EC₅₀ of 8.1 nM, closely matching the endogenous agonist orexin-B (EC₅₀ 8.2 nM in the same assay system) [2]. The compound is therefore a full agonist at OX2R with potency matching that of the endogenous peptides.

Selectivity for OX2R over OX1R is exceptional. In the calcium mobilization assay, danavorexton shows no measurable OX1R activation at concentrations up to 100 micromolar, yielding a selectivity ratio of greater than 18,000-fold [1]. In the IP accumulation assay, selectivity exceeds 5,000-fold [2]. This degree of selectivity is sub-

stantially greater than that of the endogenous ligands (orexin-A, approximately 2.6-fold selective for OX2R; orexin-B, approximately 10-fold selective) and distinguishes danavorexton from the dual orexin receptor antagonists (suvorexant, lemborexant, daridorexant) that engage both receptor subtypes [1, 2].

4.3 Structural basis of agonism and selectivity

The molecular mechanism of OX2R activation by danavorexton has been resolved at atomic resolution. Yin et al. (2022) determined two cryo-EM structures of the OX2R-danavorexton-G protein ternary complex: the receptor coupled to an engineered Gq mimetic (mGsqiN, 3.3 angstrom resolution, PDB 7SR8) and coupled to Gi1 (3.2 angstrom resolution, PDB 7SQO) [2]. In both structures, danavorexton occupies the orthosteric pocket in the compact U-shaped conformation, burying approximately 460 square angstroms of solvent-accessible surface area [2]. The binding interactions span five transmembrane helices:

The methylsulfonamide pharmacophore forms a hydrogen bond with Gln134 (Ballesteros-Weinstein position 3.32), a residue conserved between OX1R and OX2R [2]. This interaction is essential: the Q134A mutation abolishes signaling by both orexin-B and danavorexton in the IP accumulation assay [2]. The critical role of the sulfonamide was independently confirmed by the medicinal chemistry data: N-methylation (compound 10, EC₅₀ > 30,000 nM) or replacement with acetamide (compound 11, EC₅₀ > 30,000 nM) each reduced agonist activity by greater than 5,000-fold [1].

The phenylcyclohexyl tail engages a hydrophobic subpocket formed by Val138 (3.36), Phe227 (5.42), and Ile320 (6.51) [2].

The carbamate carbonyl makes a weak hydrogen bond with Asn324 (6.55) in the Gq-coupled state [2]. Unlike orexin-B, which requires Asn324 for activation (the N324A mutant is nonfunctional for the peptide), danavorexton retains near-full activity at the N324A mutant (EC₅₀ 18 nM versus 7.5 nM at wild-type), indicating that this interaction is dispensable for small-molecule agonism [2].

The ether oxygen makes solvent-mediated contacts with Thr111 (2.61) [2].

Selectivity over OX1R arises from subtle steric and desolvation differences at only two residues that differ between the receptor subtypes within the orthosteric pocket: Thr111 (2.61) in OX2R is replaced by Ser in OX1R, and Thr135 (3.33) in OX2R is replaced by Ala in OX1R [2]. Subtype-swap mutagenesis experiments confirmed

this mechanism: introduction of both OX2R-corresponding residues into OX1R (the S103T/A127T double mutant) converted OX1R from insensitive to danavorexton (EC₅₀ greater than 100 micromolar) to partially responsive (EC₅₀ 300 nM), while the reciprocal mutations in OX2R (T111S/T135A) reduced potency from 7.5 nM to 3.6 micromolar [2]. The selectivity therefore arises from subtly diminished steric complementarity and less favorable desolvation at the OX1R pocket rather than from allosteric or extracellular loop mechanisms [2].

4.4 G protein coupling and downstream signaling

Both orexin-B and danavorexton induce robust Gq-mediated IP accumulation through OX2R but show poor ability to stimulate Gi1-mediated cAMP reduction [2]. The receptor-Gq interface buries 1,039 square angstroms of surface area, compared to 814 square angstroms for the Gi1 complex, consistent with preferential Gq coupling [2]. The downstream consequences of Gq activation at OX2R include phospholipase C activation, intracellular calcium elevation, and depolarization of postsynaptic neurons in wakefulness-promoting circuits [17].

Ishikawa et al. (2022) characterized the electrophysiological activation of OX2R by danavorexton and found that the activation mode was "very similar to orexin peptide" with rapid association and dissociation kinetics [5]. The rapid kinetics distinguish danavorexton from compounds with slow off-rates that might produce sustained receptor desensitization, and the electrophysiological similarity to the endogenous peptide supports the translational premise that the compound can functionally replace lost orexin signaling in NT1.

4.5 Respiratory circuit activation

Beyond wakefulness promotion, OX2R is expressed on neurons in the respiratory control circuitry, including inspiratory neurons in the pre-Botzinger complex and motoneurons in the phrenic and hypoglossal motor nuclei [9]. Yamada et al. (2024) demonstrated in rodent medullary slice and in vivo preparations that OX2R agonists activate both the diaphragm (via phrenic motoneurons) and the genioglossus muscle (via hypoglossal motoneurons) [9]. Intravenous administration of OX-201 (a related OX2R agonist) at 1 and 3 mg/kg in rats significantly increased diaphragm burst frequency ($p = 0.040$ and $p < 0.001$, respectively), and at 1 mg/kg significantly increased genioglossus burst amplitude ($p < 0.001$) [9]. In unanesthetized mice, oral OX-201 at 3 mg/kg increased minute volume ($p < 0.001$), tidal volume ($p = 0.0017$),

and respiratory rate ($p < 0.001$) [9]. These effects were absent in OX2R knockout mice, confirming receptor dependence [9]. The respiratory circuit activation underlies the clinical observation that danavorexton reverses opioid-induced respiratory depression without reversing analgesia [8] and provides the rationale for the compound's investigation in obstructive sleep apnea [7].

4.6 Off-target pharmacology and desensitization

Published data do not identify significant off-target activity for danavorexton. The greater than 18,000-fold selectivity for OX2R over OX1R indicates negligible OX1R engagement at clinical concentrations [1]. Comprehensive off-target profiling specifically for TAK-925 has not been published; however, the structurally related oral compound TAK-861 showed no greater than 50% inhibition or stimulation at 10 micromolar against 102 tested targets (including monoamine receptors, ion channels, and enzymes), with the exception of cannabinoid receptor 1 (58% inhibition) and progesterone receptor B (62% inhibition) [14]. The structural similarity suggests a similarly clean profile for danavorexton, though this inference requires direct confirmation.

Receptor desensitization risk is low. Repeated administration of danavorexton in the orexin/ataxin-3 mouse model over multiple days produced no evidence of tachyphylaxis [5]. The compound's E_{max} in calcium mobilization assays matches that of orexin-A, indicating full agonism rather than partial agonism [1]. The rapid association/dissociation kinetics are consistent with the physiological pattern of pulsatile orexin release and support the clinical utility of repeated dosing [5].

5. Pharmacokinetics

5.1 Route of administration

Danavorexton is administered exclusively by intravenous infusion. No oral formulation has been developed, and oral bioavailability in humans has not been published. In clinical studies, danavorexton was delivered as a 9-hour continuous intravenous infusion at doses ranging from 5 to 180 mg in healthy volunteers and 5 to 112 mg in patient populations [3, 4, 6]. In the opioid-induced respiratory depression study, sequential 90-minute intravenous infusions of 11 mg and 19 mg were used [8]. The intravenous route provides rapid, controllable onset and offset of pharmacological effect, consistent with the compound's positioning as a clinical pharmacology tool rather than a chronic therapeutic.

5.2 Plasma pharmacokinetics

After single and multiple intravenous infusions, mean plasma concentrations of danavorexton are proportional to dose over the studied dose range [3]. The terminal elimination half-life across all doses ranges from approximately 3.3 to 5.1 hours, with a mean half-life of approximately 3.05 hours reported in the idiopathic hypersomnia study [3, 6]. Plasma concentrations plateau during the 9-hour infusion, with time to plateau estimated between 3 and 7 hours after the start of infusion [6].

In the multiple-rising-dose study (NCT03748979), once-daily 9-hour infusions for 7 consecutive days produced accumulation ratios (AUC at steady state versus after the first dose) of approximately 1, indicating that the compound does not accumulate with repeated daily dosing at this schedule [3].

Exposure in older adults (approximately 65 to 80 years) was 18 to 27 percent higher than in younger adults at the same dose, reflecting age-related changes in distribution volume or clearance [3]. This difference did not produce differential adverse event rates in the single-rising-dose study [3].

In the opioid-induced respiratory depression study, mean plasma concentrations at the end of the 90-minute infusion periods were 82.4 +/- 14.1 ng/mL (maintenance phase) at the 11 mg dose and 155 +/- 28.5 ng/mL (maintenance phase) at the 19 mg

dose [8]. Danavorexton had no apparent effect on remifentanyl pharmacokinetics when coadministered [8].

5.3 Distribution

Volume of distribution has not been formally published for danavorexton in humans. In mice, brain-to-plasma concentration ratios at 0.5 and 1 hour after 10 mg/kg intraperitoneal dosing were 0.2 at both timepoints, indicating moderate but consistent brain penetration [1]. The compound is not a significant substrate of P-glycoprotein at the blood-brain barrier: the multidrug resistance protein 1 (MDR-1) efflux ratio was 0.8, with an apparent permeability (A-to-B) of 169 nm/s, indicating no efflux-mediated limitation of brain exposure [1].

Cerebrospinal fluid penetration in humans was directly measured in healthy volunteers: the mean CSF-to-plasma concentration ratio was approximately 2.8 percent [3]. While this fraction is low in absolute terms, the CSF concentration achieved is sufficient for receptor engagement, as demonstrated by dose-dependent wakefulness promotion and cataplexy suppression at clinical doses [3].

5.4 Metabolism and elimination

Formal metabolic pathway characterization (cytochrome P450 enzyme identification, phase II conjugation, metabolite profiling) has not been published for danavorexton. The compound contains a methyl carbamate and a methylsulfonamide, both susceptible to oxidative metabolism; the piperidine nitrogen is protected by the carbamate, reducing the potential for N-oxidation. The short plasma half-life (3 to 5 hours) is consistent with moderate hepatic clearance.

Investigators combining danavorexton with strong CYP inhibitors or inducers should note that metabolic drug-drug interaction predictions are not available from primary sources, as formal CYP substrate/inhibitor/inducer characterization has not been published. This represents a significant gap in the pharmacokinetic profile and is relevant to study design for combination investigations.

5.5 Pharmacokinetic-pharmacodynamic relationship

A threshold pharmacokinetic-pharmacodynamic relationship has been characterized preclinically. In orexin/ataxin-3 narcolepsy model mice, danavorexton induced a potent, sustained wakefulness-promoting effect when plasma concentrations exceeded a threshold of approximately 100 ng/mL [3]. Below this threshold, wakefulness promotion was partial or absent; above it, the effect was sustained for the duration of exposure. This threshold relationship, combined with the short half-life, is consistent with the clinical observation that wakefulness returns rapidly after infusion cessation and that pharmacological effect is tightly coupled to plasma exposure.

In the multiple-rising-dose study, the dose that produced maximal MWT sleep latency in NT1 (44 mg over 9 hours) maintained plasma concentrations above the mouse efficacy threshold for the duration of infusion [3]. The narcolepsy model mice showed approximately threefold greater sensitivity than wild-type mice [3], consistent with receptor upregulation or denervation supersensitivity from chronic orexin deficiency.

5.6 Special populations

Age-related increases in exposure (18 to 27 percent higher in older versus younger adults) were observed and did not produce differential safety signals [3]. Renal impairment, hepatic impairment, and pregnancy pharmacokinetics have not been characterized. No pharmacogenomic influences (CYP2D6 or other polymorphisms) on danavorexton pharmacokinetics have been identified, a notable distinction from compounds such as tropisetron that are metabolized predominantly by polymorphic enzymes.

6. Preclinical Pharmacology

6.1 In vitro pharmacology

The primary in vitro characterization of danavorexton has been reported across two assay platforms. In the calcium mobilization assay (CHO cells expressing human OX2R), the EC₅₀ is 5.5 nM with an E_{max} comparable to orexin-A [1]. In the inositol phosphate accumulation assay (Gq-mediated signaling), the EC₅₀ is 8.1 nM, matching orexin-B at 8.2 nM [2]. The compound shows no activation of OX1R at concentrations up to 100 micromolar [1].

Electrophysiological characterization in neurons expressing OX2R demonstrated that danavorexton activates the receptor with rapid association and dissociation kinetics, producing an activation pattern described as "very similar to orexin peptide" [5]. This kinetic profile distinguishes the compound from slower-acting agonists that might promote receptor desensitization and supports the functional replacement hypothesis for NT1 treatment.

6.2 Wakefulness promotion in wild-type mice

The first in vivo demonstration was reported by Fujimoto et al. (2022) [1]. ICR mice were administered TAK-925 subcutaneously at 3 mg/kg during the sleep phase (light period) and monitored by electroencephalography (EEG) and electromyography (EMG) for 3 hours. Treated mice showed significantly increased total wakefulness time compared to vehicle controls ($p < 0.001$) [1]. Brain concentrations at 0.5 hours after 10 mg/kg intraperitoneal dosing were 183 ng/g (plasma 880 ng/mL, brain-to-plasma ratio 0.2) and at 1 hour were 63 ng/g (plasma 288 ng/mL, brain-to-plasma ratio 0.2), confirming brain penetration and indicating a rapid central nervous system elimination profile [1].

6.3 Narcolepsy mouse models

Three narcolepsy mouse models have been used to characterize danavorexton:

Orexin/ataxin-3 transgenic mice (selective ablation of orexin neurons): Evans et al. (2022) administered subcutaneous danavorexton at 0.3, 1, 3, and 10 mg/kg during the active phase [3]. The compound dose-dependently increased total wakefulness time (significant at 1, 3, and 10 mg/kg; $p \leq 0.05$, $p \leq 0.05$, and $p \leq 0.01$, respectively), decreased total time in both NREM and REM sleep, and produced longer individual wakefulness episodes (significant at 10 mg/kg, $p \leq 0.05$) with fewer wakefulness-to-sleep transitions (significant at 3 and 10 mg/kg) [3]. Cataplexy-like episodes were suppressed at the lower doses of 0.3 and 1 mg/kg ($p \leq 0.05$ and $p \leq 0.01$, respectively), with the narcolepsy model mice demonstrating approximately threefold greater sensitivity than wild-type mice [3].

Ishikawa et al. (2022) independently confirmed and extended these findings to repeated dosing [5]. Acute and repeated subcutaneous administration promoted wakefulness and ameliorated fragmentation of wakefulness during the active phase. EEG power spectral analysis demonstrated that danavorexton normalized the dysregulated power spectrum observed in orexin/ataxin-3 mice [5]. Repeated administration significantly suppressed body weight gain, consistent with the known role of orexin signaling in metabolic regulation [5]. Critically, repeated dosing produced no evidence of receptor desensitization or tachyphylaxis [5].

Orexin/tTA; TetO-DTA mice (doxycycline-inducible selective degeneration of orexin neurons): Sun et al. (2023) evaluated TAK-925 at 1, 3, and 10 mg/kg subcutaneously alongside the related OX2R agonist ARN-776 at the same doses intraperitoneally [10]. Both compounds produced dose-related delays in NREM sleep onset and reduced cumulative cataplexy during a 6-hour post-dosing period [10]. TAK-925 appeared more potent: all doses produced continuous wakefulness during the first hour after dosing, whereas ARN-776's wakefulness-promoting effects were more dose-dependent, and lower doses of TAK-925 produced substantially longer sleep onset latencies than comparable doses of ARN-776 [10]. Both compounds also increased gross motor activity, running wheel activity, and body temperature [10].

6.4 Non-human primate pharmacology

Evans et al. (2023) characterized danavorexton in two non-human primate species [4]. In common marmosets, subcutaneous danavorexton at 0.1 mg/kg significantly increased wakefulness by EEG analysis ($p < 0.05$), with doses of 1 to 10 mg/kg producing highly significant effects ($p < 0.001$) [4]. In cynomolgus monkeys, subcutaneous doses of 1 to 3 mg/kg significantly increased wakefulness ($p \leq 0.05$) [4]. The

minimum effective dose in cynomolgus monkeys (1 mg/kg) matches that of the oral successor TAK-861 [14]. The cross-species translatability of OX2R agonism informed dose selection for the first-in-human clinical studies.

6.5 Respiratory pharmacology

The respiratory effects of OX2R agonism have been characterized in complementary rodent preparations. Yamada et al. (2024) demonstrated that OX2R agonists activate inspiratory neurons in the pre-Botzinger complex and motoneurons in the phrenic and hypoglossal motor nuclei, producing coordinated activation of the diaphragm and genioglossus muscles [9]. In anesthetized rats, intravenous OX-201 (a related OX2R agonist) at 1 and 3 mg/kg significantly increased diaphragm burst frequency ($p = 0.040$ and $p < 0.001$, respectively) [9]. In unanesthetized mice, oral OX-201 at 3 mg/kg increased minute volume ($p < 0.001$), tidal volume ($p = 0.0017$), and respiratory rate ($p < 0.001$), and decreased inspiratory time ($p < 0.001$) [9]. These effects were absent in OX2R knockout mice, confirming receptor dependence [9]. The respiratory stimulant mechanism provides the pharmacological basis for danavorexton's observed reversal of opioid-induced respiratory depression in human clinical studies [8].

6.6 Preclinical toxicology

Published preclinical toxicology data for danavorexton are limited. No organ toxicity signals were identified in the published preclinical literature, and the safety profile in all clinical studies is consistent with the expected pharmacological effect (wakefulness promotion) without evidence of target-organ toxicity [3, 5, 6, 7, 8]. No hepatotoxicity was observed in any preclinical study of danavorexton, in contrast to the oral successor TAK-994, which produced hepatocellular single-cell necrosis in mouse studies at doses of 300 mg/kg/day or greater following CYP450 induction [15]. The structurally distinct piperidine carbamate scaffold of danavorexton, combined with its intravenous route of administration (bypassing first-pass hepatic metabolism), may contribute to the absence of a hepatic signal.

7. Clinical Evidence Base

The following section summarizes clinical data from published studies conducted under institutional review board approval and registered clinical trial protocols. Danavorexton is not approved for any indication in any jurisdiction. All clinical applications described represent investigational use under controlled research conditions.

7.1 Phase 1 single-rising-dose study in healthy volunteers and narcolepsy type 1 (NCT03332784)

Evans et al. (2022) reported a Phase 1, randomized, double-blind, placebo-controlled, single-rising-dose study in 58 participants: 36 healthy adults, 8 older adults (65 to 80 years), and 14 adults with NT1 (median age 32.5 years) [3]. Participants with NT1 received single 9-hour intravenous infusions of danavorexton at 5, 11.2, or 44.8 mg, or placebo.

The Maintenance of Wakefulness Test (MWT) was the principal pharmacodynamic endpoint. Placebo-adjusted changes in average sleep latency (95% CI) in NT1 participants were 18.79 minutes (11.99, 25.60) for danavorexton 5 mg, 36.06 minutes (27.73, 44.40) for 11.2 mg, and 36.66 minutes (27.34, 45.98) for 44.8 mg [3]. Karolinska Sleepiness Scale (KSS) scores were reduced: mean change from baseline at 9 hours was negative 2.5 (SD 1.52) for danavorexton 5 mg versus positive 0.3 (SD 2.87) for placebo [3]. One NT1 participant experienced systolic blood pressure and heart rate increases judged related to study drug; one experienced a hypnagogic hallucination; and one experienced cataplexy episodes and sleep paralysis 14 hours after the infusion had stopped [3].

7.2 Phase 1b study in sleep-deprived healthy volunteers (NCT03522506)

Evans et al. (2023) reported a Phase 1b, randomized, double-blind, placebo-controlled, four-way crossover study in 18 sleep-deprived healthy adults [4]. Participants received single 9-hour intravenous infusions of danavorexton 44 mg, danavorexton 112 mg, modafinil 300 mg oral (active comparator), or placebo.

Mean MWT sleep latencies were 21.4 minutes (danavorexton 44 mg), 31.8 minutes (danavorexton 112 mg), and 9.2 minutes (placebo); both danavorexton doses were significantly superior to placebo ($p < 0.001$) [4]. KSS scores were significantly lower with danavorexton than with placebo (44 mg: $p = 0.010$; 112 mg: $p < 0.001$) [4].

7.3 Phase 1 multiple-rising-dose study in narcolepsy type 1 and type 2 (NCT03748979)

Evans et al. (2022) reported a Phase 1, randomized, double-blind, placebo-controlled, multiple-rising-dose study with 7-day dosing in 24 healthy adults, 13 adults with NT1 (median age 32 years), and 14 adults with NT2 (median age 24.5 years) [3]. NT1 participants received danavorexton 11 or 44 mg intravenously over 9 hours daily; NT2 participants received 44 or 112 mg.

Narcolepsy type 1 results: MWT sleep latency improved from baseline by 35.85 minutes with danavorexton 11 mg on day 1 (95% CI, 27.66 to 44.04; $p < 0.0001$) and by 38.72 minutes with 44 mg on day 7 (95% CI, 29.95 to 47.50; $p < 0.0001$) [3]. All participants receiving the 44 mg dose achieved the maximum MWT sleep latency of 40 minutes in all sessions on both day 1 and day 7 [3]. ESS scores normalized from a baseline of 18.6 to 0.0 on day 7 in the 44 mg group, and from 18.0 to 9.8 in the 11 mg group [3]. Cataplexy episodes decreased to zero in both danavorexton dose groups during infusion, compared to a mean of 1.8 episodes in the placebo group [3]. Psychomotor vigilance testing improved at the 44 mg dose: change in mean reciprocal 10% slowest reaction time of positive 0.59 ($p = 0.0062$) [3]. On the Patient Global Impression of Change (PGI-C) at day 7, 4 of 5 (80%) NT1 participants receiving 44 mg rated themselves as "very much improved" and 1 of 5 (20%) as "much improved," compared to 2 of 4 (50%) placebo participants reporting "no change" [3].

Narcolepsy type 2 results: MWT sleep latency improved from baseline on day 1 by 22.44 minutes with 44 mg (95% CI, 14.88 to 30.00; $p < 0.0001$) and 29.92 minutes with 112 mg (95% CI, 23.23 to 36.61; $p < 0.0001$) [3]. The demonstration of efficacy in NT2, in which CSF orexin levels are not necessarily deficient, established that OX2R agonism promotes wakefulness through mechanisms beyond simple replacement of lost signaling [3].

7.4 Phase 1b study in idiopathic hypersomnia (NCT04091438)

Mignot et al. (2023) reported a Phase 1b, randomized, double-blind, placebo-controlled, two-period crossover study in 28 adults with idiopathic hypersomnia (IH) diagnosed according to International Classification of Sleep Disorders, Third Edition criteria [6]. Participants (mean age 31.7 years, 78% female) received a single 9-hour intravenous infusion of danavorexton 112 mg or placebo with a 1-day washout between periods.

MWT sleep latency improved by 29.4 minutes versus placebo (95% CI, 25.64 to 33.17; $p < 0.0001$) [6]. Ninety-six percent of danavorexton-treated participants achieved the maximum sleep latency of 40 minutes versus 3.8 percent on placebo [6]. KSS score was reduced by 3.31 points (95% CI, negative 4.15 to negative 2.48; $p < 0.0001$) [6]. Psychomotor vigilance task lapses decreased (difference negative 0.85; 95% CI, negative 1.3 to negative 0.4; $p = 0.001$) and reaction time improved (difference negative 25.17 ms; 95% CI, negative 38.05 to negative 12.29; $p < 0.001$) [6]. Plasma half-life in this study was estimated at 3.05 hours [6].

Arnulf and Maranci (2023) noted in an accompanying editorial that this proof-of-concept result in a population without established orexin deficiency has implications for understanding IH pathophysiology and expands the potential therapeutic scope of OX2R agonism [13].

7.5 Phase 1b study in obstructive sleep apnea (NCT05180890)

Bogan et al. (2023) reported a Phase 1b, randomized, placebo-controlled, three-period crossover study of single intravenous infusions of danavorexton 44 mg and 112 mg in 25 adults (ages 18 to 67 years) with obstructive sleep apnea experiencing residual excessive daytime sleepiness despite adequate continuous positive airway pressure therapy [7]. Improvements in MWT sleep latency, KSS scores, and psychomotor vigilance task performance were observed with both doses compared to placebo [7]. Treatment-emergent adverse events (TEAEs) occurred in 16 participants (64%), all mild or moderate in severity; 12 participants (48%) had treatment-related events; and 7 participants (28%) reported urinary adverse events [7]. No deaths or discontinuations due to adverse events occurred [7].

7.6 Phase 1 study in opioid-induced respiratory depression

Van Lemmen et al. (2025) reported a Phase 1, double-blind, placebo-controlled, two-way crossover study in 12 healthy male volunteers (13 randomized; ages 18 to 55) evaluating danavorexton as a countermeasure for remifentanyl-induced respiratory depression and sedation [8]. Participants received sequential 90-minute intravenous infusions of danavorexton at 11 mg (low dose) and 19 mg (high dose) during a continuous remifentanyl infusion titrated to produce a 30 to 40 percent decrease in minute ventilation under isohypercapnic conditions.

Compared to placebo, minute volume increased by 8.2 L/min (95% CI, 5.0 to 11.4; $p < 0.001$) at the low dose and 13.0 L/min (95% CI, 9.4 to 16.5; $p < 0.001$) at the high dose [8]. Tidal volume increased by 312 mL (low dose) and 483 mL (high dose); respiratory rate increased by 3.8 and 5.2 breaths per minute, respectively (all $p < 0.001$ versus placebo) [8]. Sedation was reversed: the Visual Analog Scale decreased by 29.7 mm at the high dose ($p < 0.001$), and the Richmond Agitation-Sedation Scale improved by 0.4 points ($p < 0.001$) [8].

Danavorexton did not reverse opioid analgesia: no significant differences in pain tolerance were observed between danavorexton and placebo (low dose $p = 0.491$; high dose $p = 0.140$) [8]. Lambert and Hirota (2024) observed in a British Journal of Anaesthesia editorial that danavorexton "could be a useful addition to the postoperative drug cupboard" as an agent promoting recovery from opioid sedation while preserving analgesia [12].

7.7 Biomarker development

Tracey et al. (2024) conducted a secondary analysis of MWT data from the danavorexton clinical studies to develop novel biomarkers of sleepiness and treatment response [11]. Beyond traditional sleep onset latency, the authors identified microsleep metrics (rate and duration of brief 3-to-15-second sleep episodes), AI-derived sleep probability scores, and theta/alpha ratio qEEG measures as treatment-response predictors [11]. Danavorexton significantly reduced microsleep rate in NT1 cohorts (days 1 and 7; $p \leq 0.005$) and NT2 cohorts ($p < 0.0001$), with microsleep episodes "basically eliminated" at the highest dose on day 1 [11]. KSS reductions were 3.3 to 4.1 points in NT1 cohorts by day 7 [11]. Sleepiness slope (rate of increase in log-transformed sleepiness) correlated strongly with sleep onset latency ($R = 0.90$ in NT1, $R = 0.95$ in NT2) and may represent a clinically measurable outpatient endpoint for future studies [11].

7.8 Development status

As of May 2026, no Phase 2 or Phase 3 clinical trials of danavorexton are registered or anticipated. The therapeutic development pathway has transitioned to the oral successor TAK-861 (oveporexton), which is in Phase 3 development for NT1 [18]. Danavorexton's continuing role is as a pharmacological tool for mechanistic investigations, enabled by its precisely controllable pharmacokinetic profile.

8. Sourcing and Quality Verification

Danavorexton is not approved for any indication in any jurisdiction and is not manufactured as a pharmaceutical-grade product. No commercial drug product (capsule, tablet, or injectable solution) is marketed. The compound is available exclusively as a research-grade chemical from specialized suppliers.

Research-grade danavorexton (CAS 2114324-48-8) is supplied by multiple chemical research vendors including MedChemExpress, MedKoo Biosciences, DC Chemicals, and Probechem Biochemicals. Typical purity is greater than 98 percent by HPLC. Supply is in milligram-to-gram quantities as the free base; salt forms (hydrochloride, tosylate) may be available from individual vendors but are not standardized. Pricing is characteristic of investigational-phase research compounds: at the time of monograph preparation, typical cost is in the range of \$100 to \$500 per 10 milligrams, with volume-dependent discounting.

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

High-performance liquid chromatography area-percent purity, ideally greater than 98 percent. Reverse-phase C18 columns with UV detection at 220 to 254 nm are standard.

High-resolution mass spectrometry confirmation of molecular weight: expected $[M+H]^+ = 425.21$ for the protonated free base ($C_{21}H_{33}N_2O_5S^+$). Deviation of greater than 5 ppm from the theoretical exact mass warrants investigation.

Nuclear magnetic resonance spectroscopy (1H and ^{13}C) for structural confirmation, particularly verification of the (2R,3S) stereochemistry and the cis-cyclohexane configuration. Comparison to published spectral data in the Fujimoto et al. (2022) supplementary materials is recommended [1].

Chiral HPLC or optical rotation measurement for diastereomeric purity confirmation. The (2R,3S)-cis diastereomer is the active form; contamination with other diastereomers (particularly the less-active trans isomer) would reduce apparent potency in dose-response experiments.

Residual solvent analysis by gas chromatography, particularly for common synthesis solvents (dichloromethane, methanol, ethyl acetate, dimethylformamide).

The clinical formulation used in Takeda's Phase 1 studies was a proprietary intravenous preparation manufactured under Good Manufacturing Practice conditions [3, 6]. The composition, excipients, and stability characteristics of the clinical formulation have not been publicly disclosed. Research-grade material reconstituted by individual investigators will differ from the clinical formulation; investigators conducting parenteral administration in preclinical studies should ensure appropriate sterile filtration and endotoxin testing.

9. Reconstitution and Handling

Research-grade danavorexton is supplied as a white to off-white solid (free base). Comprehensive physical property data (melting point, aqueous solubility, logP) have not been published; the following handling recommendations are based on structural considerations and published clinical formulation parameters.

Solubility and stock preparation: The compound contains both a basic piperidine nitrogen (partially masked by the carbamate) and a methylsulfonamide, conferring moderate aqueous solubility. For in vitro studies, stock solutions are typically prepared in dimethyl sulfoxide (DMSO) at 10 to 50 mM concentrations and diluted into aqueous assay buffer immediately before use. For in vivo subcutaneous or intraperitoneal administration in rodent studies, the published literature describes formulation in standard vehicle systems without specifying composition [1, 3, 5].

Clinical formulation parameters: In the idiopathic hypersomnia study, Mignot et al. (2023) described the clinical formulation as 675 mL containing 112 mg of danavorexton (approximately 0.17 mg/mL), delivered at 75 mL/h over 9 hours [6]. In the opioid-induced respiratory depression study, sequential 90-minute infusions were used at higher effective delivery rates [8]. The clinical infusion vehicle has not been publicly disclosed.

Storage: Solid compound should be stored desiccated at negative 20 degrees Celsius for long-term storage or at 2 to 8 degrees Celsius for short-term working stock. DMSO stock solutions should be aliquoted for single use and stored at negative 20 degrees Celsius; freeze-thaw stability has not been characterized, and single-use aliquoting is recommended as a precaution. Aqueous solutions should be prepared fresh for each experiment or stored at 2 to 8 degrees Celsius for no more than 7 days, pending published stability data.

Light and oxygen sensitivity: No specific light or oxygen stability data have been published for danavorexton. As a general precaution for compounds with aromatic and heterocyclic structural elements, storage in amber vials under inert atmosphere (nitrogen or argon) is recommended for long-term solid and solution storage.

Aliquoting for in vivo studies: For studies requiring repeated dosing, preparation of single-use aliquots from concentrated stock is recommended to minimize contamination and degradation from repeated ambient exposure.

10. Stack Interactions and Combinations

10.1 Pharmacokinetic interactions

Formal drug-drug interaction studies for danavorexton (substrate, inhibitor, and inducer status for CYP enzymes and drug transporters) have not been published. The following considerations are based on limited available data and structural inference.

P-glycoprotein: Danavorexton is not a significant P-glycoprotein (MDR-1) substrate. The efflux ratio in a bidirectional transport assay was 0.8, with an apparent permeability (A-to-B) of 169 nm/s [1]. Coadministration with P-glycoprotein inhibitors (ketoconazole, ritonavir, cyclosporine) is unlikely to substantially alter central nervous system exposure.

Opioid pharmacokinetics: In the crossover study with remifentanyl, danavorexton had no apparent effect on remifentanyl plasma pharmacokinetics [8]. This observation, while limited to a single opioid in a small cohort, suggests that danavorexton does not inhibit the carboxylesterase pathway responsible for remifentanyl metabolism.

CYP enzyme interactions: The absence of published CYP substrate/inhibitor/inducer data represents a significant gap. The methyl carbamate and methylsulfonamide functional groups are susceptible to CYP-mediated oxidation, but the specific enzymes involved have not been identified. Investigators combining danavorexton with strong CYP inhibitors (ketoconazole, itraconazole, paroxetine, fluconazole) or inducers (rifampin, carbamazepine, phenytoin) should anticipate potential alterations in danavorexton exposure pending formal interaction characterization.

10.2 Pharmacodynamic interactions

Opioids: Danavorexton reverses opioid-induced respiratory depression and sedation without reversing analgesia [8]. The mechanism is through wakefulness-promoting and respiratory-stimulating pathways (OX2R-mediated activation of cortical

arousal circuits and brainstem respiratory centers) that are independent of opioid receptor signaling [8, 9]. This pharmacodynamic profile positions danavorexton as a potential adjunct in opioid-containing regimens rather than an opioid antagonist.

Orexin receptor antagonists: Coadministration of an OX2R agonist with an orexin receptor antagonist (suvorexant, lemborexant, daridorexant) produces pharmacological antagonism. The clinical scenario is pharmacologically irrational but may arise inadvertently in research participants receiving orexin antagonists for insomnia. Investigators should ensure adequate washout of orexin antagonists before danavorexton administration.

Stimulants and wakefulness-promoting agents: Combination with modafinil, solriamfetol, pitolisant, or amphetamine-based stimulants produces additive wakefulness promotion through complementary mechanisms. Evans et al. (2023) included modafinil 300 mg as an active comparator in the sleep-deprived volunteer study but no direct combination arm was studied [4]. The combination is pharmacologically additive with potential for excessive wakefulness, cardiovascular stimulation (particularly blood pressure and heart rate elevation), and insomnia.

Sodium oxybate: Sodium oxybate (a GABA-B agonist with sedating and sleep-consolidating properties) and danavorexton have opposing acute pharmacological effects. Theoretical combinations (sodium oxybate at bedtime for sleep consolidation, danavorexton by daytime infusion for wakefulness) have not been studied but represent a plausible research direction given complementary mechanisms [17, 18].

Cardiovascular agents: Danavorexton produces transient, dose-dependent blood pressure elevation and tachycardia [3, 8]. Coadministration with other cardiovascular stimulants (sympathomimetics, anticholinergics) may produce additive hemodynamic effects. One NT1 participant showed PR interval prolongation (180 to 235 ms) that occurred during both placebo and active treatment [3]; caution is warranted with concurrent atrioventricular node-active agents (beta-blockers, calcium channel blockers, digitalis).

11. Adverse Events and Safety Signal

11.1 Common adverse events

The adverse event profile of danavorexton has been characterized across six clinical studies enrolling over 150 participants including healthy volunteers, NT1, NT2, idiopathic hypersomnia, and obstructive sleep apnea populations [3, 4, 6, 7, 8]. The compound is generally well tolerated. All treatment-emergent adverse events (TEAEs) across all studies have been mild or moderate in severity, with no deaths, no serious adverse events attributed to study drug, and no discontinuations due to adverse events.

Pollakiuria (urinary frequency): The most distinctive drug-related adverse event, observed consistently across patient populations. In the multiple-rising-dose study, pollakiuria occurred in 4 of 5 NT1 participants receiving 44 mg and 2 of 5 NT2 participants receiving 112 mg, and was considered drug-related by investigators [3]. In the idiopathic hypersomnia study, 4 participants (16.0%) reported urinary TEAEs, all mild [6]. In the obstructive sleep apnea study, 28 percent reported urinary adverse events [7]. The mechanism is plausibly attributable to OX2R-mediated activation of central autonomic circuits regulating bladder function.

Blood pressure elevation: Transient, dose-dependent increases in systolic and diastolic blood pressure were observed across studies. In the multiple-rising-dose study on day 7, mean changes were: SBP positive 5.6 mmHg and DBP positive 9.2 mmHg in healthy volunteers at 180 mg, SBP 0.0 mmHg and DBP positive 5.9 mmHg in NT1 at 44 mg, and SBP positive 9.4 mmHg and DBP positive 9.3 mmHg in NT2 at 112 mg [3]. In the idiopathic hypersomnia study, placebo-adjusted mean increases were SBP positive 3.99 mmHg and DBP positive 3.58 mmHg [6]. In the OIRD study, 69.2 percent of participants (9 of 13) had a systolic blood pressure increase greater than 20 mmHg from baseline at some point during danavorexton administration [8]. Blood pressure effects are consistent with OX2R-mediated sympathetic activation and resolved after cessation of infusion.

Heart rate increase: Tachycardia was observed most prominently in the NT1 population at 44 mg (mean pulse increase positive 15.9 bpm on day 7 of the multiple-rising-dose study) [3]. The mechanism is likely sympathetic activation sec-

ondary to wakefulness promotion.

Insomnia: Expected pharmacological effect of a wakefulness-promoting agent. One participant in the OIRD study experienced insomnia lasting 1 day (drug-related) [8]. One case of severe insomnia was reported in the idiopathic hypersomnia study [6].

Headache and dizziness: Reported at low frequency across studies, among the most common TEAEs in the idiopathic hypersomnia population alongside pollakiuria and rhinorrhea [6].

11.2 Uncommon and notable adverse events

Cardiac conduction: One NT1 participant in the single-rising-dose study showed PR interval prolongation from 180 to 235 ms during placebo treatment and again from 180 to 234 ms during the 112 mg danavorexton treatment period [3]. The occurrence during both placebo and active treatment periods suggests a pre-existing conduction variant rather than a drug effect, though monitoring is warranted.

Post-infusion rebound phenomena: One NT1 participant experienced cataplexy episodes and sleep paralysis 14 hours after danavorexton infusion cessation, and one participant experienced a hypnagogic hallucination [3]. These events likely represent withdrawal from acute OX2R agonism in the context of underlying orexin deficiency, analogous to rebound phenomena with discontinuation of other wakefulness-promoting agents.

11.3 Absence of hepatotoxicity

No hepatic adverse events or clinically significant liver enzyme changes were reported in any danavorexton clinical study [3, 6, 7, 8]. This profile distinguishes danavorexton from the oral successor TAK-994 (firazorexton), which produced dose-dependent hepatotoxicity with five cases of significant liver enzyme elevation and three cases meeting Hy's law criteria across 73 participants in the Phase 2 trial [15, 17]. Shinozawa et al. (2025) attributed the TAK-994 hepatotoxicity to reactive metabolite covalent binding to hepatic proteins, with a daily covalent binding burden of 2.94 to 17.6 mg exceeding the 1 mg threshold for idiosyncratic DILI risk [15]. The absence of hepatotoxicity with danavorexton may reflect the different struc-

tural scaffold (piperidine carbamate versus TAK-994), the intravenous route (bypassing first-pass hepatic metabolism), or a genuinely lower intrinsic hepatotoxic liability.

11.4 Safety database limitations

The danavorexton safety database encompasses approximately 150 participants across six short-duration studies (single-dose to 7-day dosing). This database is sufficient to detect common adverse events (frequency greater than approximately 5 percent) but is not powered to exclude rare idiosyncratic toxicities. No long-term safety data exist. Investigators should weight the favorable short-term tolerability profile against the absence of chronic exposure data when designing research protocols.

11.5 Laboratory and vital sign monitoring

No clinically significant changes in laboratory values (hematology, clinical chemistry, urinalysis) were reported in any study [3, 6]. Electrocardiographic monitoring identified the isolated PR interval prolongation described above; no QT prolongation, arrhythmias, or other clinically significant ECG changes were reported [3]. All vital sign changes resolved after cessation of infusion.

12. Comparative Assessment

This section presents a structured comparative assessment of danavorexton against four alternative compounds in the narcolepsy and excessive daytime sleepiness pharmacotherapy space, evaluated against five competency standards: novelty, effect size, promising potential (current development state and trajectory), side-effect profile, and overall validation. The comparators span the mechanistic and development-stage landscape relevant to danavorexton's positioning: two OX2R agonist successors (TAK-994 and TAK-861) and two approved non-orexin-agonist alternatives (pitolisant and solriamfetol).

12.1 TAK-994 (firazorexton)

Mechanism: Oral orexin 2 receptor-selective agonist. EC50 approximately 19 nM at human OX2R, with selectivity approximately 3,000-fold over OX1R [14]. Same receptor target as danavorexton but a distinct chemical scaffold enabling oral bioavailability.

Development trajectory: Takeda advanced TAK-994 through a Phase 2 randomized, double-blind, placebo-controlled trial (NCT04820842) in NT1 published in the New England Journal of Medicine [31]. Seventy-three participants received 30, 90, or 180 mg twice daily or placebo for 8 weeks [17].

Clinical outcome: TAK-994 produced the largest effect sizes reported in narcolepsy pharmacotherapy: ESS reductions of 10.1 to 13.0 points versus placebo, and near-complete eradication of cataplexy (incidence ratio 0.05 to 0.20 versus placebo) [17, 31]. The trial was terminated early due to dose-dependent hepatotoxicity: five significant liver enzyme elevations and three Hy's law cases [15, 17]. Mechanistic investigation attributed hepatotoxicity to reactive metabolite covalent binding with a daily burden exceeding the 1 mg threshold for idiosyncratic DILI [15].

Comparison to danavorexton: TAK-994 validates the clinical utility of oral OX2R agonism with effect sizes exceeding those achievable by indirect mechanisms. Danavorexton established the proof of concept; TAK-994 confirmed it could translate to oral administration with even larger clinical effects. The hepatotoxic liability absent in danavorexton appears specific to TAK-994's metabolism.

Novelty: 4/5. Effect size: 5/5. Promising potential: 1/5. Side-effect profile: 1/5.
Overall validation: 3/5.

12.2 TAK-861 (oveporexton)

Mechanism: Oral OX2R-selective agonist. EC50 of 2.5 nM at human OX2R, with 3,000-fold selectivity over OX1R [14]. Structurally distinct from both danavorexton and TAK-994; contains a difluoropyrrolidine core [14]. Approximately tenfold more potent than TAK-994 and comparable to danavorexton at OX2R [14].

Development trajectory: Mitsukawa et al. (2024) demonstrated a minimum effective dose of 1 mg/kg orally in mice and monkeys, with narcolepsy model mice showing 30-fold greater sensitivity [14]. Phase 2b (NCT05687903) in 112 NT1 participants showed MWT improvements of 13.7 to 26.6 minutes versus placebo, ESS reductions of 6.4 to 11.3 points, and cognitive improvements (PVT lapses reduced by 8.60 to 10.77 versus placebo, all $p < 0.01$) at doses of 0.5 to 7 mg [16, 17]. No hepatotoxicity [18]. Phase 3 underway.

Comparison to danavorexton: TAK-861 is the clinical realization of the mechanism danavorexton validated. The oral route and favorable hepatic safety profile address both major limitations of the danavorexton (IV-only) and TAK-994 (hepatotoxicity) programs. Effect sizes at Phase 2 are clinically robust though modestly smaller than TAK-994, possibly reflecting more conservative dosing informed by the TAK-994 safety experience.

Novelty: 4/5. Effect size: 4/5. Promising potential: 5/5. Side-effect profile: 4/5.
Overall validation: 4/5.

12.3 Pitolisant (Wakix)

Mechanism: Inverse agonist/antagonist at the histamine H3 receptor. Ki of 0.16 nM and EC50 of 1.5 nM at human H3R [20]. By blocking presynaptic H3 autoreceptors, pitolisant enhances histaminergic neurotransmission in the tuberomammillary nucleus, promoting wakefulness through a mechanism independent of the orexin system [20]. Oral administration. Does not address the underlying orexin deficiency.

Development trajectory: Bioprojet advanced pitolisant through Phase 3 trials (HARMONY I, HARMONY CTP) to EMA approval in 2016 and FDA approval in 2019 for excessive daytime sleepiness and cataplexy in narcolepsy [20, 29, 30].

Clinical outcome: In Phase 3, ESS responders (reduction ≥ 3 points) were 69.0% with pitolisant versus 35.1% with placebo ($p = 0.001$); 36.2% normalized to ESS ≤ 10 versus 10.5% placebo ($p = 0.005$) [20]. MWT sleep latency increased from 3.5 to 10.4 minutes versus 3.4 to 6.8 minutes with placebo ($p = 0.017$) [20]. Weekly cataplexy rate decreased by 75% from baseline versus 38% with placebo [30].

Comparison to danavorexton: Pitolisant's MWT improvements (approximately 3.6 minutes over placebo) are substantially smaller than danavorexton's (29 to 39 minutes over placebo). The mechanistic distinction is fundamental: pitolisant modulates a downstream effector (histamine) of the broader arousal network, while danavorexton directly engages the lost receptor signaling in NT1. Pitolisant's advantages are oral administration, regulatory approval, established long-term safety, and low abuse potential.

Novelty: 3/5. Effect size: 3/5. Promising potential: 3/5. Side-effect profile: 4/5. Overall validation: 4/5.

12.4 Solriamfetol (Sunosi)

Mechanism: Selective dopamine and norepinephrine reuptake inhibitor with lower binding affinity than traditional stimulants and no monoamine-releasing effects at therapeutic doses [19]. Oral administration. Does not address orexin deficiency or cataplexy.

Development trajectory: Jazz Pharmaceuticals advanced solriamfetol through a Phase 3 trial in 236 narcolepsy participants (75, 150, 300 mg for 12 weeks) to FDA approval in 2019 for excessive daytime sleepiness in narcolepsy and obstructive sleep apnea [19].

Clinical outcome: At 12 weeks, ESS changes were negative 6.4 (300 mg), negative 5.4 (150 mg), and negative 1.6 (placebo); placebo-adjusted difference negative 4.7 points at 300 mg (95% CI, negative 6.6 to negative 2.9; $p < 0.0001$) [19]. MWT improved by 12.3 minutes (300 mg) and 9.8 minutes (150 mg) versus 2.1 minutes (placebo); treatment difference 10.14 minutes at 300 mg (95% CI, 6.39 to 13.90) [19]. Most common adverse events: headache (21.5%), nausea (10.7%), decreased appetite (10.7%), anxiety (5.1%) [19]. No effect on cataplexy.

Comparison to danavorexton: Solriamfetol provides moderate wakefulness improvement through a non-disease-modifying mechanism. MWT improvements of approximately 10 minutes at 300 mg are clinically significant but substantially

smaller than OX2R agonist effects. The absence of cataplexy benefit limits its value in NT1. Solriamfetol's advantages are oral availability, regulatory approval, and well-characterized safety over 12 weeks. The modest abuse potential associated with dopaminergic agents is a consideration absent from the OX2R agonist class.

Novelty: 2/5. Effect size: 3/5. Promising potential: 3/5. Side-effect profile: 3/5. Overall validation: 4/5.

12.5 Comparator summary

The four compounds occupy distinct positions in the narcolepsy pharmacotherapy landscape. **TAK-994** demonstrated that oral OX2R agonism produces the largest effect sizes in the field but was terminated by hepatotoxicity; it validates the mechanism while demonstrating the safety challenge. **TAK-861** is the most advanced OX2R agonist in development, with strong Phase 2 data, no hepatic signal, and Phase 3 underway; it represents the commercial realization of the proof of concept danavorexton established. **Pitolisant** is approved with a favorable safety profile and addresses both EDS and cataplexy through an indirect histaminergic mechanism, but its effect sizes are substantially smaller than those of OX2R agonists. **Solriamfetol** provides moderate wakefulness improvement through dopamine/norepinephrine reuptake inhibition but offers no cataplexy benefit and has a less favorable consideration as a dopaminergic agent.

Danavorexton occupies a unique position as the pharmacological parent compound of the OX2R agonist class. Its intravenous route limits therapeutic utility, but it established clinical proof of concept for OX2R agonism across the broadest range of indications in the class: NT1, NT2, idiopathic hypersomnia, obstructive sleep apnea, and opioid-induced respiratory depression. For investigators, danavorexton's primary value is as a precisely controllable research tool. The short half-life (3 to 5 hours) and intravenous route provide rapid onset and offset of OX2R agonism, enabling pharmacodynamic studies with temporal resolution not achievable with oral agents. The absence of hepatotoxicity, dose-proportional pharmacokinetics, and characterized CSF penetration further support its utility as an investigational probe of orexin receptor function.

13. References

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