

RESEARCH MONOGRAPH . COMPOUND PROFILE

Cebranopadol

A first-in-class spiro-indole analgesic with near-equipotent agonism at nociceptin/orphanin FQ peptide and classical opioid receptors, developed by Grunenthal and advanced by Tris Pharma through Phase 3 acute pain trials, distinguished from conventional opioids by NOP receptor-mediated attenuation of respiratory depression and abuse liability.

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ABSTRACT

Cebranopadol (GRT-6005, PRK-101, TRN-228) is a first-in-class small-molecule analgesic that acts as a high-affinity agonist at the nociceptin/orphanin FQ peptide (NOP) receptor and at the three classical opioid receptor subtypes (mu, kappa, and delta), with near-equipotent activation of the NOP and mu-opioid receptors at low-nanomolar concentrations. The compound was discovered at Grunenthal GmbH in Aachen, Germany, and first described in patent literature in 2002. Scientific characterization beginning in 2013 established cebranopadol as a spiro[cyclohexane-dihydropyrano[3,4-b]indole] derivative with binding affinities (K_i) of 0.7 nM at the human mu-opioid receptor, 0.9 nM at the human NOP receptor, 2.6 nM at the kappa-opioid receptor, and 18 nM at the delta-opioid receptor, and with functional potencies (EC_{50}) of 1.2 nM (mu), 13 nM (NOP), 17 nM (kappa), and 110 nM (delta) in calcium mobilization assays, yielding a rank order of potency mu approximately equal to NOP, then kappa, then delta. The compound acts as a full agonist at the mu-opioid and delta-opioid receptors, a near-full agonist at the NOP receptor (89 percent relative efficacy), and a partial agonist at the kappa-opioid receptor (67 percent relative efficacy). A distinctive signaling feature is G-protein bias at the NOP receptor, where cebranopadol promotes G-protein coupling without measurable beta-arrestin 2 recruitment, while retaining full beta-arrestin 2 coupling at the mu-opioid receptor.

The dual NOP and opioid receptor agonism produces a pharmacological profile that is differentiated from conventional mu-selective opioid analgesics in three respects: (1) enhanced

relative potency in models of chronic neuropathic and inflammatory pain compared with acute nociceptive pain, with a seven-fold potency advantage in the mouse formalin test relative to the tail-withdrawal paradigm; (2) attenuation of opioid-type respiratory depression, with preclinical evidence of a ceiling effect on respiratory suppression attributable to the NOP receptor contribution; and (3) reduced abuse liability, demonstrated in a Phase 1 human abuse potential study showing less drug-liking and lower subjective effects relative to hydromorphone in non-dependent recreational opioid users, and in a separate study showing less abuse potential than tramadol and oxycodone. Additionally, preclinical studies demonstrated delayed analgesic tolerance development (26 days in cebranopadol-treated animals versus 11 days for morphine at equianalgesic doses in the chronic constriction injury model).

Pharmacokinetics in humans are characterized by complete oral absorption with approximately 40 percent bioavailability reflecting first-pass hepatic metabolism, a late time to maximum plasma concentration (4 to 6 hours), a long terminal elimination half-life of 62 to 96 hours, and an operational half-life of approximately 24 hours supporting once-daily dosing. Steady-state plasma concentrations are achieved after approximately two weeks of daily administration, with an accumulation factor of approximately 2-fold and low peak-trough fluctuation (70 to 80 percent). Clearance is influenced by CYP2C9 phenotype, with poor and intermediate metabolizers showing reduced clearance relative to extensive metabolizers. The compound does not inhibit CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, or CYP3A4/5 at concentrations up to 250 nM, indicating a low potential for metabolic drug-drug interactions.

Clinical development has encompassed more than 32 clinical trials involving more than 2,200 participants. A Phase 2 randomized, double-blind, placebo-controlled and active-controlled (tapentadol) trial in chronic low back pain (Christoph et al. 2017) demonstrated statistically significant and clinically relevant analgesic efficacy at doses of 200, 400, and 600 micrograms once daily over 14 weeks. A Phase 2a trial in postoperative acute pain demonstrated efficacy at 400 and 600 microgram doses. Two pivotal Phase 3 trials (ALLEVIATE-1, in post-abdominoplasty pain, and ALLEVIATE-2, in post-bunionectomy pain) met their primary efficacy endpoints, with cebranopadol 400 micrograms demonstrating significant reduction in pain intensity versus placebo. The ALLEVIATE-2 trial additionally showed that a higher proportion of cebranopadol-treated patients required no opioid rescue medication compared with placebo. Tris Pharma, which acquired worldwide rights to cebranopadol through its 2021 acquisition of Park Therapeutics, has announced plans for FDA submission. The compound is not yet approved by any regulatory authority and is not a scheduled controlled substance as of 2025. This monograph reviews the chemistry, synthesis, dual-receptor pharmacology, pharmacokinetics, preclinical and clinical evidence, sourcing, handling, stack interactions, safety profile, and a comparative assessment of five analgesic candidates against cebranopadol on five competency standards.

1. Compound Identification

1.1 Names, synonyms, and registry identifiers

International Nonproprietary Name: Cebranopadol (proposed; not yet formally assigned by the World Health Organization as the compound remains investigational).

Development codes: GRT-6005 (Grunenthal GmbH), PRK-101 (Park Therapeutics), TRN-228 (Tris Pharma). The GRT-6005 designation is the canonical identifier in the early pharmacology and patent literature.

Chemical Abstracts Service registry numbers: 863513-91-1 (free base), 863513-92-2 (hemicitrate salt). The free base is the standard synthetic and research-grade form; the hemicitrate salt has been used in some clinical formulations.

International Union of Pure and Applied Chemistry name: 6'-fluoro-N,N-dimethyl-4-phenyl-4',9'-dihydro-3'H-spiro[cyclohexane-1,1'-pyrano[3,4-b]indol]-4-amine. Alternative IUPAC designation: (1-(1-(1-(6-fluoropyrano[3,4-b]indol-1(9H)-ylidene)cyclohexyl)(phenyl)amino)-N,N-dimethylamine).

1.2 Structural class and chemistry

Cebranopadol is a spiro[cyclohexane-dihydropyrano[3,4-b]indole] derivative. The structural class is defined by a spiro junction between a cyclohexane ring and a dihydropyrano[3,4-b]indole heterocyclic system, with a fluorine substituent at the 6-position of the indole ring, a dimethylamino group, and a pendant phenyl group on the cyclohexane ring. The compound belongs to the benzenoid chemical class and is structurally unrelated to the morphinan, benzomorphan, or piperidine scaffolds of conventional opioid analgesics [1, 2].

Molecular formula: C₂₄H₂₇FN₂O (free base).

Exact mass: 378.2107 g/mol (free base, monoisotopic).

Molecular weight: 378.49 g/mol (free base).

Physical properties: White to off-white crystalline powder. The compound has low aqueous solubility, which is reflected in the slow oral absorption profile. Soluble in dimethyl sulfoxide and in organic solvents. The hemicitrate salt form improves aqueous handling for clinical formulations.

Stereochemistry: Cebranopadol contains a single stereocenter at the spiro carbon. The compound is supplied as the racemic mixture in some research-grade preparations and as the pharmacologically active enantiomer in clinical material. Investigators acquiring research-grade cebranopadol should confirm stereochemical purity by chiral chromatography against a reference standard.

1.3 Synthesis

The published synthesis of cebranopadol proceeds through construction of the pyrano[3,4-b]indole core via Fischer indole cyclization or related indole annulation, followed by spiro-cyclization to form the cyclohexane-indole junction. The fluorine substituent is introduced either at the aniline precursor stage or by late-stage electrophilic fluorination. The dimethylamino and phenyl groups are installed through reductive amination and cross-coupling or Grignard addition on the cyclohexanone intermediate [1]. The synthesis is proprietary to Grunenthal GmbH and is protected by composition-of-matter and process patents filed beginning in 2002. Industrial-scale synthesis has been performed by Grunenthal and by contract manufacturing organizations under license. Research-grade material is available from multiple suppliers at greater than 98 percent purity by high-performance liquid chromatography.

2. Abstract

Cebranopadol (GRT-6005) is a first-in-class analgesic that acts as a high-affinity agonist at both the nociceptin/orphanin FQ peptide (NOP) receptor and the three classical opioid receptor subtypes (mu, kappa, and delta), with near-equipotent activation of NOP and mu-opioid receptors at low-nanomolar concentrations [1, 2, 3]. The dual NOP/opioid mechanism is the defining pharmacological feature of the compound and distinguishes it from all currently marketed analgesics, including conventional mu-selective opioids (morphine, oxycodone, fentanyl), mixed opioid agonists/antagonists (buprenorphine), and non-opioid analgesics.

The principal clinical application under development is the treatment of moderate-to-severe acute and chronic pain. Clinical evidence from more than 32 trials involving more than 2,200 participants includes a positive Phase 2 trial in chronic low back pain demonstrating analgesic efficacy at 200, 400, and 600 microgram once-daily doses over 14 weeks (Christoph et al. 2017) [4], a positive Phase 2a trial in post-operative acute pain at 400 and 600 microgram doses [5], and two positive pivotal Phase 3 trials (ALLEVIATE-1 and ALLEVIATE-2) in post-abdominoplasty and post-bunionectomy pain at a 400 microgram dose [6, 7]. The compound has additionally been studied in Phase 2 trials for cancer pain and diabetic neuropathic pain [8, 9].

The safety profile is differentiated from conventional opioids in three important respects. First, cebranopadol produces less respiratory depression than oxycodone and fentanyl at equianalgesic doses, with preclinical evidence of a ceiling effect on respiratory suppression attributable to NOP receptor agonism [10, 11]. Second, human abuse potential studies have demonstrated less drug-liking and lower subjective opioid effects relative to hydromorphone, tramadol, and oxycodone in non-dependent recreational opioid users [12, 13]. Third, analgesic tolerance development is delayed relative to morphine in preclinical models [2, 14].

Pharmacokinetics are characterized by complete oral absorption with approximately 40 percent bioavailability, a late peak (4 to 6 hours), a long terminal half-life (62 to 96 hours) with a clinically operational half-life of approximately 24 hours supporting once-daily dosing, and clearance influenced by CYP2C9 phenotype [15].

The compound is not yet approved by any regulatory authority. Tris Pharma has announced plans for FDA submission based on the ALLEVIATE Phase 3 program and supporting safety data [6, 7].

3. Discovery and Development History

3.1 Origin

Cebranopadol was discovered at Grunenthal GmbH in Aachen, Germany, through a systematic medicinal chemistry program aimed at identifying analgesics with combined NOP receptor and classical opioid receptor agonism [1, 2]. The program was motivated by the hypothesis that simultaneous activation of the NOP receptor and the mu-opioid receptor would produce analgesic synergy while mitigating the respiratory depression, abuse liability, and tolerance development associated with selective mu-opioid agonism. The compound was first described in Grunenthal patent literature in 2002 and was assigned the development code GRT-6005.

3.2 Preclinical characterization

The initial preclinical characterization of cebranopadol was published by Linz et al. (2014) and established the receptor binding profile, functional pharmacology, and in vivo analgesic efficacy in rodent pain models [2]. The compound demonstrated antinociceptive, antihyperalgesic, and antiallodynic activity across a broad range of acute nociceptive, inflammatory, neuropathic, bone cancer, and visceral pain models. A distinctive finding was the relatively greater potency in chronic neuropathic and inflammatory pain models compared with acute nociceptive models, a profile attributed to the NOP receptor contribution to antihyperalgesia [2, 14]. Safety pharmacology studies demonstrated delayed analgesic tolerance development and reduced respiratory depression relative to equianalgesic doses of morphine and fentanyl [10, 11].

3.3 Clinical development under Grunenthal

Grunenthal initiated clinical development of cebranopadol (GRT-6005) in the late 2000s. First-in-human Phase 1 studies established safety, tolerability, and pharmacokinetic characteristics in healthy volunteers [15]. Phase 2 clinical trials were conducted in chronic low back pain, postoperative acute pain, cancer pain, and diabetic neuropathic pain between approximately 2010 and 2016 [4, 5, 8, 9]. In 2013,

Grunenthal entered a licensing agreement with Actavis (subsequently Allergan) for the development and commercialization of cebranopadol. Grunenthal announced the termination of this agreement effective October 1, 2014 [16].

3.4 Transfer to Park Therapeutics and Tris Pharma

Following the Actavis termination, development rights for cebranopadol were consolidated and subsequently transferred to Park Therapeutics, a specialty pharmaceutical company. In April 2021, Tris Pharma, Inc. announced the acquisition of Park Therapeutics, thereby obtaining worldwide rights and all accompanying intellectual property for cebranopadol [17]. Tris Pharma redesignated the compound as TRN-228 and initiated the pivotal Phase 3 development program.

3.5 Phase 3 program and regulatory trajectory

Tris Pharma initiated two pivotal Phase 3 trials (ALLEVIATE-1 and ALLEVIATE-2) evaluating cebranopadol 400 micrograms in moderate-to-severe acute postoperative pain [6, 7]. ALLEVIATE-1 enrolled patients undergoing abdominoplasty; ALLEVIATE-2 enrolled 242 patients undergoing unilateral bunionectomy with first metatarsal osteotomy. Both trials met their primary endpoints. Tris Pharma presented debut data from both trials at the American Academy of Pain Medicine (AAPM) PainConnect 2026 Annual Meeting and has announced plans for FDA submission [6, 7, 18]. Cebranopadol is not yet approved by any regulatory authority and is not a scheduled controlled substance as of 2025, though scheduling determination is expected upon regulatory approval.

4. Mechanism of Action

Cebranopadol is a multi-target receptor agonist. Its principal molecular activities, characterized in heterologous expression systems and confirmed in native tissue and behavioral models, are agonism at the nociceptin/orphanin FQ peptide (NOP) receptor and agonism at the three classical opioid receptor subtypes (mu, kappa, and delta). These activities operate at functionally relevant concentrations and contribute differentially to the observed analgesic, antihyperalgesic, antiallodynic, and safety-modulating effects.

4.1 NOP receptor agonism

The nociceptin/orphanin FQ peptide receptor (NOP, also designated ORL1 or OP4) is a G-protein-coupled receptor of the opioid receptor family that is activated by the endogenous heptadecapeptide nociceptin/orphanin FQ (N/OFQ). The NOP receptor is expressed throughout the central nervous system, with high densities in the cortex, hippocampus, amygdala, hypothalamus, periaqueductal gray, and dorsal horn of the spinal cord, and in peripheral tissues including dorsal root ganglia and immune cells [19, 20].

Cebranopadol binds the human NOP receptor with a K_i of 0.9 nM and activates it with an EC_{50} of 13 nM and 89 percent relative efficacy in calcium mobilization assays [2, 3]. In BRET (bioluminescence resonance energy transfer) G-protein coupling assays, cebranopadol shows high potency at the NOP receptor (pEC_{50} 7.87 at 5-minute incubation, 8.49 at 60-minute incubation) [3]. A distinctive signaling feature is that cebranopadol does not recruit beta-arrestin 2 at the NOP receptor, indicating G-protein-biased agonism at this target [3]. This bias may contribute to the favorable safety and tolerance profile, as beta-arrestin 2 signaling has been implicated in opioid tolerance and certain adverse effects.

The functional consequence of NOP receptor agonism in the context of cebranopadol pharmacology is threefold. First, NOP receptor activation in the spinal cord and dorsal root ganglia produces antihyperalgesic and antiallodynic effects that are mechanistically distinct from mu-opioid analgesia and that contribute to the enhanced potency of cebranopadol in neuropathic and inflammatory pain models relative to acute nociceptive models [2, 14]. Second, NOP receptor agonism

in the brainstem respiratory centers produces a partial counterbalancing effect against mu-opioid-mediated respiratory depression, establishing a ceiling on the respiratory depressant action of the compound [10, 11]. Third, NOP receptor activation in mesolimbic reward circuits modulates the reinforcing properties of mu-opioid agonism, contributing to the reduced abuse liability observed in human abuse potential studies [12, 13].

4.2 Mu-opioid receptor agonism

The mu-opioid receptor (MOR, MOP) is the principal mediator of opioid analgesia. Cebranopadol binds the human mu-opioid receptor with a K_i of 0.7 nM and activates it with an EC_{50} of 1.2 nM and 104 percent relative efficacy (full agonist) in calcium mobilization assays [2, 3]. In BRET G-protein coupling assays, cebranopadol is highly potent at the mu-opioid receptor (pEC_{50} 8.85 at 5-minute incubation, 9.74 at 60-minute incubation) [3]. Unlike at the NOP receptor, cebranopadol retains full beta-arrestin 2 coupling at the mu-opioid receptor (pEC_{50} 7.30 to 8.36) [3].

The mu-opioid receptor agonism is the primary driver of the acute analgesic effect in nociceptive pain models (tail-flick, hot plate, tail-withdrawal) and contributes substantially to the analgesic effect in all studied pain paradigms. The mu-opioid component is blocked by naloxone, confirming the receptor assignment [3].

4.3 Kappa-opioid receptor partial agonism

Cebranopadol binds the human kappa-opioid receptor (KOR, KOP) with a K_i of 2.6 nM and activates it with an EC_{50} of 17 nM and 67 percent relative efficacy in calcium mobilization assays, indicating partial agonism [2, 3]. In some assay systems the kappa intrinsic activity has been reported as approximately 55 percent [3]. The kappa-opioid partial agonism may contribute to spinal analgesia and to modulation of visceral pain, and the partial (rather than full) agonist character may limit the dysphoric and psychotomimetic effects that characterize selective kappa agonists.

4.4 Delta-opioid receptor agonism

Cebranopadol binds the human delta-opioid receptor (DOR, DOP) with a K_i of 18 nM and activates it with an EC_{50} of 110 nM and 105 percent relative efficacy (full agonist) in calcium mobilization assays [2, 3]. The delta-opioid receptor contribution at clinically relevant concentrations is uncertain given the approximately 20-fold

lower binding affinity relative to the mu and NOP receptors; however, delta-opioid agonism has been associated with anxiolytic and antidepressant-like effects in pre-clinical models and may contribute to the overall pharmacological profile in chronic pain patients with comorbid affective disturbances.

4.5 Composite pharmacology and synergism

The composite pharmacology of cebranopadol at clinically relevant doses produces a synergistic interaction between NOP and opioid receptor activation. Schunk et al. (2014) and Rizzi et al. (2016) demonstrated that the analgesic effect of cebranopadol is partially blocked by the selective NOP receptor antagonist SB-612111 and partially blocked by the opioid antagonist naloxone, with the combination of both antagonists producing near-complete reversal [3, 21]. This dual antagonist sensitivity confirms that both receptor systems contribute to the *in vivo* analgesic effect and that neither alone fully accounts for the observed potency.

The synergistic profile produces a therapeutic window advantage: the NOP receptor contribution enhances analgesia (particularly in neuropathic and inflammatory pain) while simultaneously attenuating the mu-opioid-driven side effects of respiratory depression, reinforcement, and constipation. The clinical consequence is an analgesic with efficacy comparable to or exceeding conventional opioids at doses that produce fewer opioid-type adverse events [4, 6, 7, 12].

5. Pharmacokinetics and Routes of Administration

5.1 Absorption

After oral administration of the immediate-release formulation, cebranopadol absorption is complete (based on mass balance radioactivity studies) but slow, with a time to maximum plasma concentration (T_{max}) of 4 to 6 hours [15]. The slow absorption rate is attributed to the low aqueous solubility of the compound. Oral bioavailability is approximately 40 percent, reflecting substantial first-pass hepatic metabolism [15]. Immediate-release tablets, liquid-filled capsules, and oral solution formulations show similar absorption profiles. Food intake increases C_{max} and AUC by approximately 30 percent; this effect has been determined to be not clinically relevant, and the compound can be administered without food restrictions [15].

5.2 Distribution

Cebranopadol has a very large apparent volume of distribution (V_z/f of 7,635 to 12,269 liters after single oral dosing), reflecting extensive tissue partitioning and high central nervous system penetration [15]. Population pharmacokinetic modeling estimates a central compartment volume of approximately 225 liters and a peripheral compartment volume of approximately 6,750 liters [15]. The compound crosses the blood-brain barrier readily, consistent with its lipophilic character and central analgesic mechanism. Protein binding data have not been formally published in the available literature.

5.3 Metabolism

Cebranopadol undergoes hepatic metabolism. In vitro CYP450 isozyme assays (CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4/5) demonstrated that cebranopadol does not inhibit any of these isozymes at concentrations up to 250 nM, indicating a low potential for metabolic drug-drug interactions as a perpetrator [15].

Population pharmacokinetic analysis identified CYP2C9 phenotype as a significant covariate on clearance. Poor and intermediate CYP2C9 metabolizers showed mean apparent clearance of 58.7 L/h compared with 82.4 L/h in extensive metabolizers, a difference of approximately 29 percent [15]. This pharmacogenomic effect is smaller in magnitude than the CYP2D6-driven polymorphism observed with tropisetron but is nonetheless clinically relevant for dose-response interpretation.

5.4 Elimination

Total plasma clearance after intravenous administration is approximately 50.4 liters per hour; apparent oral clearance is 102 to 117 liters per hour [15]. The mean terminal elimination half-life is 62 to 96 hours, reflecting slow redistribution from the large peripheral compartment. However, the operationally relevant half-life for predicting accumulation and steady-state behavior with once-daily dosing is approximately 24 hours [15]. Pharmacokinetics are linear across the studied oral dose range of 200 to 1,600 micrograms.

5.5 Steady-state characteristics

With once-daily oral dosing, steady-state plasma concentrations are achieved after approximately 13 to 15 days (approximately 2 weeks). The accumulation factor at steady state is approximately 2-fold. Peak-trough fluctuation at steady state is 70 to 80 percent, which is low and contributes to sustained analgesic coverage over the 24-hour dosing interval [15]. The half-value duration (time above 50 percent of C_{max}) is 14 to 15 hours.

5.6 Special populations

Renal impairment: Low creatinine clearance (45 mL/min) increases cebranopadol exposure by approximately 30 to 34 percent. A dedicated Phase 1 study (NCT03882762) evaluated the pharmacokinetics of cebranopadol in subjects with renal impairment [22].

Hepatic impairment: Alanine aminotransferase (ALT) showed an exponential effect on clearance in population pharmacokinetic modeling (effect coefficient: -0.156), indicating that hepatic impairment reduces cebranopadol clearance [15].

Sex: Females showed approximately 13 percent higher C_{max} at steady state and approximately 17 percent higher AUC at steady state compared with males; this difference was considered not clinically relevant [15].

Age and body weight: Age contributed less than 3 percent and body weight less than 2 percent to variability in exposure, indicating minimal impact [15].

5.7 Routes of administration

The primary route of administration in clinical development is oral. Cebranopadol has been studied as immediate-release tablets, liquid-filled capsules, and oral solution. Intravenous formulations have been used in pharmacokinetic characterization studies and in animal pharmacology. No parenteral clinical formulation is in active development.

6. Preclinical Pharmacology

6.1 Acute nociceptive pain models

In the mouse tail-withdrawal test, cebranopadol produced dose-dependent antinociception with an ED₅₀ of 0.2 mg/kg intravenous [3]. Onset of action occurred within 30 minutes, and the duration of effect exceeded 2 hours. In the rat tail-flick test, cebranopadol demonstrated a long duration of action (up to 7 hours after intravenous 12 micrograms per kilogram; greater than 9 hours after oral 55 micrograms per kilogram) [2]. The effect was blocked by naloxone (opioid antagonist) and by SB-612111 (NOP antagonist), confirming the dual-receptor mechanism [3].

6.2 Inflammatory pain models

In the mouse formalin test, cebranopadol demonstrated ED₅₀ values of 0.04 mg/kg (Phase I, acute nociceptive) and 0.03 mg/kg (Phase II, inflammatory), with statistically significant effects observed at 0.01 mg/kg [3]. The seven-fold greater potency in the inflammatory phase relative to the tail-withdrawal test (ED₅₀ 0.03 vs 0.2 mg/kg) was a distinctive pharmacological feature attributed to the NOP receptor contribution to antihyperalgesia. In the rat complete Freund's adjuvant (CFA)-induced arthritis model, cebranopadol produced robust antihyperalgesic effects at doses lower than those required for antinociception in acute models [2].

6.3 Neuropathic pain models

In the rat chronic constriction injury (CCI) model of neuropathic pain, cebranopadol produced dose-dependent antiallodynic and antihyperalgesic effects after peripheral, spinal, and supraspinal administration [14, 23]. Notably, cebranopadol was more potent in the CCI neuropathic model than in the acute tail-flick test when compared on a dose basis with conventional mu-selective agonists, a comparative advantage attributed to the NOP receptor contribution [2, 14]. In the rat streptozotocin-induced diabetic neuropathic pain model, cebranopadol demonstrated antihyperalgesic effects supporting the clinical development in diabetic neuropathic pain [2].

In mouse models of chemotherapy-induced neuropathic pain (paclitaxel and vincristine), cebranopadol produced dose-dependent antiallodynic and antihyperalgesic effects, extending the neuropathic pain evidence to clinically relevant etiologies [24].

6.4 Bone cancer pain model

In the rat bone cancer pain model, cebranopadol demonstrated antihyperalgesic and antinociceptive effects, supporting the clinical development in cancer pain [2].

6.5 Respiratory depression

A critical preclinical finding is the attenuated respiratory depression profile of cebranopadol relative to conventional mu-opioid agonists. Koch et al. (2017) demonstrated that cebranopadol produced considerably less respiratory depression than oxycodone and fentanyl at comparably analgesic doses [10]. Furthermore, a ceiling effect on respiratory depression was observed with increasing cebranopadol doses, a property not observed with conventional mu-opioid agonists. Mechanistic studies using selective antagonists confirmed that the NOP receptor agonist component of cebranopadol partially counteracts the mu-opioid-driven respiratory depression, establishing the NOP receptor as the mechanistic basis for the respiratory safety advantage [10, 11].

6.6 Tolerance development

In the rat CCI model, analgesic tolerance development to cebranopadol was significantly delayed compared with equianalgesic doses of morphine (26 days versus 11 days) [2, 14]. The delayed tolerance is plausibly attributable to the NOP receptor component, as NOP receptor agonism has been independently associated with resistance to analgesic tolerance in preclinical models. This finding supports the potential for sustained efficacy with chronic cebranopadol administration relative to conventional opioids.

6.7 Motor function and safety pharmacology

At antinociceptive peak doses (0.3 to 1 mg/kg intravenous), cebranopadol produced Straub tail and hyperactivity in mice but did not impair rotarod performance, indicating preserved motor coordination at analgesic doses [3]. This profile is distin-

guished from NOP-selective agonists, which produce sedation and motor impairment, and from high-dose mu-selective agonists, which produce sedation.

7. Clinical Evidence Base

7.1 Chronic low back pain (Phase 2)

The Christoph et al. (2017) study was a randomized, multicenter, double-blind, double-dummy, placebo-controlled and active-controlled (tapentadol prolonged release 200 mg twice daily) Phase 2 trial in patients with moderate-to-severe chronic low back pain with and without a neuropathic pain component [4]. Patients were treated for 14 weeks with cebranopadol 200, 400, or 600 micrograms once daily, tapentadol, or placebo. Both primary endpoints were met: cebranopadol demonstrated statistically significant and clinically relevant analgesic improvement over placebo at all tested doses. The responder analysis (proportion achieving 30 percent or 50 percent pain reduction) confirmed the dose-response relationship. Tapentadol also demonstrated efficacy, providing an active-comparator context for the cebranopadol effect sizes. Higher cebranopadol doses led to higher treatment discontinuation rates, primarily due to treatment-emergent adverse events during the titration phase; patients who reached target doses showed an acceptable tolerability profile with an incidence of most frequent adverse events of 10 percent or less during the maintenance phase [4].

7.2 Postoperative acute pain (Phase 2a)

A Phase 2a randomized, double-blind, placebo-controlled trial evaluated cebranopadol in patients with moderate-to-severe acute pain following surgery [5]. Cebranopadol at 400 and 600 microgram doses was more effective than placebo in reducing pain intensity from 2 hours until approximately 22 hours after first treatment intake. This trial established the acute pain efficacy of cebranopadol and informed dose selection for the subsequent Phase 3 acute pain program.

7.3 Diabetic neuropathic pain (Phase 2)

Cebranopadol has been evaluated in Phase 2 trials for diabetic peripheral neuropathic pain (DPN). The compound demonstrated analgesic efficacy in this neuropathic pain population, consistent with the preclinical finding of enhanced potency in neuropathic relative to acute nociceptive pain models [8, 9]. Population pharma-

cokinetic analysis showed approximately 13 percent higher exposure in DPN patients compared with nociceptive pain patients, a difference attributed to disease-related pharmacokinetic variability [15].

7.4 Cancer pain (Phase 2)

Phase 2 evaluation in cancer pain has been conducted, extending the clinical evidence to this high-burden population [8]. Published results confirm analgesic activity in cancer pain patients, consistent with the broad-spectrum preclinical efficacy.

7.5 Pivotal Phase 3 program (ALLEVIATE trials)

ALLEVIATE-1: A Phase 3, multicenter, randomized, double-blind, placebo-controlled study evaluating cebranopadol for the management of moderate-to-severe acute pain following abdominoplasty. The trial met its primary efficacy endpoint [6].

ALLEVIATE-2: A Phase 3, multicenter, randomized, double-blind, placebo-controlled study enrolling 242 patients undergoing unilateral bunionectomy with first metatarsal osteotomy. The trial compared cebranopadol 400 micrograms with oxycodone immediate release 10 mg and placebo. Cebranopadol met the primary endpoint of reduction in pain intensity as measured by the Pain Numeric Rating Scale (NRS) area under the curve from 2 through 48 hours following dosing. A significantly higher proportion of patients receiving cebranopadol 400 micrograms required no opioid rescue medication compared with those receiving placebo [7].

Tris Pharma presented debut data from both ALLEVIATE trials at the AAPM PainConnect 2026 Annual Meeting and has announced plans for FDA submission based on these trials combined with safety data from human abuse potential (HAP) studies [6, 7, 18].

7.6 Human abuse potential studies

A Phase 1 randomized, double-blind, placebo-controlled and active-controlled (hydromorphone) crossover study assessed the abuse potential of cebranopadol in 47 non-dependent recreational opioid users [12]. Cebranopadol showed less drug-liking and lower subjective opioid effects compared with hydromorphone at equianalgesic doses. A separate study compared cebranopadol with tramadol and oxy-

codone and demonstrated significantly less potential for abuse [13]. These findings support the hypothesis that NOP receptor agonism modulates the reinforcing properties of the mu-opioid component.

7.7 Respiratory effects study

A clinical study (NCT05491785) evaluated the effects of cebranopadol on ventilatory drive, central nervous system function, and pain, extending the preclinical respiratory safety findings to the human setting [25].

8. Sourcing and Quality Verification

Cebranopadol is an investigational compound not yet approved for any clinical indication. It is not available as a pharmaceutical-grade commercial product. Research-grade cebranopadol is supplied by multiple chemical and pharmaceutical research suppliers (MedChemExpress, Cayman Chemical, Xcess Biosciences, AbMole BioScience, MedKoo, Tocris, Selleckchem, and others) at greater than 98 percent purity by HPLC. Supply is available in milligram quantities as the free base (CAS 863513-91-1) or the hemicitrate salt (CAS 863513-92-2).

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
- Mass spectrometry confirmation of molecular weight (379.22 for the protonated free base $[M+H]^+$)
- Nuclear magnetic resonance spectroscopy (1H and ^{13}C) for structural confirmation
- Chiral chromatography for enantiomeric purity assessment
- Karl Fischer or loss-on-drying analysis for residual water content
- Residual solvent analysis for common synthesis solvents

Third-party analytical laboratories (Janoshik Analytical, Anabolic Lab, and others) provide independent confirmation of vendor certificates of analysis. Given that cebranopadol is an investigational compound with limited commercial supply history, lot-to-lot variability should be expected and on-receipt analytical confirmation is essential for any investigation where dose-response precision is important.

9. Reconstitution and Handling

Cebranopadol free base has low aqueous solubility. For in vitro research applications, the compound is typically dissolved in dimethyl sulfoxide (DMSO) at concentrations of 10 to 100 mM to prepare stock solutions, which are then diluted into assay buffer immediately before use. The final DMSO concentration in assay wells should generally not exceed 0.1 to 0.5 percent to avoid solvent effects on cell viability and receptor function.

For in vivo research applications, cebranopadol can be formulated in aqueous vehicles containing cosolvents or surfactants (e.g., polyethylene glycol 400, polysorbate 80, hydroxypropyl-beta-cyclodextrin) to achieve the low concentrations required for systemic administration. Published preclinical studies have used intravenous, oral, intrathecal, and intraperitoneal routes of administration [2, 3, 14, 23, 24].

Storage of the solid compound should be at -20 degrees Celsius in a desiccated container protected from light and moisture. DMSO stock solutions are stable at -20 degrees Celsius for at least 6 months when stored in sealed aliquots. Repeated freeze-thaw cycles should be avoided; preparation of single-use aliquots is recommended. Aqueous solutions should be prepared fresh and used within 24 hours unless stability data support longer storage under specific conditions.

The hemicitrate salt form has improved aqueous handling characteristics relative to the free base and may be preferred for applications requiring aqueous dissolution. Investigators should note that molecular weight calculations and dose conversions must account for the salt form used.

10. Stack Interactions and Combinations

Cebranopadol interacts with several drug classes through its multi-receptor pharmacology and its hepatic metabolism. Investigators conducting research with cebranopadol, especially in combination studies or in subjects receiving concurrent medications, should consider:

CYP2C9 inhibitors and inducers: CYP2C9 phenotype significantly affects cebranopadol clearance. Strong CYP2C9 inhibitors (fluconazole, amiodarone, sulfinpyrazone) may increase cebranopadol exposure. CYP2C9 inducers (rifampin, carbamazepine) may reduce cebranopadol exposure. Dose adjustment considerations apply.

Other opioid agonists: Concurrent use with other mu-opioid agonists (morphine, oxycodone, fentanyl, hydromorphone, tapentadol) produces additive or synergistic analgesic effects but also additive respiratory depression. The NOP receptor ceiling effect on respiratory depression observed with cebranopadol monotherapy may be partially overridden by additive mu-opioid agonism from a second agent. The combination is generally not recommended in clinical settings.

Opioid antagonists: Naloxone and naltrexone antagonize the mu-opioid component of cebranopadol analgesia. The selective NOP receptor antagonist SB-612111 antagonizes the NOP component. Both antagonists are partial in reversing cebranopadol analgesia; complete reversal requires both [3, 21].

Benzodiazepines and CNS depressants: Concurrent use with benzodiazepines, barbiturates, alcohol, or other central nervous system depressants is expected to produce additive sedation and respiratory depression, as with all opioid-active agents.

Serotonergic agents: Given the lack of reported serotonergic activity of cebranopadol, serotonin syndrome risk is not a characterized concern; however, concurrent use with serotonin reuptake inhibitors and other serotonergic agents should be approached with standard caution in opioid-treated populations.

QT-prolonging agents: Cebranopadol has not been associated with clinically significant QT prolongation in published data. Formal thorough QT studies have not been published. Concurrent use with QT-prolonging agents should follow standard precautionary practice.

NOP receptor ligands: Concurrent administration with other NOP receptor agonists (Ro 65-6570, SCH-221510) or antagonists (SB-612111, J-113397) produces predictable pharmacological interactions at the NOP receptor. These combinations are principally of interest for mechanistic dissection in preclinical research and are not clinically relevant at this stage of development.

Naloxone precipitated withdrawal considerations: In opioid-dependent individuals, cebranopadol would be expected to produce physical dependence through its mu-opioid agonism, and naloxone administration could precipitate withdrawal. However, the low abuse potential and low withdrawal potential observed in clinical studies suggest that physical dependence may develop more slowly or be of lesser severity than with conventional opioids [12, 13].

11. Adverse Events and Safety

11.1 Common adverse events

The principal treatment-emergent adverse events reported across clinical trials include:

- Nausea (dose-dependent; the most frequently reported adverse event in Phase 2 and Phase 3 trials)
- Vomiting (dose-dependent)
- Constipation (consistent with mu-opioid receptor agonism in the enteric nervous system)
- Somnolence and sedation
- Dizziness
- Headache
- Indigestion/dyspepsia
- Miosis (pupil constriction; consistent with opioid receptor activation)

Adverse-event rates were generally dose-dependent, with higher discontinuation rates at the 600 microgram dose than at the 200 or 400 microgram dose in the Phase 2 chronic low back pain trial. Most discontinuations due to adverse events occurred during the titration phase; patients who achieved stable dosing showed acceptable tolerability with most adverse-event incidence rates at or below 10 percent during the maintenance phase [4].

11.2 Respiratory depression

Cebranopadol produces less respiratory depression than equianalgesic doses of conventional opioids in both preclinical and clinical assessments [10, 11, 25]. Preclinical studies demonstrated a ceiling effect on respiratory suppression attributable to the NOP receptor agonist component, a property not observed with selective mu-opioid agonists. This respiratory safety advantage is a key differentiating feature of cebranopadol relative to conventional opioids and a central component of the regulatory and clinical positioning.

11.3 Abuse potential and dependence

Human abuse potential studies have demonstrated that cebranopadol produces less drug-liking and lower subjective opioid effects compared with hydromorphone, oxycodone, and tramadol in non-dependent recreational opioid users [12, 13]. The compound demonstrates a low potential for withdrawal symptoms. These findings are consistent with the hypothesis that NOP receptor agonism modulates the reinforcing properties of mu-opioid agonism. Cebranopadol is not yet a scheduled controlled substance as of 2025; scheduling classification will be determined as part of the regulatory approval process [26].

11.4 Euphoria

Euphoria has been reported as an adverse event in clinical trials, consistent with mu-opioid receptor agonism. The incidence appears lower than that observed with equianalgesic doses of conventional opioids, consistent with the abuse potential findings [12, 13].

11.5 Titration-phase adverse events

A notable feature of the cebranopadol safety profile is the concentration of adverse events during the dose-titration phase, with improved tolerability once stable dosing is achieved. This pattern is consistent with the long half-life and the approximately two-week period required to achieve steady-state concentrations, during which plasma levels are rising and adverse events may transiently exceed steady-state frequencies [4, 15].

11.6 CYP2C9 considerations

CYP2C9 poor and intermediate metabolizers show approximately 29 percent reduced clearance relative to extensive metabolizers, leading to higher steady-state plasma concentrations on the same dose. This pharmacogenomic effect should be considered in dose-response and adverse-event interpretation, particularly in populations with higher frequencies of CYP2C9 loss-of-function alleles [15].

12. Comparable Compounds Assessment

This section presents a structured comparative assessment of five analgesic candidates against cebranopadol, 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 to represent the principal pharmacological strategies for opioid analgesia with improved safety profiles, spanning conventional opioids, mixed opioid agonists/antagonists, and novel receptor-targeting approaches.

12.1 Tapentadol (Nucynta)

Mechanism: Dual mu-opioid receptor agonist and norepinephrine reuptake inhibitor. The compound combines opioid analgesia with monoaminergic pain modulation through a single molecular entity [27].

Development trajectory: Tapentadol was developed by Grunenthal (the same originator as cebranopadol) and Johnson and Johnson. It was approved by the FDA in 2008 for moderate-to-severe acute pain (immediate release) and in 2011 for chronic pain and diabetic neuropathic pain (extended release). The compound is the only approved analgesic with a dual mu-opioid/norepinephrine reuptake mechanism.

Novelty: Moderate. The dual mechanism is clinically validated but conceptually established prior to cebranopadol.

Effect size: Phase 3 trials demonstrated clinically meaningful pain reduction versus placebo in acute and chronic pain, with effect sizes broadly comparable to conventional opioids. Tapentadol served as the active comparator in the cebranopadol Phase 2 chronic low back pain trial, with both compounds demonstrating efficacy [4].

Promising potential: High. The compound is approved and marketed. Clinical experience encompasses millions of patient-exposures.

Side-effect profile: Reduced gastrointestinal adverse events (nausea, vomiting, constipation) relative to equianalgesic doses of oxycodone, attributed to the lower mu-opioid receptor load required for analgesia when supplemented by norepinephrine reuptake inhibition. Respiratory depression and abuse potential remain, though the Schedule II classification reflects the opioid component.

Overall validation: High. Approved, marketed, and clinically established.

Comparison to cebranopadol: Tapentadol and cebranopadol share the Grunenthal origin and the dual-mechanism concept but employ fundamentally different second mechanisms (norepinephrine reuptake inhibition versus NOP receptor agonism). Cebranopadol has the potential advantage of greater respiratory safety (NOP-mediated ceiling) and lower abuse potential. Tapentadol has the established advantage of regulatory approval and extensive clinical experience. In the head-to-head Phase 2 context, both compounds demonstrated analgesic efficacy in chronic low back pain [4].

12.2 Buprenorphine (Subutex, Belbuca, Butrans)

Mechanism: Partial agonist at the mu-opioid receptor, antagonist at the kappa-opioid receptor, and agonist at the NOP receptor. Buprenorphine shares the NOP receptor agonism of cebranopadol but differs fundamentally in its partial (rather than full) mu-opioid agonism [28].

Development trajectory: Buprenorphine was developed by Reckitt Benckiser (now Indivior/Reckitt) and has been approved for pain management (sublingual, transdermal, and buccal formulations) and for opioid use disorder treatment (sublingual and subcutaneous depot formulations).

Novelty: Low. The compound has been in clinical use since the 1970s.

Effect size: Effective for moderate-to-severe chronic pain at approved doses (sublingual, transdermal). The partial mu-opioid agonism establishes an analgesic ceiling that limits efficacy in severe acute pain at standard doses but provides a safety advantage through a respiratory depression ceiling.

Promising potential: High for opioid use disorder; moderate for pain (limited by the analgesic ceiling).

Side-effect profile: Respiratory depression ceiling at higher doses (a shared property with cebranopadol's NOP-mediated ceiling). Constipation, nausea, headache, and dizziness at standard doses. Withdrawal precipitation risk in opioid-dependent individuals due to the partial agonist profile.

Overall validation: High. Decades of clinical use and extensive regulatory support.

Comparison to cebranopadol: Buprenorphine and cebranopadol share NOP receptor agonism and respiratory depression ceiling effects. Cebranopadol has the advantage of full mu-opioid agonism (producing analgesia without an efficacy ceiling in severe pain), while buprenorphine has the advantage of established clinical use, multiple approved formulations, and a validated role in opioid use disorder treatment. The compounds represent different pharmacological strategies for achieving opioid-class analgesia with improved safety: partial agonism (buprenorphine) versus dual full agonism with NOP modulation (cebranopadol).

12.3 Oliceridine (Olinvyk)

Mechanism: G-protein-biased mu-opioid receptor agonist. Oliceridine preferentially activates the G-protein signaling pathway over the beta-arrestin pathway at the mu-opioid receptor, a bias hypothesized to reduce opioid-related adverse events while preserving analgesia [29].

Development trajectory: Developed by Trevena, Inc. Approved by the FDA in August 2020 for moderate-to-severe acute pain in adults when intravenous administration is required. Limited to hospital and ambulatory surgical center use.

Novelty: High. The G-protein-biased agonist concept is mechanistically distinct from cebranopadol's NOP/opioid dual-agonist approach.

Effect size: Phase 3 trials demonstrated analgesic efficacy superior to placebo and non-inferior to morphine in acute postoperative pain [29]. Effect sizes are modest relative to conventional opioids.

Promising potential: Moderate. Approved but commercially limited by the intravenous-only formulation and restricted clinical setting.

Side-effect profile: Reduced incidence of nausea, vomiting, and respiratory depression relative to morphine in Phase 3 trials, though the magnitude of the safety advantage has been debated. The biased agonism hypothesis has been challenged by subsequent pharmacological analyses suggesting that the observed clinical differences may be attributable to potency differences rather than signaling bias.

Overall validation: Moderate. Approved but with limited clinical uptake and ongoing scientific debate about the mechanistic basis of the safety advantages.

Comparison to cebranopadol: Oliceridine and cebranopadol represent different strategies for opioid safety improvement: signaling bias at the mu receptor (oliceridine) versus multi-receptor agonism with NOP modulation (cebranopadol). Cebranopadol has the advantage of oral administration, once-daily dosing, and broader pain-type coverage (nociceptive, neuropathic, inflammatory, and cancer pain). Oliceridine has the advantage of current FDA approval and fast onset for acute pain management.

12.4 Difelikefalin (Korsuva)

Mechanism: Selective kappa-opioid receptor agonist. Difelikefalin is a peripherally restricted D-amino acid tetrapeptide agonist at the kappa-opioid receptor that does not cross the blood-brain barrier, thereby avoiding the dysphoric and psychotomimetic central effects of kappa-opioid agonism [30].

Development trajectory: Developed by Cara Therapeutics (now Vanda Pharmaceuticals). Approved by the FDA in August 2021 for the treatment of moderate-to-severe pruritus associated with chronic kidney disease in adults undergoing hemodialysis. Under investigation for pruritus in other settings.

Novelty: High for the peripheral kappa-opioid mechanism; low for analgesic applications (not developed for pain).

Effect size: Effective for pruritus reduction in the approved indication. Not demonstrated for pain management.

Promising potential: Low for pain indications. The compound addresses a fundamentally different therapeutic need (pruritus rather than analgesia).

Side-effect profile: Diarrhea, dizziness, nausea, and somnolence at approved doses. No central opioid effects (euphoria, respiratory depression, abuse potential) due to peripheral restriction.

Overall validation: Moderate for pruritus. Not validated for pain.

Comparison to cebranopadol: Difelikefalin and cebranopadol share kappa-opioid receptor activity, but the comparison is limited by the fundamentally different clinical applications (pruritus versus analgesia) and the peripheral-restriction strategy of difelikefalin versus the centrally penetrant multi-receptor strategy of cebranopadol. Difelikefalin represents a proof-of-concept for peripheral opioid receptor targeting but is not a clinical alternative to cebranopadol for pain management.

12.5 Tanezumab

Mechanism: Humanized monoclonal antibody against nerve growth factor (NGF). Tanezumab binds and neutralizes NGF, preventing its interaction with the TrkA and p75NTR receptors on nociceptive neurons, thereby reducing peripheral sensitization and pain signaling [31].

Development trajectory: Developed by Pfizer and Eli Lilly. Advanced through extensive Phase 3 clinical trials for chronic low back pain and osteoarthritis. The compound received a Complete Response Letter from the FDA in March 2021 citing safety concerns (rapidly progressive osteoarthritis leading to joint replacement). The European Medicines Agency Committee for Medicinal Products for Human Use (CHMP) issued a negative opinion in 2022. The compound is not approved in any jurisdiction.

Novelty: High. The anti-NGF mechanism is fundamentally distinct from opioid and NOP receptor pharmacology and represents a non-opioid approach to chronic pain.

Effect size: Phase 3 trials demonstrated statistically significant pain reduction versus placebo in chronic low back pain and osteoarthritis, with effect sizes comparable to non-steroidal anti-inflammatory drugs.

Promising potential: Low to moderate. Regulatory rejection in two major jurisdictions due to safety concerns.

Side-effect profile: The principal safety concern is rapidly progressive osteoarthritis (RPOA), including cases requiring total joint replacement, observed at higher incidence in tanezumab-treated patients than in controls. Peripheral neuropathy, paresthesia, and hypoesthesia have also been reported. No opioid-type adverse events (respiratory depression, constipation, abuse potential).

Overall validation: Low. Extensive Phase 3 data but regulatory rejection due to safety signal.

Comparison to cebranopadol: Tanezumab represents the most mechanistically distinct comparator in this panel, targeting a fundamentally different node in the pain pathway (peripheral neurotrophic signaling rather than central opioid/NOP receptor activation). Cebranopadol has the advantage of a more favorable regulatory trajectory (positive Phase 3 results, planned FDA submission) and a broader pain-type coverage. Tanezumab has the theoretical advantage of a non-opioid mechanism without respiratory depression or abuse potential, offset by the RPOA safety signal that prevented approval.

12.6 Comparator summary

The five comparators represent distinct pharmacological strategies for analgesia. **Tapentadol** is the approved dual-mechanism opioid analgesic most closely related to cebranopadol by originator and concept, with the advantage of established clinical use and the limitation of retained opioid-class adverse events. **Buprenorphine** shares NOP receptor agonism but achieves its safety profile through partial mu agonism rather than full agonism, producing an analgesic ceiling absent from cebranopadol. **Oliceridine** pursues opioid safety through G-protein signaling bias but is limited to intravenous use. **Difelikefalin** demonstrates peripheral kappa-opioid targeting for pruritus but is not relevant to centrally mediated pain. **Tanezumab** represents the non-opioid anti-NGF strategy that failed on safety despite efficacy.

Cebranopadol occupies a unique position in this comparator landscape: it is the only compound that combines full mu-opioid agonism (for efficacy comparable to conventional opioids) with NOP receptor agonism (for attenuation of respiratory depression, abuse liability, and tolerance). The compound is the first NOP/opioid dual-agonist to advance through a positive Phase 3 program with planned FDA submission, and the only investigational analgesic in this comparator panel that has demonstrated reduced abuse potential relative to conventional opioids in human abuse potential studies while maintaining full analgesic efficacy. The principal re-

maining question is whether the FDA will grant approval based on the ALLEVIATE Phase 3 data and the supporting safety package, and whether the scheduling classification will reflect the reduced abuse liability relative to conventional Schedule II opioids.

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before any research application. Compound class generalizations are noted where compound-specific data are sparse; investigators should weight the evidence accordingly.