

RESEARCH MONOGRAPH . COMPOUND PROFILE

Navacaprant

A fluorinated quinoline-oxadiazole kappa opioid receptor antagonist discovered at Scripps Research and advanced through Phase 3 clinical trials for major depressive disorder, distinguished from earlier KOR antagonists by full receptor antagonism without mu or delta cross-reactivity, rapid reversibility, and a favorable tolerability profile in controlled clinical studies.

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ABSTRACT

Navacaprant (BTRX-335140, NMRA-140, CYM-53093) is a potent, highly selective, and reversible antagonist of the kappa opioid receptor (KOR) under clinical development for the treatment of major depressive disorder (MDD). The compound was discovered in collaboration between Scripps Research faculty members Hugh Rosen and Edward Roberts and was advanced through clinical development first by BlackThorn Therapeutics and subsequently by Neumora Therapeutics. Navacaprant blocks the KOR with an IC₅₀ of 1.2 nanomolar in native ventral tegmental area dopamine neurons and 29 nanomolar in recombinant CHO-K1 cells, with approximately 300-fold selectivity over the mu opioid receptor and greater than 340-fold selectivity over the delta opioid receptor. The compound exhibits no detectable agonist activity at any opioid receptor subtype in vitro (EC₅₀ greater than 10 micromolar) and no opioid agonist effects in vivo, including no alteration of extracellular dopamine in the nucleus accumbens at oral doses up to 100 mg/kg in rats. The pharmacological profile differentiates navacaprant from earlier KOR antagonists: unlike JDTic (which activates c-Jun N-terminal kinase and produced cardiac toxicity in humans), nor-binaltorphimine (which has an impractically long duration of action), and aticaprant (which partially blocks mu and delta opioid receptor responses in native tissue electrophysiology), navacaprant combines full KOR antagonism with rapid reversibility, clean selectivity, and no off-target opioid effects. In a Phase 1 program in healthy volunteers, navacaprant demonstrated favorable pharmacokinetics across single oral doses of 5 to 240 mg and multiple daily doses of 20 to 160 mg for 10 days, with good tolerability and no serious adverse

events. A positron emission tomography receptor occupancy study confirmed brain KOR engagement, with a single 160 mg dose producing approximately 90 percent occupancy and pharmacokinetic-pharmacodynamic modeling projecting approximately 90 percent occupancy at steady state with 80 mg once daily. In a Phase 2a randomized, double-blind, placebo-controlled trial in 204 adults with MDD (Mathew et al. 2025), navacaprant 80 mg once daily for 8 weeks did not meet the primary endpoint in the full efficacy population (Hamilton Depression Rating Scale least-squares mean difference versus placebo of negative 1.7 points, p equals 0.121), but demonstrated statistically significant improvements in the moderate-to-severe MDD subgroup on both depressive symptoms and anhedonia as measured by the Snaith-Hamilton Pleasure Scale, with response rates of 45.5 percent versus 24.1 percent for placebo (number needed to treat equals 5) and remission rates of 26.1 percent versus 10.8 percent (number needed to treat equals 7). Fewer treatment-emergent adverse events occurred in the navacaprant group than in the placebo group, and no serious adverse events, weight gain, or sexual dysfunction were reported with navacaprant. In Phase 3, the KOASTAL-1 trial (n equals 383) failed to demonstrate separation from placebo on the Montgomery-Asberg Depression Rating Scale primary endpoint, with both treatment arms reporting identical 12.5-point reductions (p equals 0.993); exploratory subgroup analyses suggested a differential response in female participants. The KOASTAL-2 and KOASTAL-3 Phase 3 trials were paused for protocol modifications and are expected to report data in 2026. This monograph reviews the chemistry and structural pharmacology of navacaprant; the molecular pharmacology including receptor binding, selectivity, and electrophysiological characterization; the available

pharmacokinetic data; the preclinical pharmacology in stress and cognitive models; the clinical evidence base including the Phase 2 and Phase 3 programs; sourcing and quality verification; handling considerations; stack interactions; adverse events; and a comparative assessment of five kappa opioid receptor candidates (aticaprant, buprenorphine-samidorphane, JDTic, nor-binaltorphimine, and PF-04455242) against navacaprant. The compound is investigational and is not approved by any regulatory authority. It is available as a research-grade preparation; investigators should obtain analytical confirmation of identity and purity on every lot.

1. Compound Identification

1.1 Names, synonyms, and registry identifiers

International Nonproprietary Name: Navacaprant.

Development codes: BTRX-335140 (BlackThorn Therapeutics), BTRX-140 (abbreviated form used in some clinical communications), NMRA-335140 (Neumora Therapeutics designation following corporate transition), NMRA-140 (abbreviated Neumora designation), CYM-53093 (Scripps Research internal designation). The BTRX-335140 code is the canonical identifier in the earliest pharmacology literature and in the Phase 1 and Phase 2 clinical trial registrations [1, 2]. The NMRA-335140 designation appears on the Phase 3 KOASTAL program registrations [3, 4].

Chemical Abstracts Service registry number: 2244614-14-8 (free base).

International Union of Pure and Applied Chemistry name: 1-[6-ethyl-8-fluoro-4-methyl-3-(3-methyl-1,2,4-oxadiazol-5-yl)quinolin-2-yl]-N-(oxan-4-yl)piperidin-4-amine [5]. The name reflects a substituted quinoline core bearing a 1,2,4-oxadiazole heterocycle, a piperidine ring appended at the 2-position of the quinoline, and a tetrahydropyran (oxane) group linked through an amine to the piperidine nitrogen.

1.2 Structural class and chemistry

Navacaprant belongs to the class of substituted quinoline kappa opioid receptor antagonists. The structural framework comprises three principal pharmacophoric elements: (1) a 6-ethyl-8-fluoro-4-methylquinoline core that provides the planar aromatic scaffold for receptor binding; (2) a 3-methyl-1,2,4-oxadiazole substituent at the 3-position of the quinoline ring, contributing to metabolic stability and receptor affinity; and (3) a 4-aminopiperidine moiety at the 2-position, bearing a tetrahydro-2H-pyran-4-yl (oxan-4-yl) group on the exocyclic amine nitrogen, which contributes to the pharmacokinetic profile including brain penetration and oral bioavailability [5, 6].

Molecular formula: C₂₅H₃₂FN₅O₂ (free base).

Molecular weight: 453.56 g/mol (free base) [5].

Canonical **SMILES:** CCc1cc(F)c2nc(N3CCC(CC3)NC3CCOCC3)c(-c3nc(C)no3)c(C)c2c1 [5].

Physical properties: The compound contains a fluorine atom at the 8-position of the quinoline ring, placing it within the fluorinated heterocyclic class. The calculated cLogP for the free base is in the range of 3 to 4, consistent with moderate lipophilicity and blood-brain barrier permeability. The 1,2,4-oxadiazole is a five-membered heteroaromatic ring containing two nitrogen atoms and one oxygen atom; it is a bioisostere of ester and amide functional groups commonly employed in medicinal chemistry for metabolic stability and resistance to hydrolysis. The tetrahydropyran (oxane) ring contributes aqueous solubility through its ether oxygen and is a common medicinal chemistry motif for replacing cyclohexyl groups while improving pharmacokinetic properties. The quinoline-oxadiazole-piperidine architecture is structurally distinct from the morphinan scaffold of classical opioid receptor ligands (naltrexone, naloxone, buprenorphine), from the trans-decahydroisoquinoline scaffold of JDTic, and from the phenylpiperidine scaffold of PF-04455242, representing a novel chemotype for KOR antagonism [7].

Salt forms: The compound is available as the free base (CAS 2244614-14-8) and as the hydrochloride salt (molecular formula C₂₅H₃₃ClFN₅O₂; molecular weight 490.02 g/mol) [5]. Research-grade suppliers offer predominantly the free base form. The hydrochloride salt may be employed in formulations requiring enhanced aqueous solubility.

Stereochemistry: The published structural representations of navacaprant do not indicate defined stereocenters at the piperidine or tetrahydropyran rings. The piperidine ring at the 2-position of the quinoline adopts a chair conformation in which the 4-amino substituent can occupy either axial or equatorial positions; the tetrahydropyran ring similarly adopts a chair conformation. No chiral resolution or enantiopure designation has been reported in the published pharmacology or clinical literature, suggesting that the compound is either achiral or that the pharmacologically active form is the racemate. The absence of defined chirality is consistent with the structural representation in PubChem (CID 137434175) and with supplier catalog entries [5]. Investigators should confirm the stereochemical identity of research-grade material by comparison with the reference standard used in the published pharmacology studies.

1.3 Synthesis

The detailed synthesis of navacaprant has not been published in a peer-reviewed journal. The compound was discovered in the laboratories of Hugh Rosen and Edward Roberts at Scripps Research and was advanced through medicinal chemistry optimization as part of the BlackThorn Therapeutics founding collaboration [8]. The structural elements (substituted quinoline, 1,2,4-oxadiazole, aminopiperidine, tetrahydropyran) suggest a convergent synthetic route involving: (a) construction of the 6-ethyl-8-fluoro-4-methyl-3-(3-methyl-1,2,4-oxadiazol-5-yl)quinoline core through a modified Friedlander or Doebner-Miller quinoline synthesis with subsequent introduction of the oxadiazole by cyclodehydration of an amidoxime precursor; (b) preparation of the 4-aminopiperidine bearing the tetrahydropyranyl group through reductive amination of piperidin-4-one with tetrahydro-2H-pyran-4-amine; and (c) coupling of the aminopiperidine to the 2-position of the quinoline through nucleophilic aromatic substitution or palladium-catalyzed amination. Patent literature associated with BlackThorn Therapeutics and Scripps Research may contain the specific synthetic procedures; investigators requiring synthetic detail should consult the patent filings under CAS 2244614-14-8. Research-grade navacaprant is currently available from multiple chemical suppliers as the free base [5].

2. Abstract

Navacaprant is a potent, highly selective kappa opioid receptor (KOR) antagonist under clinical investigation for major depressive disorder. The compound blocks KOR-mediated responses with an IC₅₀ of 1.2 nanomolar in native ventral tegmental area neurons and approximately 29 nanomolar in recombinant cell systems, with no agonist activity and no clinically meaningful cross-reactivity at mu or delta opioid receptors. The compound has completed Phase 1, Phase 2, and the first Phase 3 trial in MDD. Phase 2 data showed efficacy signals in the moderate-to-severe subgroup and favorable tolerability; the Phase 3 KOASTAL-1 trial did not meet its primary endpoint. Two additional Phase 3 trials are ongoing. This monograph covers the chemistry, molecular pharmacology, pharmacokinetics, preclinical and clinical evidence, safety profile, and comparative positioning of navacaprant.

3. Discovery and Development History

3.1 Origin

Navacaprant was discovered in collaboration between Scripps Research faculty members Hugh Rosen, MD, PhD (Professor in the Department of Molecular Medicine) and Edward Roberts, PhD, as part of a medicinal chemistry program targeting selective kappa opioid receptor antagonists for neurobehavioral disorders [8]. The compound was designated CYM-53093 in the Scripps internal nomenclature. BlackThorn Therapeutics, Inc. was established as a spin-off company from Scripps Research, founded with the objective of advancing navacaprant and related neuroscience assets through clinical development [8]. The company was headquartered in San Francisco, California, and was led by William J. Martin, PhD, as President and Chief Operating Officer.

3.2 Phase 1 development

BlackThorn Therapeutics initiated the Phase 1 clinical study of BTRX-335140 in healthy volunteers in June 2018 [9]. The Phase 1 program comprised single ascending dose (SAD) and multiple ascending dose (MAD) components. Single oral doses ranged from 5 mg to 240 mg; multiple daily oral doses ranged from 20 mg to 160 mg administered for 10 days [10]. On April 1, 2019, the company announced positive Phase 1 results: BTRX-335140 exhibited favorable pharmacokinetics with increased plasma exposures across the dose range and was well tolerated in healthy human subjects, with no serious adverse events reported [11].

A positron emission tomography (PET) receptor occupancy study in healthy volunteers was conducted as part of the Phase 1 program. The results, presented at the 58th Annual Meeting of the American College of Neuropsychopharmacology (ACNP) in Orlando, Florida, in December 2019, demonstrated that a single oral dose of 160 mg achieved approximately 90 percent KOR occupancy in the brain [10]. Pharmacokinetic-pharmacodynamic modeling of the aggregate Phase 1 data projected that an 80 mg once-daily dose at steady state would also achieve approximately 90 percent KOR occupancy, establishing the 80 mg dose as the clinical candidate dose for subsequent efficacy studies [4, 10].

3.3 Corporate transition

BlackThorn Therapeutics underwent a corporate reorganization and rebranding. The company was merged into Neumora Therapeutics, Inc., a clinical-stage biopharmaceutical company focused on precision neuroscience. The development codes for the compound were updated from BTRX-335140 to NMRA-335140, and the abbreviated form from BTRX-140 to NMRA-140. Neumora Therapeutics assumed responsibility for all ongoing and planned clinical programs for navacaprant.

3.4 Phase 2 clinical trial

The Phase 2a randomized, double-blind, placebo-controlled trial (Study K2-MDD-201, NCT04221230) was initiated in late 2019, enrolling adults with major depressive disorder at sites in the United States [3, 4]. A total of 204 participants were randomized 1:1 to receive navacaprant 80 mg once daily or placebo for 8 weeks [4]. The trial employed the Hamilton Depression Rating Scale 17-item version (HAM-D-17) as the primary efficacy measure and the Snaith-Hamilton Pleasure Scale (SHAPS) as a key secondary measure of anhedonia. The primary endpoint (HAM-D-17 change from baseline at week 8 by mixed-model repeated measures analysis) was not met in the full efficacy population (n=171), with a least-squares mean difference of negative 1.7 points (standard error 1.08, p=0.121) [4]. However, statistically significant improvements were observed in the moderate-to-severe MDD subgroup (baseline HAM-D-17 score of 22 or greater, n=100) on both the HAM-D-17 (LSMD negative 2.8, p=0.037) and the SHAPS (LSMD negative 4.8, p=0.001) at week 8 [4]. Response rates (50 percent or greater HAM-D-17 reduction) were 45.5 percent for navacaprant versus 24.1 percent for placebo (p=0.004, number needed to treat equals 5), and remission rates (HAM-D-17 of 7 or less) were 26.1 percent versus 10.8 percent (p=0.011, number needed to treat equals 7) [4]. These data were published in the Journal of Clinical Psychopharmacology in 2025 by Mathew et al. [4].

3.5 Phase 3 clinical program

Neumora Therapeutics advanced navacaprant to Phase 3 clinical development with a three-trial registration program designated KOASTAL. The KOASTAL-1 trial (NCT06029426) was a randomized, double-blind, placebo-controlled, Phase 3 study evaluating navacaprant 80 mg once daily versus placebo for 6 weeks in 383 adults with moderate-to-severe MDD (Montgomery-Asberg Depression Rating Scale [MADRS] score of 25 or greater at baseline) [12]. On January 2, 2025, Neumora an-

nounced that KOASTAL-1 did not meet its primary endpoint: both the navacaprant and placebo groups reported identical mean MADRS reductions of 12.5 points from baseline, yielding a least-squares mean difference of 0.0 ($p=0.993$) [12]. The key secondary endpoint (SHAPS) was also non-significant in the overall population ($p=0.648$) [12]. Exploratory subgroup analyses suggested a differential signal in female participants (MADRS LSMD negative 2.6, $p=0.072$; SHAPS LSMD negative 2.3, $p=0.015$), with male participants showing no drug-placebo separation [12]. The compound was well tolerated in KOASTAL-1, with no serious adverse events reported [12]. The announcement precipitated an approximately 80 percent decline in the Neumora Therapeutics share price [12].

Following the KOASTAL-1 readout, Neumora paused the companion Phase 3 trials (KOASTAL-2 and KOASTAL-3) to implement protocol modifications, including reduced site counts, enhanced medical oversight through the Massachusetts General Hospital Trials network, and a screening tool to prevent concurrent multi-trial enrollment [13]. The KOASTAL-4 trial (a separate study) was halted [13]. Neumora expects to report data from KOASTAL-3 in the first quarter of 2026 and from KOASTAL-2 in the second quarter of 2026 [13].

4. Mechanism of Action

4.1 The kappa opioid receptor system and depression

The kappa opioid receptor (KOR) is a G-protein-coupled receptor of the opioid receptor family, expressed widely in the central nervous system including at high density in the ventral tegmental area, nucleus accumbens, prefrontal cortex, hippocampus, amygdala, and hypothalamus [14]. The endogenous ligand for the KOR is dynorphin, a peptide product of the prodynorphin gene whose expression is upregulated by stress, glucocorticoids, and corticotropin-releasing factor [14]. Activation of the KOR by dynorphin or synthetic agonists produces dysphoria, anhedonia, aversion, and anxiety-like behaviors in preclinical models; these effects are mediated through inhibition of mesolimbic dopaminergic neurotransmission (KOR-expressing neurons in the ventral tegmental area directly inhibit dopamine release in the nucleus accumbens), modulation of serotonergic and noradrenergic circuits, and activation of intracellular stress-kinase pathways including p38 mitogen-activated protein kinase [1, 14].

The dynorphin-KOR system is therefore an effector arm of the stress response, and chronic stress-induced upregulation of dynorphin signaling has been proposed as a contributor to the core symptoms of major depressive disorder, particularly anhedonia, motivational deficits, and cognitive impairment [14, 28, 29]. The dysphoric component of stress has been shown to be specifically encoded by activation of the dynorphin-KOR system in rodent models: forced swim stress, social defeat stress, and uncontrollable shock all produce dynorphin release in the nucleus accumbens, and the resulting behavioral deficits are blocked by KOR antagonists or absent in prodynorphin knockout mice [27, 32]. KOR activation in the human brain produces dysphoria and psychotomimetic effects; the selective KOR agonist spiradoline produces dose-dependent dysphoria in healthy human volunteers, establishing that the aversive consequences of KOR activation are conserved across species [30].

KOR antagonists block the downstream consequences of dynorphin release and are hypothesized to restore dopaminergic tone in mesolimbic circuits, thereby reducing stress-induced depressive phenotypes [1, 14, 35]. This hypothesis has been supported by consistent preclinical evidence: systemic administration of KOR an-

tagonists in rodent models reliably reverses escalated stress responses, ameliorates depression-like phenotypes in the forced swim test and learned helplessness paradigm, and prevents the behavioral consequences of chronic stress [2, 15, 16, 31, 32]. The clinical translation of the KOR antagonist hypothesis has been pursued by several pharmaceutical sponsors, with navacaprant and aticaprant representing the most advanced selective KOR antagonist programs [4, 18, 35].

4.2 Kappa opioid receptor antagonism

Navacaprant is a competitive, reversible antagonist of the KOR. In recombinant cell systems (CHO-K1 cells expressing human KOR), navacaprant inhibits KOR agonist-stimulated signaling with an IC₅₀ of 0.029 micromolar (29 nanomolar) [2]. In the same assay format, navacaprant inhibits mu opioid receptor (MOR) agonist signaling with an IC₅₀ of 3.3 micromolar and delta opioid receptor (DOR) agonist signaling with an IC₅₀ of greater than 10 micromolar, establishing approximately 114-fold selectivity for KOR over MOR and greater than 340-fold selectivity over DOR [2]. The compound has been characterized as having approximately 300-fold selectivity for KOR over MOR in the published clinical literature [4].

In native neuronal tissue, navacaprant has been characterized by whole-cell electrophysiology in acute rat midbrain slices at 33 degrees Celsius, using 3 to 5 megaohm pipettes, with recordings from ventral tegmental area dopaminergic neurons held at negative 60 millivolts [1]. In this preparation, the KOR-selective agonist U-69,593 produces outward potassium currents in approximately half of VTA dopamine neurons; navacaprant fully blocked U-69,593-induced outward currents with an IC₅₀ of 1.2 plus or minus 0.9 nanomolar [1]. The full blockade (asymptoting at complete reversal of the agonist-induced current) distinguishes navacaprant from partial KOR antagonists such as PF-04455242, which asymptoted at only 55 percent blockade (IC₅₀ of 6.7 plus or minus 15.1 nanomolar) in the same preparation [1].

4.3 Selectivity in native tissue

The selectivity of navacaprant was further characterized by testing for cross-reactivity at mu and delta opioid receptors in the same VTA dopamine neuron preparation. At a concentration of 10 nanomolar (a concentration producing near-complete KOR blockade), navacaprant did not affect responses to saturating concentrations of the mu opioid receptor agonist DAMGO or the delta opioid receptor agonist

DPDPE [1]. This clean selectivity profile in native neuronal tissue is a differentiating feature relative to aticaprant (JNJ-67953964), which at 10 nanomolar partially blocked both DAMGO responses ($p=0.019$) and DPDPE responses ($p=0.033$) in the same electrophysiological preparation [1].

4.4 Reversibility and washout kinetics

Navacaprant is a rapidly reversible KOR antagonist. In the VTA electrophysiology preparation, 10 nanomolar BTRX-335140 washed out completely, with full recovery of U-69,593-induced outward currents within 10 minutes [1]. This rapid reversibility contrasts sharply with the prototypical KOR antagonist nor-binaltorphimine (nor-BNI), which showed no reversal of KOR blockade at 20 minutes in the same preparation [1]. The long-acting pharmacology of nor-BNI (and of the structurally related JDTic) has been attributed to activation of c-Jun N-terminal kinase (JNK), a stress kinase, rather than to simple competitive receptor blockade; navacaprant does not appear to share this JNK-activating mechanism [17].

4.5 Absence of agonist activity

Navacaprant showed no agonist activity at any opioid receptor subtype in vitro, with EC₅₀ values greater than 10 micromolar across KOR, MOR, and DOR in CHO-K1 functional assays [2]. In vivo, navacaprant exhibited no analgesic effect in the mouse tail-flick assay at oral doses up to 100 mg/kg, confirming the absence of opioid receptor agonist activity [2]. This pharmacological profile is critical to the abuse-potential assessment: navacaprant did not alter extracellular dopamine concentrations in the nucleus accumbens shell of freely moving rats following oral doses up to 100 mg/kg, whereas the positive control morphine (10 and 20 mg/kg intraperitoneal) significantly increased dopamine levels [2]. The absence of dopaminergic activation in the nucleus accumbens, the neurochemical substrate of reward and reinforcement, supports the conclusion that navacaprant has no pharmacological properties implicated in opioid-related abuse [2].

4.6 Downstream signaling consequences

KOR activation by dynorphin or synthetic agonists produces cellular effects through coupling to inhibitory G proteins (Gi/Go), leading to inhibition of adenylyl cyclase, activation of G-protein-gated inwardly rectifying potassium channels (GIRKs, which produce the outward currents measured in the electrophysiology

preparation), inhibition of voltage-gated calcium channels, and activation of beta-arrestin-dependent pathways including p38 mitogen-activated protein kinase [14]. KOR activation also engages beta-arrestin-2-dependent signaling, which has been implicated in the dysphoric and aversive components of KOR agonism through p38 MAPK phosphorylation in serotonergic neurons of the dorsal raphe nucleus [26, 27]. The dysphoric component of stress has been specifically attributed to dynorphin release and KOR activation in the nucleus accumbens and ventral tegmental area [27].

In the mesolimbic dopamine system, KOR activation manifests as direct inhibition of VTA dopamine neuron firing and reduced dopamine release in the nucleus accumbens, producing anhedonia and motivational deficits [1, 28]. KOR activation in the prefrontal cortex impairs working memory and executive function, contributing to the cognitive symptoms of stress-related psychiatric disorders [15, 29]. In the amygdala, dynorphin-KOR signaling promotes anxiety-like behavior and fear conditioning [29]. Navacaprant, by blocking KOR activation across these circuits, prevents dynorphin-driven suppression of dopaminergic neurotransmission, restores prefrontal cortical function under stress conditions, and is hypothesized to ameliorate the anhedonic, motivational, cognitive, and anxious components of major depressive disorder [1, 2, 14, 15].

4.7 Composite pharmacology at the clinical dose

At the clinical dose of 80 mg once daily, navacaprant is projected to achieve approximately 90 percent KOR occupancy at steady state based on PET receptor occupancy modeling [4, 10]. Near-complete KOR blockade at this occupancy level would be expected to substantially attenuate dynorphin-mediated signaling across the mesolimbic, mesocortical, and limbic circuits described above. The compound's selectivity ensures that MOR-mediated and DOR-mediated opioid signaling remain unperturbed at this dose; the absence of MOR agonism means no euphoria, respiratory depression, or dependence liability, while the absence of DOR modulation avoids potential convulsant or proconvulsant effects that have been associated with some DOR agonists [2, 30]. The pharmacological profile is therefore that of a selective stress-circuit modulator, blocking the KOR-dynorphin effector arm without engaging the reward (MOR) or analgesic/seizure-threshold (DOR) components of the opioid system.

5. Pharmacokinetics and Routes of Administration

5.1 Overview of available data

Detailed human pharmacokinetic parameters for navacaprant (elimination half-life, time to maximum concentration, maximum plasma concentration, area under the curve, oral bioavailability, volume of distribution, protein binding, and specific cytochrome P450 metabolism) have not been published in peer-reviewed form as of the date of this monograph. The available pharmacokinetic data derive from sponsor press releases summarizing the Phase 1 program in healthy volunteers, from the published Phase 2 clinical trial report, and from preclinical pharmacokinetic studies in rodents. Investigators requiring formal pharmacokinetic parameters should treat the data below as sponsor-reported values pending peer-reviewed publication of the complete Phase 1 pharmacokinetic dataset.

5.2 Phase 1 pharmacokinetics in healthy volunteers

The Phase 1 program evaluated single ascending oral doses from 5 mg to 240 mg and multiple ascending daily oral doses from 20 mg to 160 mg for 10 days in healthy volunteers [10, 11]. Navacaprant exhibited dose-proportional increases in plasma exposure across the tested dose range, with pharmacokinetics described as favorable for once-daily oral administration without dose titration [4, 10, 11]. The compound was characterized as having rapid absorption and brain penetration [10, 11]. The wide dose range tested in Phase 1 (48-fold range for single doses, 8-fold range for multiple doses) without dose-limiting toxicity indicates a broad therapeutic window [10]. The absence of dose titration requirements in the clinical program suggests that the compound does not produce clinically significant receptor-mediated adverse effects at supratherapeutic exposures, consistent with the pharmacological expectation for a pure antagonist (which, unlike agonists and partial agonists, does not produce progressive on-target effects at increasing receptor occupancy beyond blockade of endogenous ligand activity).

5.3 Receptor occupancy

A positron emission tomography (PET) receptor occupancy study in healthy volunteers demonstrated that navacaprant engages KOR in the human brain at therapeutically relevant exposures [10]. A single oral dose of 160 mg produced approximately 90 percent KOR occupancy. Pharmacokinetic-pharmacodynamic modeling of the Phase 1 data, incorporating plasma concentration-time profiles and the PET occupancy relationship, projected that an 80 mg once-daily dose at steady state would achieve approximately 90 percent KOR occupancy [4, 10]. This projection established the 80 mg dose as the clinical candidate dose for the Phase 2 and Phase 3 efficacy programs.

5.4 Preclinical pharmacokinetics

In mice, single oral doses of navacaprant at 10 mg/kg produced maximum plasma concentrations at 1 hour of 80.9 plus or minus 11.7 ng/mL [2]. In rats, single oral doses of 10 mg/kg and 30 mg/kg produced plasma concentrations at 60 minutes of 122 ng/mL and 263 ng/mL, respectively, indicating approximately dose-proportional exposure in the range studied [2]. The rodent data support rapid oral absorption with time to maximum concentration of approximately 1 hour. The ratio of rat plasma concentrations at 10 and 30 mg/kg (122 to 263 ng/mL, approximately 2.2-fold for a 3-fold dose increase) suggests slightly less than dose-proportional exposure at higher doses, which may reflect saturable first-pass metabolism or non-linear absorption; however, the deviation is modest and consistent with approximately linear pharmacokinetics over the studied range [2].

In the rhesus macaque working memory study, navacaprant was administered intramuscularly at 0.1, 0.3, and 1.0 mg/kg, with the full pharmacological effect (protection of working memory from stress) achieved at all three doses [15]. The pharmacodynamic activity at 0.1 mg/kg intramuscularly in primates suggests substantial potency and bioavailability by the parenteral route, consistent with the nanomolar KOR binding affinity.

5.5 Route of administration and dosing

The clinical route of administration is oral, once daily, at a dose of 80 mg. The compound does not require dose titration [4]. No intravenous, subcutaneous, or intramuscular formulations have been described in the published literature. The Phase

2 and Phase 3 programs employed once-daily oral administration without food restriction [4, 12].

5.6 Metabolism and elimination

Specific cytochrome P450 enzymes responsible for the metabolism of navacaprant have not been identified in the published literature. The structural features of the compound (fluorinated quinoline, oxadiazole, piperidine) suggest likely hepatic metabolism through CYP3A4-mediated oxidation of the quinoline and piperidine rings and potential contributions from CYP2D6, though these attributions are structural predictions rather than published experimental findings. The fluorine atom at the 8-position of the quinoline ring may confer partial metabolic resistance to oxidative metabolism at that position, a common medicinal chemistry strategy for extending half-life [5]. The 1,2,4-oxadiazole ring is generally resistant to hydrolysis under physiological conditions, which is the principal advantage of this bioisostere over ester and amide linkages.

The elimination half-life in humans has not been reported in the peer-reviewed literature. The pharmacokinetic profile supports once-daily dosing, suggesting a half-life in the range compatible with 24-hour dosing intervals [4, 10]. By comparison, the closely related KOR antagonist aticaprant (which shares the selective KOR antagonist mechanism but has a distinct chemical scaffold) has a reported terminal half-life of approximately 30 to 40 hours in healthy subjects [14]; the half-life of navacaprant may or may not fall in a similar range. Until the Phase 1 pharmacokinetic data are published in peer-reviewed form, investigators planning research applications that require precise pharmacokinetic modeling should contact Neumora Therapeutics or consult the clinical trial protocol documents (available through ClinicalTrials.gov) for additional pharmacokinetic detail.

5.7 Drug-drug interaction potential

The drug-drug interaction profile of navacaprant has not been formally characterized. Given the likely involvement of CYP3A4 in metabolism, co-administration with strong CYP3A4 inhibitors (ketoconazole, itraconazole, clarithromycin, ritonavir, grapefruit juice) could increase navacaprant exposure, and co-administration with strong CYP3A4 inducers (rifampin, carbamazepine, phenytoin, phenobarbital)

could decrease exposure. The clinical significance of such interactions cannot be assessed without published metabolic pathway data. The Phase 2 trial excluded subjects on strong CYP3A4 inhibitors or inducers as a precautionary measure [4].

6. Preclinical Pharmacology

6.1 In vitro receptor pharmacology

The in vitro pharmacological characterization of navacaprant was reported by Morrison et al. (2024) in *Neuropharmacology* [2]. Using CHO-K1 cells stably expressing human kappa, mu, or delta opioid receptors, the investigators demonstrated: (a) selective antagonist activity at KOR ($IC_{50} = 0.029$ micromolar) with substantially lower potency at MOR ($IC_{50} = 3.3$ micromolar) and DOR (IC_{50} greater than 10 micromolar); (b) absence of agonist activity at all three opioid receptor subtypes (EC_{50} greater than 10 micromolar); and (c) a selectivity ratio of approximately 114-fold for KOR over MOR and greater than 340-fold over DOR [2].

The electrophysiological characterization in native tissue was reported by Margolis et al. (2020) in *PLoS One* [1]. Using whole-cell voltage-clamp recordings from VTA dopamine neurons in acute horizontal midbrain slices (150 micrometers thick) from male Sprague-Dawley rats, the investigators evaluated four novel KOR antagonists. Navacaprant fully blocked U-69,593-induced outward potassium currents with an IC_{50} of 1.2 plus or minus 0.9 nanomolar [1]. The corresponding IC_{50} in a heterologous expression system was 3.2 nanomolar, indicating close agreement between recombinant and native-tissue potency [1]. The compound was tested alongside BTRX-395750 ($IC_{50} = 1.2$ plus or minus 1.3 nanomolar, full antagonist), JNJ-67953964 (aticaprant, $IC_{50} = 3.0$ plus or minus 4.6 nanomolar, full antagonist but with partial MOR and DOR cross-reactivity), and PF-04455242 ($IC_{50} = 6.7$ plus or minus 15.1 nanomolar, partial antagonist asymptoting at 55 percent blockade) [1].

6.2 In vivo KOR antagonism

Morrison et al. (2024) confirmed KOR antagonism in vivo through two functional paradigms [2]. In the mouse tail-flick assay, navacaprant at 10 to 30 mg/kg intraperitoneally dose-dependently abolished the analgesic effect of the KOR agonist U-50,488, demonstrating complete blockade of KOR-mediated analgesia [2]. In a prolactin release paradigm, navacaprant at 10 and 30 mg/kg orally significantly reduced KOR agonist-stimulated prolactin release in both mice and rats, confirming

systemic KOR antagonism following oral administration [2]. The compound exhibited no analgesic effect of its own in the tail-flick assay at doses up to 100 mg/kg orally, confirming the absence of agonist activity in vivo [2].

6.3 Abuse potential assessment

The absence of opioid-related abuse liability was assessed by Morrison et al. (2024) using in vivo microdialysis in freely moving rats [2]. Navacaprant did not alter extracellular dopamine concentrations in the nucleus accumbens shell at oral doses up to 100 mg/kg, whereas the positive control morphine (10 and 20 mg/kg intraperitoneally) produced significant increases in nucleus accumbens dopamine [2]. The nucleus accumbens shell is the principal neuroanatomical substrate of drug reward and reinforcement; the absence of dopaminergic activation at this site supports the classification of navacaprant as a compound without abuse potential [2]. This finding is consistent with the pharmacological expectation for a pure KOR antagonist, which, unlike KOR agonists (which are aversive) or MOR agonists (which are rewarding), should be pharmacologically neutral with respect to reward circuitry.

6.4 Stress-induced cognitive impairment in nonhuman primates

Wallace, Martin, and Arnsten (2022) evaluated navacaprant (designated NMRA-140) in a rhesus macaque (*Macaca mulatta*) model of stress-induced working memory impairment [15]. Six rhesus macaques (2 male, 4 female; 12 to 27 years of age) were administered NMRA-140 at 0, 0.1, 0.3, and 1.0 mg/kg intramuscularly, 30 minutes prior to testing on a delayed-response working memory task in the Wisconsin General Testing Apparatus [15]. Stress was induced pharmacologically by co-administration of FG7142 (a benzodiazepine inverse agonist that produces a mild anxiety-like stress response and reliably impairs prefrontal cortex-dependent working memory) at individually titrated doses of 0.1 to 1.0 mg/kg [15].

Under non-stress conditions, NMRA-140 had no significant effect on working memory performance ($F(2.6, 13) = 1.7$, $p = 0.21$), demonstrating that KOR antagonism does not impair baseline cognitive function [15]. Under stress conditions, FG7142 plus vehicle reduced working memory accuracy to approximately chance levels. NMRA-140 at all three doses (0.1, 0.3, and 1.0 mg/kg) significantly protected working memory performance from the stress-induced impairment, restoring accuracy to vehicle-control levels (main effect of treatment: $F(1.6, 6.5) = 8.8$, $p = 0.02$;

all post hoc comparisons between FG7142 plus vehicle and FG7142 plus NMRA-140 at each dose, p less than 0.05) [15]. The effect was dose-independent across the tested range, suggesting that even the lowest dose tested (0.1 mg/kg) was sufficient for full KOR occupancy in this primate model. No behavioral side effects, omissions, or adverse observations were reported at any dose [15].

These data provide translational evidence that KOR antagonism protects executive cognitive function under stress conditions in a primate species, supporting the hypothesis that KOR blockade may ameliorate the cognitive and motivational deficits associated with stress-related disorders including MDD.

6.5 Supporting class-wide preclinical evidence

The preclinical rationale for KOR antagonism in depression extends beyond the navacaprant-specific data to a broader literature demonstrating antidepressant-like and anxiolytic-like effects of KOR antagonists across multiple species, paradigms, and chemical scaffolds. The prototype selective KOR antagonist nor-binaltorphimine produces antidepressant-like effects in both the forced swim test and the learned helplessness paradigm in rodents [14, 31]. Social defeat stress, which produces lasting depression-like behavioral changes in mice through dynorphin release in the nucleus accumbens, is blocked by KOR antagonism and is absent in prodynorphin knockout mice [32]. These findings establish that the dynorphin-KOR system is both necessary and sufficient for stress-induced depressive phenotypes in rodent models.

Aticaprant (JNJ-67953964) has been evaluated in the unpredictable chronic mild stress (UCMS) paradigm in mice by Jacobson et al. (2020), providing a direct pre-clinical comparator to navacaprant [16]. In that study, 4 weeks of UCMS produced significant deficits in sucrose preference (a measure of anhedonia), nest building (self-care), and forced swim test immobility (passive coping). Aticaprant at 10 mg/kg daily for 11 treatments significantly reversed the sucrose preference deficit ($p=0.01$), nest building deficit ($p=0.0003$ after a single injection; p less than 0.0001 after 10 treatments), and forced swim immobility ($p=0.02$) [16]. The effects persisted through a treatment-free recovery period, suggesting a sustained rather than acute mechanism [16]. Aticaprant was not effective at reversing stress-induced deficits in the light-dark test (anxiety-like behavior) or social interaction test, indicating that KOR antagonism selectively addresses anhedonic, self-care, and coping-related symptoms rather than the full spectrum of stress-induced behavioral changes [16].

These class-wide findings support the specificity of the KOR antagonist mechanism for anhedonia and motivational symptoms rather than generalized anxiolytic or antidepressant effects, a distinction that has implications for patient selection in clinical trials and for the interpretation of the navacaprant Phase 2 and Phase 3 results.

7. Clinical Evidence Base

The following section summarizes the clinical evidence for navacaprant in major depressive disorder. Navacaprant is an investigational compound and is not approved by any regulatory authority for any indication. Clinical data are presented as reported in the published literature and in sponsor communications; investigators should consult the primary publications and trial registrations for complete datasets.

7.1 Phase 1 program

The Phase 1 clinical program comprised single ascending dose (SAD) and multiple ascending dose (MAD) studies in healthy adult volunteers, initiated in June 2018 by BlackThorn Therapeutics [9]. Single oral doses ranged from 5 to 240 mg; multiple daily doses ranged from 20 to 160 mg for 10 days [10, 11]. The compound was well tolerated across the dose range with no serious adverse events [11]. Pharmacokinetic analysis demonstrated dose-proportional increases in plasma exposure, and the PET receptor occupancy study confirmed brain KOR engagement at the projected clinical dose [10].

7.2 Phase 2a trial (Mathew et al. 2025)

The pivotal Phase 2a trial (Study K2-MDD-201, NCT04221230) was a United States-based, randomized, double-blind, placebo-controlled, parallel-group, multicenter study in adults with major depressive disorder [3, 4]. The study enrolled 204 participants, randomized 1:1 to navacaprant 80 mg once daily or placebo for 8 weeks, with a 7- to 28-day screening period and a 4-week safety follow-up [4]. The efficacy population comprised 171 participants [4].

Primary endpoint: The primary efficacy measure was the change from baseline in the HAM-D-17 total score at week 8, analyzed by mixed-model repeated measures (MMRM). The primary endpoint was not met: the least-squares mean difference between navacaprant and placebo was negative 1.7 (standard error 1.08, $p = 0.121$) [4].

The full efficacy population included participants with mild depression (HAMD-17 as low as 14 at baseline), which may have contributed to the attenuated drug-placebo separation.

Sensitivity analyses: A last-observation-carried-forward (LOCF) sensitivity analysis demonstrated statistically significant separation at week 4 (LSMD negative 2.9, SE 0.88, $p = 0.002$) and at week 8 (LSMD negative 2.2, SE 0.98, $p = 0.024$) [4].

Moderate-to-severe subgroup: In the pre-specified subgroup of participants with baseline HAMD-17 scores of 22 or greater ($n = 100$), navacaprant demonstrated significant improvements at week 8 on the HAMD-17 (LSMD negative 2.8, SE 1.33, $p = 0.037$) and on the Snaith-Hamilton Pleasure Scale (SHAPS, a validated measure of anhedonia; LSMD negative 4.8, SE 1.35, $p = 0.001$) [4].

Response and remission rates: In the full efficacy population, response rates (defined as 50 percent or greater reduction in HAMD-17) at week 8 were 45.5 percent for navacaprant versus 24.1 percent for placebo ($p = 0.004$; number needed to treat = 5) [4]. Remission rates (HAMD-17 score of 7 or less) were 26.1 percent versus 10.8 percent ($p = 0.011$; number needed to treat = 7) [4]. In the moderate-to-severe subgroup, the number needed to treat was 4 for response and 5 for remission [4].

Safety: Fewer treatment-emergent adverse events (TEAEs) were reported in the navacaprant group than in the placebo group (35.3 percent versus 44.1 percent) [4]. No serious adverse events were reported in the navacaprant group [4]. The most frequent adverse events were headache (4.9 percent in both groups) and nausea (4.9 percent navacaprant versus 1.0 percent placebo) [4]. There were no reports of weight gain, sexual dysfunction, or suicidal behavior in the navacaprant group [4]. Treatment discontinuation due to adverse events was 1.0 percent in the navacaprant group versus 11.8 percent in the placebo group [4].

7.3 Phase 3 KOASTAL-1 trial

The KOASTAL-1 trial (NCT06029426) was a randomized, double-blind, placebo-controlled, Phase 3 study in 383 adults with moderate-to-severe MDD (MADRS score of 25 or greater at baseline) [12]. Participants were randomized to navacaprant 80 mg once daily or placebo for 6 weeks [12].

Primary endpoint: The primary endpoint was the change from baseline in the MADRS total score at week 6. The trial did not demonstrate any separation between navacaprant and placebo: both groups reported mean MADRS reductions of 12.5

points, yielding a least-squares mean difference of 0.0 ($p = 0.993$) [12].

Key secondary endpoint: The SHAPS anhedonia measure was non-significant in the overall population ($p = 0.648$) [12].

Subgroup analyses: Exploratory analyses revealed a differential response by sex. Female participants showed a numerically larger improvement with navacaprant (MADRS negative 14.0 versus negative 11.4, $p = 0.072$) and a statistically significant difference on the SHAPS (negative 7.2 versus negative 4.9, $p = 0.015$) [12]. Male participants showed no drug-placebo separation on the MADRS, with placebo outperforming navacaprant numerically [12].

Safety: The compound was generally well tolerated, with no serious adverse events reported. The most common adverse events were headache (6.8 percent) and diarrhea (5.2 percent); treatment discontinuation was 2.1 percent [12].

Placebo response: The identical 12.5-point MADRS reductions in both arms represent a high placebo response, a well-recognized challenge in MDD clinical trials that has contributed to the failure of multiple mechanistically distinct antidepressant candidates. The elevated placebo response in KOASTAL-1 may reflect trial-conduct factors including multi-site enrollment variability and concurrent-trial participation [12, 13].

7.4 Interpretation of Phase 2 versus Phase 3 discrepancy

The discrepancy between the Phase 2 subgroup efficacy signals and the Phase 3 KOASTAL-1 null result warrants consideration. Several factors may account for the difference. First, the Phase 2 trial used the HAMD-17 as the primary endpoint while KOASTAL-1 used the MADRS; these instruments, while correlated, weight different symptom domains differently, and the MADRS may be more sensitive to anxious and somatic symptoms relative to the HAMD-17 [4, 12]. Second, the Phase 2 trial was 8 weeks in duration while KOASTAL-1 was 6 weeks; if the KOR antagonist mechanism requires longer exposure to produce robust antidepressant effects (consistent with the hypothesis that circuit-level restoration rather than acute neurotransmitter modulation is the therapeutic mechanism), the shorter Phase 3 duration may have reduced the treatment effect [4, 12]. Third, the high and identical placebo response in KOASTAL-1 (12.5-point MADRS reduction in both arms) is consistent with trial-conduct factors known to inflate placebo responses in MDD trials, including multi-site enrollment variability, professional trial participants, and rater in-

consistency [12, 13]. The protocol modifications implemented for KOASTAL-2 and KOASTAL-3 (reduced sites, enhanced oversight, screening against concurrent enrollment) are designed to address these factors [13].

The sex-differential signal in KOASTAL-1 (female participants showing a trend toward efficacy, male participants showing no signal) is consistent with known sex differences in the dynorphin-KOR system. Preclinical evidence indicates that female rodents show greater dynorphin expression and greater stress-induced KOR activation than males, which may predict greater sensitivity to KOR antagonism in female populations [12]. This finding, if replicated, could inform sex-stratified or biomarker-enriched trial designs.

7.5 Ongoing Phase 3 trials

The KOASTAL-2 and KOASTAL-3 Phase 3 trials were paused following the KOASTAL-1 readout for protocol modifications designed to reduce placebo response and improve signal detection [13]. Modifications included reduced site counts, enhanced medical oversight (Massachusetts General Hospital Trials network collaboration), and implementation of a screening tool to prevent concurrent multi-trial enrollment [13]. Neumora expects topline data from KOASTAL-3 in the first quarter of 2026 and from KOASTAL-2 in the second quarter of 2026 [13]. The KOASTAL-4 trial was halted [13].

7.6 Regulatory status

Navacaprant is not approved by the United States Food and Drug Administration, the European Medicines Agency, or any other regulatory authority for any indication. The compound remains investigational and is in active Phase 3 clinical development.

8. Sourcing and Quality Verification

Navacaprant is not available as a pharmaceutical-grade preparation from any registered manufacturer, as the compound has not received regulatory approval in any jurisdiction. Research-grade navacaprant (BTRX-335140) is available from multiple chemical and pharmaceutical research suppliers (MedChemExpress, MedKoo Biosciences, TargetMol, Cayman Chemical, Probechem Biochemicals, GlpBio, AbMole, Sun-Shine Chemical, Biosynth, and others) as the free base under CAS number 2244614-14-8, typically at greater than 98 percent purity by high-performance liquid chromatography [5].

Supply is in milligram quantities (1 mg, 5 mg, 10 mg, 25 mg, and 50 mg packaging are typical from multiple vendors). The compound is priced in the range of \$100 to \$500 per 10 mg of research-grade material at the time of monograph preparation, consistent with the pricing of early-clinical-stage investigational compounds.

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

- High-performance liquid chromatography (HPLC) area-percent purity, ideally greater than 98 percent
- Mass spectrometry confirmation of molecular weight (expected $[M+H]^+$ of 454.26 for the protonated free base, $C_{25}H_{33}FN_5O_2^+$)
- Nuclear magnetic resonance (1H -NMR and ^{13}C -NMR) confirmation of structure, with particular attention to the diagnostic signals of the quinoline aromatic protons, the oxadiazole methyl singlet, the piperidine ring protons, and the tetrahydropyran ring protons
- Liquid chromatography-mass spectrometry (LC-MS) analysis for related impurities and synthetic intermediates
- Karl Fischer or loss-on-drying analysis for residual water content

Third-party analytical laboratories (Janoshik Analytical, Anabolic Lab, and others) can provide independent confirmation of vendor certificates of analysis. Given the investigational status of the compound and the absence of pharmacopoeial monographs, the vendor certificate of analysis should be verified against an authenti-

cated reference standard where available. The research-grade navacaprant market is relatively recent (first appearing in supplier catalogs circa 2020 to 2022), and lot-to-lot variability in purity and impurity profiles should be expected.

9. Reconstitution and Handling

Navacaprant is supplied as a solid (free base form), typically as a white to off-white powder. For in vitro research applications, the compound is reconstituted in dimethyl sulfoxide (DMSO) to prepare concentrated stock solutions (typically 10 to 50 millimolar). Working concentrations for receptor binding and functional assays are typically in the nanomolar to low micromolar range, consistent with the in vitro IC₅₀ values reported in the pharmacology literature [1, 2].

For in vivo research applications, navacaprant has been administered orally (by gavage) in rodent studies at doses of 10 to 100 mg/kg, formulated in standard oral vehicles [2]. In the rhesus macaque study, the compound was administered intramuscularly at 0.1 to 1.0 mg/kg [15]; the specific vehicle for intramuscular formulation has not been detailed in the published literature.

Storage recommendations for the solid compound are at negative 20 degrees Celsius in a desiccated, light-protected environment. DMSO stock solutions should be aliquoted for single use and stored at negative 20 degrees Celsius to avoid freeze-thaw degradation. Stability data for research-grade navacaprant have not been published; standard practices for small-molecule investigational compounds (use within 6 months of preparation for DMSO stocks, within 24 hours for aqueous dilutions at room temperature) should be applied.

The compound is not intended for human administration outside of approved clinical trial protocols. Investigators handling the compound should employ standard laboratory safety practices for investigational pharmaceutical agents, including use of gloves, fume hood for weighing and dissolution, and proper disposal of contaminated materials.

10. Stack Interaction Considerations

10.1 Opioid receptor pharmacology interactions

Navacaprant is a selective KOR antagonist with no agonist activity at KOR, MOR, or DOR [2]. The principal pharmacological interaction of concern is with KOR agonists: navacaprant will block the effects of endogenous dynorphin and of synthetic KOR agonists (salvinorin A, U-50,488, U-69,593). In research applications where KOR agonism is the dependent variable, navacaprant administration will confound the measurement.

Concurrent administration with MOR agonists (morphine, oxycodone, fentanyl, buprenorphine) is not expected to produce a pharmacokinetic interaction based on the selectivity profile, as navacaprant does not block MOR responses at concentrations up to 10 nanomolar in native tissue [1]. However, the KOR system modulates certain MOR-mediated phenomena (including conditioned place aversion to MOR withdrawal), and KOR antagonism may alter the behavioral and motivational consequences of MOR agonist exposure in research contexts.

Concurrent administration with buprenorphine is a specific consideration: buprenorphine is a partial MOR agonist and a KOR antagonist. Co-administration with navacaprant would result in additive KOR antagonism and no pharmacodynamic conflict at the KOR; the MOR partial agonism of buprenorphine would be unaffected by navacaprant. This combination has not been studied in clinical research.

10.2 Metabolic interactions

The cytochrome P450 enzymes responsible for the metabolism of navacaprant have not been published. Until the metabolic pathway is characterized, investigators should consider potential interactions with strong CYP3A4 inhibitors (ketoconazole, itraconazole, clarithromycin, ritonavir) and strong CYP3A4 inducers (rifampin, carbamazepine, phenytoin, St. John's wort), as the quinoline-piperidine structural class is commonly metabolized through CYP3A4. Interactions with

CYP2D6 inhibitors (paroxetine, fluoxetine, bupropion, quinidine) should also be considered given the common involvement of CYP2D6 in piperidine ring metabolism.

10.3 Antidepressant co-administration

The Phase 2 trial of navacaprant was a monotherapy study; participants were not on concurrent antidepressant therapy [4]. The KOASTAL Phase 3 trials also evaluated navacaprant as monotherapy. In contrast, the comparator aticaprant was evaluated as adjunctive therapy to SSRIs and SNRIs [18]. The interaction of navacaprant with serotonergic antidepressants (SSRIs, SNRIs, tricyclics, MAOIs) has not been characterized in published studies. The KOR and serotonergic systems interact at the level of dorsal raphe serotonin neuron modulation; concurrent KOR antagonism and serotonin reuptake inhibition could produce additive antidepressant effects through complementary circuit-level mechanisms, but this hypothesis has not been tested.

10.4 QT-prolonging agents

No QT interval prolongation signal has been reported for navacaprant in the published Phase 1, Phase 2, or Phase 3 safety data [4, 12]. However, the cardiac safety database is limited. Investigators should exercise standard caution when co-administering navacaprant with drugs known to prolong the QT interval until comprehensive cardiac safety data are available.

10.5 Combinations of research interest

The combination of KOR antagonism with dopaminergic agents (pramipexole, aripiprazole) is of theoretical interest for anhedonia and motivational deficits, as both KOR antagonism and dopamine receptor agonism or partial agonism target the mesolimbic reward circuit from different mechanistic entry points. The combination with glutamatergic modulators (ketamine, esketamine) is of interest given the rapid antidepressant effects of ketamine and the stress-buffering effects of KOR antagonism. Neither combination has been studied in published research.

11. Adverse Events and Safety Signal

11.1 Phase 2 adverse event profile

The Phase 2a trial reported a favorable safety profile for navacaprant 80 mg once daily [4]. Fewer treatment-emergent adverse events (TEAEs) occurred in the navacaprant group (35.3 percent) than in the placebo group (44.1 percent) [4]. The most common adverse events were:

- Headache: 4.9 percent (both navacaprant and placebo groups) [4]
- Nausea: 4.9 percent navacaprant versus 1.0 percent placebo [4]

No serious adverse events were reported in the navacaprant group [4]. Treatment discontinuation due to adverse events was markedly lower in the navacaprant group (1.0 percent) than in the placebo group (11.8 percent) [4]. No reports of weight gain, sexual dysfunction, or suicidal ideation or behavior occurred in the navacaprant group [4]. The absence of weight gain and sexual dysfunction is noteworthy in the context of antidepressant development, as these adverse events are common with SSRIs, SNRIs, and atypical antipsychotic augmentation strategies and are leading contributors to treatment non-adherence.

11.2 Phase 3 adverse event profile

The KOASTAL-1 Phase 3 trial confirmed the favorable tolerability of navacaprant in a larger population (n=383) over 6 weeks [12]. The compound was generally well tolerated, with no serious adverse events reported [12]. The most common adverse events were headache (6.8 percent) and diarrhea (5.2 percent) [12]. Treatment discontinuation was 2.1 percent [12]. The consistency of the safety profile across the Phase 2 (8-week, n=204) and Phase 3 (6-week, n=383) populations strengthens confidence in the tolerability assessment, with a combined safety database of approximately 293 navacaprant-treated subjects in controlled studies [4, 12].

11.2a Comparison to standard antidepressant adverse event profiles

The adverse event profile of navacaprant compares favorably to the established antidepressant classes. SSRIs and SNRIs produce sexual dysfunction in 25 to 73 percent of treated patients (depending on the assessment method), weight gain in 10 to 25 percent on chronic dosing, and gastrointestinal adverse events (nausea, diarrhea) in 15 to 30 percent [33]. Atypical antipsychotic augmentation (aripiprazole, quetiapine, olanzapine) produces metabolic effects (weight gain, dyslipidemia, hyperglycemia) in 10 to 40 percent and sedation in 10 to 30 percent [33]. The opioid system modulator buprenorphine/samidorphan (ALKS 5461) produces nausea in 27.6 percent and constipation in 12.2 percent [22]. By contrast, navacaprant produced fewer TEAEs than placebo in Phase 2 and no SAEs in either Phase 2 or Phase 3, with nausea rates of 4.9 percent and no weight gain or sexual dysfunction [4, 12]. If the efficacy of navacaprant can be established in the ongoing KOASTAL trials, the tolerability profile would represent a meaningful clinical differentiation from existing treatments.

11.3 Abuse potential

The pharmacological characterization by Morrison et al. (2024) provides the pre-clinical basis for the assessment that navacaprant lacks abuse potential [2]. The compound has no agonist activity at any opioid receptor subtype, does not produce analgesia, and does not increase dopamine in the nucleus accumbens [2]. These findings are consistent with the pharmacological expectation for a pure KOR antagonist: KOR agonism produces dysphoria and aversion (the opposite of reward), and KOR antagonism blocks these aversive states without producing positive reinforcement. The compound does not meet the pharmacological criteria for Schedule II through V classification under the United States Controlled Substances Act.

11.4 Cardiac safety

No cardiac adverse events, QT prolongation, arrhythmias, or other cardiovascular safety signals have been reported in the published Phase 1, Phase 2, or Phase 3 data for navacaprant [4, 12]. This is a meaningful differentiation from JDTC, the first selective KOR antagonist to enter Phase 1 clinical testing, which was terminated after 2 of 6 subjects at a single 1 mg dose experienced asymptomatic nonsustained ventricular tachycardia [17, 19]. The cardiac safety of navacaprant at doses up to 240

mg (single dose) and 160 mg daily for 10 days in healthy volunteers supports the conclusion that JDtic's cardiac toxicity was compound-specific (likely related to JNK activation) rather than a class effect of KOR antagonism [17].

11.5 Opioid withdrawal and dependence

No opioid withdrawal signs or symptoms have been reported following discontinuation of navacaprant in any published study [4, 12]. This is consistent with the pharmacological expectation for a KOR antagonist with no MOR agonist or partial agonist activity: opioid physical dependence is mediated through chronic MOR activation, and compounds without MOR agonism do not produce opioid dependence [2]. The Columbia Suicide Severity Rating Scale (C-SSRS) was administered in the Phase 2 trial; no suicidal ideation or behavior was reported in the navacaprant group [4].

11.6 Special populations

Safety data in special populations (hepatic impairment, renal impairment, elderly, pediatric, pregnancy, lactation) have not been published for navacaprant. The Phase 2 and Phase 3 trials enrolled adults aged 18 to 65 years; safety in elderly populations (greater than 65 years) and pediatric populations has not been characterized [4, 12]. The compound is investigational and should not be administered to human subjects outside of approved clinical trial protocols. Investigators planning preclinical studies should note that the compound has been administered safely in rodents at oral doses up to 100 mg/kg and in rhesus macaques at intramuscular doses up to 1.0 mg/kg without adverse observations [2, 15].

12. Comparable Compounds Assessment

This section presents a structured comparative assessment of five kappa opioid receptor candidates against navacaprant, evaluated against five competency standards: novelty, effect size, promising potential (current clinical state and trajectory), side-effect profile (clinical or preclinical), and overall validation. The five candidates were selected as the principal KOR-targeting compounds with substantive clinical or preclinical pharmacology programs in depression and related indications.

12.1 Aticaprant (JNJ-67953964, CERC-501, LY2456302)

Mechanism: Selective KOR antagonist. Originally developed by Eli Lilly (as LY2456302), subsequently by Cerecor (as CERC-501), and most recently by Janssen (Johnson and Johnson) (as JNJ-67953964 and aticaprant). Binding affinity K_i of 0.813 nanomolar at KOR with greater than 30-fold functional selectivity over MOR [14]. In VTA dopamine neuron electrophysiology, IC_{50} of 3.0 plus or minus 4.6 nanomolar, but partially blocked MOR agonist (DAMGO) and DOR agonist (DPDPE) responses at 10 nanomolar, indicating lower selectivity than navacaprant in native tissue [1]. Rapid oral absorption with a terminal half-life of approximately 30 to 40 hours in healthy subjects [14].

Development trajectory: A proof-of-concept pilot trial (Fava et al. 2020) evaluated CERC-501 at 10 and 20 mg/day for 6 days as adjunctive therapy in treatment-resistant depression using a sequential parallel comparison design; the study was terminated early by NIMH due to slow enrollment ($n=8$), with numerical but not statistically significant advantages for CERC-501 on the HAM-D-6 and MADRS [20]. A Phase 2 adjunctive trial (Schmidt et al. 2024, $n=166$) evaluated aticaprant 10 mg once daily added to ongoing SSRI/SNRI therapy for 6 weeks in adults with moderate-to-severe MDD and demonstrated significant MADRS improvement (LSMD negative 2.1, $p=0.044$ in the enriched intent-to-treat analysis; negative 3.1, $p=0.002$ in the full intent-to-treat analysis; effect sizes 0.23 and 0.36, respectively), with greater

benefit in participants with higher baseline anhedonia [18]. Janssen advanced aticaprant to the Phase 3 VENTURA registration program for adjunctive treatment of MDD with anhedonia.

Clinical outcome: On March 6, 2025, Johnson and Johnson announced discontinuation of the VENTURA Phase 3 program due to insufficient efficacy [21]. The safety data confirmed that aticaprant was safe and well tolerated, with no new safety signals [21]. The clinical trajectory terminates at Phase 3 negative readout, following the same pattern as navacaprant KOASTAL-1.

Novelty: 3. Selective KOR antagonist with adjunctive-therapy positioning; the mechanism is shared with navacaprant but the clinical strategy (adjunctive to SSRI/SNRI rather than monotherapy) was distinct.

Effect size: 2. Phase 2 adjunctive effect sizes of 0.23 to 0.36 on MADRS (small to moderate). Phase 3 efficacy insufficient for registration.

Promising potential: 1. VENTURA program discontinued. J&J stated intention to explore other indications.

Side-effect profile: 4. Generally well tolerated. Phase 2 adverse events: headache 11.8 percent, diarrhea 8.2 percent, nasopharyngitis 5.9 percent, pruritus 5.9 percent [18]. No serious safety concerns.

Overall validation: 2. Extensive clinical dataset from proof-of-concept through Phase 3, but Phase 3 efficacy failure limits validation.

Comparison to navacaprant: Aticaprant and navacaprant are the two selective KOR antagonists that have reached Phase 3 for MDD, and both failed at Phase 3. Aticaprant was developed as adjunctive therapy; navacaprant as monotherapy. Navacaprant has higher KOR selectivity in native tissue (clean MOR/DOR profile at 10 nanomolar versus partial MOR/DOR blockade for aticaprant) and rapid reversibility (10-minute washout versus incomplete washout at 10 minutes for aticaprant, though aticaprant's longer half-life may account for the electrophysiological difference) [1]. The Phase 3 failures of both compounds raise questions about whether selective KOR antagonism alone is sufficient for registration-quality antidepressant efficacy, or whether trial-design factors (placebo response, patient selection) masked a genuine effect.

12.2 Buprenorphine/Samidorphan (ALKS 5461)

Mechanism: Opioid system modulator. Buprenorphine is a partial agonist at MOR and an antagonist at KOR; samidorphan is a full MOR antagonist designed to block the MOR-mediated effects (euphoria, respiratory depression, abuse liability) while preserving the KOR antagonism [22]. The combination is pharmacologically distinct from selective KOR antagonists: the therapeutic effect may derive from the composite of MOR partial agonism and KOR antagonism, producing a different circuit-level modulation than KOR antagonism alone. Fixed-dose 1:1 ratio sublingual tablet; doses of 0.5/0.5, 1/1, and 2/2 mg studied in Phase 3 [22, 23].

Development trajectory: Alkermes developed ALKS 5461 as adjunctive treatment for MDD. The Phase 3 program comprised three pivotal trials: FORWARD-3 (n=295), FORWARD-4 (n=385), and FORWARD-5 (n=407) [22, 23]. FORWARD-3 did not meet the primary endpoint (MADRS LSMD negative 0.3, p=0.782) [23]. FORWARD-4 did not meet the primary endpoint at week 5 (MADRS LSMD negative 1.8, p=0.109) but showed significance in post hoc analyses [22]. FORWARD-5 met the primary endpoint (MADRS-6 LSMD negative 1.5, p=0.018; MADRS-10 LSMD negative 1.9, p=0.026) [22]. The pooled effect size (Hedges' g) was 0.22 [22]. The FDA declined to approve ALKS 5461 for MDD, citing inconsistent efficacy results across the Phase 3 program.

Novelty: 3. Opioid system modulation is a distinct therapeutic concept from selective KOR antagonism, though the contribution of KOR antagonism versus MOR partial agonism to any antidepressant effect is unresolved.

Effect size: 2. Pooled Hedges' g of 0.22 (small effect); inconsistent across individual trials.

Promising potential: 2. Not approved for MDD; development trajectory has stalled.

Side-effect profile: 2. Significant gastrointestinal burden: nausea 27.6 percent versus 6.8 percent placebo; constipation 12.2 percent; dizziness 12.2 percent; vomiting 9.8 percent; somnolence 7.3 percent [22]. No evidence of abuse or dependence [22].

Overall validation: 3. The most extensive clinical dataset among KOR-targeting compounds for depression (over 1,000 patients in Phase 3), but inconsistent efficacy and significant tolerability burden limited clinical validation.

Comparison to navacaprant: ALKS 5461 is mechanistically distinct (MOR partial agonism plus KOR antagonism versus pure KOR antagonism for navacaprant). The tolerability profile of navacaprant is substantially more favorable (TEAE rate lower than placebo in Phase 2, versus nausea rates exceeding 27 percent for ALKS 5461). The small effect size of ALKS 5461 across pooled Phase 3 data and the absence of regulatory approval do not support the dual MOR/KOR mechanism as superior to selective KOR antagonism for antidepressant efficacy.

12.3 JDtic

Mechanism: Selective KOR antagonist with high binding affinity ($K_i = 0.32$ nanomolar) and extreme selectivity over MOR and DOR [14]. Structurally a trans-3,4-dimethyl-4-(3-hydroxyphenyl)piperidine; the trans-decahydroisoquinoline scaffold is unrelated to the quinoline-oxadiazole structure of navacaprant. Unlike navacaprant and aticaprant, JDtic activates c-Jun N-terminal kinase (JNK), a stress kinase, and its long duration of action (days to weeks in vivo) is attributed to JNK activation rather than to simple competitive receptor antagonism [17].

Development trajectory: JDtic was the first selective KOR antagonist to enter Phase 1 clinical testing. The double-blind, placebo-controlled Phase 1 trial enrolled 12 healthy adult males (6 active, 6 placebo) at a single oral dose of 1 mg [17, 19]. Two of 6 subjects receiving JDtic experienced asymptomatic nonsustained ventricular tachycardia (NSVT), occurring at similar times following dosing. Neither placebo-treated subject exhibited this finding [17, 19]. The likelihood that the cardiac events were drug-related was assessed as high, given the timing concordance and the low expected incidence of sporadic VT in healthy subjects [17]. The safety board determined that further human trials would not be ethically justified, and the program was terminated [17].

Novelty: 2. The mechanism (selective KOR antagonism) is shared with navacaprant, though the JNK-activating pharmacology is distinct. First selective KOR antagonist in clinical testing, but the class has moved beyond this scaffold.

Effect size: 1. No efficacy data; terminated before efficacy evaluation.

Promising potential: 1. Terminated for cardiac toxicity; no further development.

Side-effect profile: 1. NSVT in 2/6 subjects at a single 1 mg dose [17, 19]. The cardiac toxicity is the defining safety liability.

Overall validation: 1. Phase 1 termination with no efficacy data and a cardiac safety signal.

Comparison to navacaprant: JDtic illustrates the importance of the pharmacological differentiation between KOR antagonists. Navacaprant is a competitive, reversible antagonist with rapid washout and no JNK activation; JDtic activates JNK and has an impractically long duration of action. The cardiac safety of navacaprant at doses up to 240 mg (single dose, approximately 240-fold higher than the JDtic dose that produced NSVT) and 160 mg daily for 10 days supports the conclusion that JDtic's cardiac toxicity was compound-specific [4, 10, 17].

12.4 Nor-binaltorphimine (nor-BNI)

Mechanism: Highly selective and potent non-peptide KOR antagonist with K_i of 0.26 nanomolar, demonstrating approximately 170-fold selectivity over MOR and 150-fold over DOR [14]. Nor-BNI is the prototypical selective KOR antagonist and was instrumental in defining the pharmacology of the KOR system. However, nor-BNI has an extremely long duration of action: a single injection produces KOR blockade lasting days to weeks in vivo, and in the VTA electrophysiology preparation, nor-BNI showed no reversal of KOR blockade at 20 minutes of washout [1]. The prolonged action has been attributed, like JDtic, to JNK activation [17].

Development trajectory: Nor-BNI has not been advanced to clinical development due to the impractically long duration of action, which prevents dose adjustment, precludes clinical dose-finding, and raises concerns about cumulative effects and safety monitoring.

Novelty: 2. Prototype compound; well-characterized but not clinically viable.

Effect size: 2. Extensive preclinical literature demonstrates antidepressant-like and anxiolytic-like effects in rodent behavioral models (forced swim test, learned helplessness), but these data do not translate to clinical effect size [14].

Promising potential: 1. Not in clinical development; serves as a pharmacological tool.

Side-effect profile: 2. Not assessed in humans. The extremely long duration of action and JNK activation create theoretical safety concerns.

Overall validation: 2. The most extensively characterized KOR antagonist in the pharmacological literature; serves as a reference tool but has no clinical validation pathway.

Comparison to navacaprant: Nor-BNI is the pharmacological ancestor of navacaprant and the other clinical KOR antagonists. Navacaprant was designed to address the principal limitation of nor-BNI: the extremely long and uncontrollable duration of action. Navacaprant achieves rapid, reversible KOR blockade (10-minute washout in electrophysiology) at comparable potency (IC₅₀ 1.2 nanomolar versus Ki 0.26 nanomolar for nor-BNI) with none of the JNK-dependent pharmacology [1].

12.5 PF-04455242

Mechanism: KOR antagonist developed by Pfizer. In VTA dopamine neuron electrophysiology, PF-04455242 exhibited partial antagonist activity, asymptoting at only 55 percent blockade of U-69,593-induced outward currents (IC₅₀ = 6.7 plus or minus 15.1 nanomolar) [1]. In 3 of 8 neurons tested, PF-04455242 at 1 micromolar generated an outward current independent of KOR activation, suggesting off-target ion channel activity [1]. The partial antagonism and off-target effects distinguish PF-04455242 from navacaprant's clean, full KOR antagonism.

Development trajectory: PF-04455242 was terminated from clinical development due to findings in animal toxicology studies [14]. The specific toxicological findings have not been fully published but were sufficient to halt the program before human clinical testing.

Novelty: 2. Conventional KOR antagonist scaffold with partial antagonist pharmacology.

Effect size: 1. Preclinical only; no clinical efficacy data.

Promising potential: 1. Terminated for preclinical toxicology.

Side-effect profile: 1. Terminated for toxicology findings; the off-target outward current in VTA neurons raises additional mechanistic concerns [1].

Overall validation: 1. Terminated preclinically; serves as a reference compound in electrophysiology comparisons.

Comparison to navacaprant: PF-04455242 illustrates the importance of full versus partial KOR antagonism and clean receptor selectivity. Navacaprant achieves complete KOR blockade in native tissue, whereas PF-04455242 achieves only 55 percent blockade. The off-target outward current observed with PF-04455242 in VTA neurons has no counterpart in the navacaprant electrophysiology data.

12.6 Comparator summary

The five comparator compounds span the development landscape of KOR-targeting therapeutics for depression. **Aticaprant** is the closest clinical comparator to navacaprant, with both compounds reaching Phase 3 and both failing to demonstrate sufficient efficacy for registration. The parallel Phase 3 failures raise the fundamental question of whether selective KOR antagonism can produce clinically meaningful antidepressant effects in broad MDD populations, or whether KOR antagonism requires patient stratification (by anhedonia severity, sex, or biomarker) to demonstrate benefit. **Buprenorphine/samidorphan** represents the most extensively studied opioid system modulator for MDD, but inconsistent Phase 3 results and significant tolerability burden limited its clinical validation. **JDTic** was the first selective KOR antagonist in Phase 1 testing but was terminated for cardiac toxicity attributable to its JNK-activating pharmacology, a mechanism that navacaprant does not share. **Nor-BNI** is the pharmacological prototype with an impractically long duration of action. **PF-04455242** was a partial antagonist with off-target activity, terminated for preclinical toxicology.

Navacaprant occupies a distinctive position in this landscape: it is the only compound combining full KOR antagonism in native tissue, rapid reversibility, clean selectivity (no MOR or DOR cross-reactivity at 10 nanomolar), absence of JNK activation, and clinical tolerability superior to placebo in controlled trials. The tolerability profile is the strongest attribute of the navacaprant dataset; the efficacy profile remains unresolved pending the KOASTAL-2 and KOASTAL-3 readouts. The Phase 3 failures of both navacaprant and aticaprant in 2025, combined with the inconsistent results for buprenorphine/samidorphan, have materially reduced enthusiasm for KOR-targeting therapeutics in MDD but have not invalidated the mechanism. The sex-differential signal in KOASTAL-1 and the consistent anhedonia signals in Phase 2 subgroup analyses may inform future trial design, biomarker-enriched enrollment, and precision-medicine approaches to KOR antagonism in depression.

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are noted where compound-specific data are sparse; investigators should weigh the evidence accordingly. Investigators should obtain analytical confirmation of identity and purity on every lot of research-grade material.