

RESEARCH MONOGRAPH . COMPOUND PROFILE

GB-115

A synthetic retrodipeptide analogue of cholecystokinin tetrapeptide (CCK-4) designed at the Zakusov Research Institute of Pharmacology, distinguished by selective central CCK-1 receptor antagonism, non-benzodiazepine anxiolytic activity, and a favorable safety profile confirmed through Phase 3 clinical evaluation under the trade name Ranquilon.

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ABSTRACT

GB-115 (N-(6-phenylhexanoyl)-glycyl-L-tryptophan amide; CAS 678996-63-9) is a synthetic retrodiptide analogue of the endogenous anxiogenic tetrapeptide cholecystokinin-4 (CCK-4, Trp-Met-Asp-Phe-NH₂), designed and synthesized at the V.V. Zakusov Research Institute of Pharmacology (Russian Academy of Medical Sciences) using the topochemical Shemyakin-Ovchinnikov-Ivanov principle for rational peptide drug design. The compound functions as a selective antagonist of the central cholecystokinin type 1 (CCK-1) receptor, producing anxiolytic activity in rodent and primate behavioral models at doses of 0.05 to 0.2 mg/kg without the sedation, tolerance, dependence, or cognitive impairment associated with benzodiazepine anxiolytics. The biologically active conformation of GB-115 has been identified by nuclear Overhauser effect NMR spectroscopy as a type II beta-turn, with the native spatial distance between the phenyl and indolyl hydrophobic pharmacophores critical for receptor interaction. Structure-activity relationship studies demonstrated that L-tryptophan-containing derivatives produce anxiolytic effects, while D-tryptophan-containing enantiomers produce anxiogenic effects mirroring CCK-4 itself, confirming the stereospecificity of the CCK-1 receptor interaction.

Preclinical pharmacology extends beyond anxiolysis. GB-115 potentiates morphine-induced analgesia through supraspinal opioidergic mechanisms and produces independent antinociceptive activity in chemical and thermal pain models with a significant non-opioid component. Anti-inflammatory effects have been demonstrated in concanavalin A-induced and

carrageenan-induced inflammation models and in experimental autoimmune encephalomyelitis in C57Bl/6 mice, where intraperitoneal administration at 1 mg/kg significantly alleviated pathological symptoms, promoted thymus weight recovery, and reduced perivascular edema and neutrophil infiltration of brain tissue. Immunomodulatory activity includes stimulation of phagocytic activity of peritoneal macrophages and humoral immune response in intact mice and immunocorrecting effects in animals with secondary immunodeficiency. The compound reverses antinociceptive tolerance to morphine on sub-chronic co-administration, a property consistent with its CCK-1 receptor antagonist mechanism given the established role of cholecystokinin in opioid tolerance.

Pharmacokinetics are characterized by rapid oral absorption, low absolute bioavailability (approximately 4.65 percent in animal models), and a short elimination half-life of approximately 1.0 hour in humans. The amide bond confers greater peptidase resistance than native peptide bonds, extending plasma detection time relative to unmodified dipeptides. Acute toxicity is very low, with an oral LD₅₀ exceeding 6000 mg/kg in rodents, providing a therapeutic index of approximately 30,000 to 60,000 relative to the effective anxiolytic dose range.

Clinical evaluation has progressed through Phase 2 and Phase 3 trials. An open-label pilot study in 25 patients with generalized anxiety disorder demonstrated significant reduction in Hamilton Anxiety Rating Scale (HAM-A) total scores from a median of 22 at baseline to 5 at day 21 on 6 mg daily oral dosing ($p < 0.001$), with concurrent improvement in cognitive processing speed, attention, and reaction time, and no stimulation-related adverse events. A Phase 3 double-blind, randomized, placebo-controlled,

multicenter trial (NCT05586789) in 220 patients with anxiety associated with neurasthenia and adjustment disorders confirmed superiority of Ranquilon 6 mg daily over placebo in reducing anxiety, with all recorded adverse events classified as mild and no serious adverse events or treatment discontinuations. A Phase 4 open-label comparative trial (NCT06843044) against fabomotizole (Afobazole) 30 mg daily is currently recruiting. This monograph reviews the chemistry, design rationale, and stereochemistry of GB-115; the CCK-1 receptor antagonist mechanism and downstream pharmacology; the preclinical evidence across anxiolytic, analgesic, anti-inflammatory, and immunomodulatory applications; the clinical evidence base including Phase 2 and Phase 3 data; pharmacokinetics across species; sourcing and quality verification; reconstitution and handling; stack interactions; adverse events and safety; and a comparative assessment of five anxiolytic or CCK-modulating alternatives against GB-115 on five competency standards.

1. Compound Identification

1.1 Names, synonyms, and registry identifiers

Proposed International Nonproprietary Name: GB-115 (laboratory designation; no INN assigned as of monograph revision).

Trade name: Ranquilon (used in Russian Federation clinical development and registration filings).

Development codes: GB-115 (V.V. Zakusov Research Institute of Pharmacology). The designation "GB" reflects the laboratory series nomenclature of the Gudasheva group at the Institute.

Chemical Abstracts Service registry number: 678996-63-9 (free amide).

DrugBank accession: DB19204.

International Union of Pure and Applied Chemistry name: N-[2-[[[(2S)-1-amino-3-(1H-indol-3-yl)-1-oxopropan-2-yl]amino]-2-oxoethyl]-6-phenylhexanamide.

Sequence notation: C₆H₅-(CH₂)₅-CO-Gly-L-Trp-NH₂.

ClinicalTrials.gov identifiers: NCT05586789 (Phase 3, completed), NCT06843044 (Phase 4, recruiting).

1.2 Structural class and chemistry

GB-115 is a synthetic retrodipeptide, meaning that the peptide bond directionality is reversed relative to the parent endogenous sequence (cholecystokinin-4, Trp-Met-Asp-Phe-NH₂). The compound belongs to the broader class of peptidomimetic cholecystokinin receptor ligands and is classified as a CCK-1 receptor antagonist. The structural class places it within the research framework of designed dipeptide neurotropic agents developed at the Zakusov Institute, which also includes Noopept (GVS-111, a prolyl dipeptide nootropic) and GD-11 (a nerve growth factor-mimetic dipeptide) [1, 2].

Molecular formula: C₂₅H₃₀N₄O₃.

Molecular weight: 434.5 g/mol.

Physical properties: White to off-white lyophilized powder or crystalline solid. Soluble in dimethyl sulfoxide (DMSO) and in aqueous buffers at moderately acidic to neutral pH. The compound is supplied as the free amide for research applications.

Stereochemistry: GB-115 contains one stereocenter at the alpha-carbon of the L-tryptophan residue (S-configuration). The stereochemistry is critical for biological activity: the L-tryptophan (S) configuration produces anxiolytic activity, while the D-tryptophan (R) enantiomer produces anxiogenic activity matching the parent CCK-4 peptide [1]. Investigators acquiring research-grade GB-115 should confirm stereochemical integrity to ensure the anxiolytic, rather than anxiogenic, form is present.

1.3 Design rationale and synthesis

GB-115 was designed using the topochemical Shemyakin-Ovchinnikov-Ivanov principle, a rational peptide drug design methodology developed over approximately 25 years at the V.V. Zakusov Research Institute of Pharmacology [1]. The design proceeded through the following strategic steps:

1. Identification of the endogenous ligand CCK-4 (Trp-Met-Asp-Phe-NH₂) as the starting structure, based on its established role as an anxiogenic neuropeptide acting through central cholecystokinin receptors.
2. Construction of a retro-analogue by reversing the peptide bond direction and identifying the minimum pharmacophoric elements required for receptor interaction.
3. Identification of the phenyl (from phenylalanine) and indolyl (from tryptophan) aromatic groups as the critical hydrophobic pharmacophores.
4. Replacement of the non-pharmacophoric methionine and aspartate residues with a glycine spacer and substitution of the Phe-Gly dipeptide fragment with a topologically equivalent phenylhexanoyl moiety to enhance metabolic stability and oral bioavailability.
5. Conversion of the terminal carboxyl to a primary amide to improve peptidase resistance.

The resulting structure, $\text{C}_6\text{H}_5\text{-(CH}_2\text{)}_5\text{-CO-Gly-L-Trp-NH}_2$, retains the native distance between the phenyl and indolyl pharmacophores. Structure-activity studies within the homologous series $\text{Ph(CH}_2\text{)}_n\text{CO-NH(CH}_2\text{)}_m\text{CO-Trp-NH}_2$ ($n = 1, 3 \text{ to } 5$; $m = 1 \text{ to } 3$) demonstrated that decreasing the inter-pharmacophore distance by even one methylene group produced a tenfold reduction in anxiolytic activity, confirming that spatial positioning is the primary determinant of receptor interaction [1].

The synthesis is a standard peptide coupling sequence: acylation of glycine with 6-phenylhexanoic acid (or its activated ester), followed by coupling to L-tryptophan amide. The final product is purified by reversed-phase high-performance liquid chromatography and characterized by nuclear magnetic resonance spectroscopy, mass spectrometry, and chiral high-performance liquid chromatography. The amide terminus is introduced during the tryptophan coupling step using tryptophan amide hydrochloride as the nucleophilic amine [1, 3].

2. Abstract

GB-115 (N-(6-phenylhexanoyl)-glycyl-L-tryptophan amide) is a selective antagonist of the central cholecystokinin type 1 (CCK-1) receptor and a rationally designed retrodipeptide analogue of the endogenous anxiogenic tetrapeptide cholecystokinin-4. The compound was designed at the V.V. Zakusov Research Institute of Pharmacology using the topochemical principle to preserve the spatial relationship between the phenyl and indolyl hydrophobic pharmacophores of the parent peptide while replacing metabolically labile internal residues with a peptidomimetic scaffold [1].

The principal pharmacological activity is anxiolysis. GB-115 produces dose-dependent anxiolytic effects in multiple rodent behavioral paradigms (elevated plus maze, light-dark box, Vogel conflict test, open field) at intraperitoneal doses of 0.002 to 0.2 mg/kg and oral doses of 0.05 to 1 mg/kg without the sedation, muscle relaxation, tolerance, dependence, or cognitive impairment characteristic of benzodiazepine anxiolytics [1, 4, 5]. The anxiolytic mechanism is mediated through antagonism of central CCK-1 receptors, as demonstrated by mutual antagonism between GB-115 and exogenous CCK-4 in behavioral models and by the abolition of the anti-anxiety effect by CCK-4 type 2 receptor activation [5, 6].

A second pharmacological activity is analgesia. GB-115 potentiates morphine-induced analgesia in the hot-plate test through a naloxone-sensitive, supraspinal opioidergic mechanism and produces independent antinociceptive activity in the acetic acid writhing test comparable to sodium diclofenac, with a significant non-opioid analgesic component [7, 8]. Sub-chronic co-administration reverses antinociceptive tolerance to morphine, consistent with the established role of cholecystokinin in opioid tolerance mechanisms [9].

A third activity is anti-inflammatory and immunomodulatory. Intraperitoneal GB-115 at 1 mg/kg significantly alleviated pathological symptoms of experimental autoimmune encephalomyelitis in C57Bl/6 mice, promoted thymus weight recovery, reduced perivascular edema and neutrophil infiltration in brain tissue, and suppressed generation of reactive oxygen species by neutrophils [10].

Immunocorrecting properties include stimulation of macrophage phagocytic activity and humoral immune response in intact mice and immunocorrection in models of secondary immunodeficiency [11].

Clinical development under the trade name Ranquilon has progressed through Phase 2 and Phase 3. An open-label pilot study in 25 patients with generalized anxiety disorder (GAD) demonstrated a reduction in median HAM-A total score from 22 to 5 over 21 days of treatment at 6 mg daily, with rapid onset of anxiolytic effect, improvement in attention and processing speed, and no stimulation-related adverse events [12, 13]. A Phase 3 double-blind, randomized, placebo-controlled, multicenter trial in 220 patients with anxiety associated with neurasthenia and adjustment disorders confirmed superiority of Ranquilon 6 mg daily over placebo, with all adverse events classified as mild and no serious adverse events [14]. A Phase 4 comparative trial against fabomotizole (Afobazole) is currently recruiting [15].

The compound has very low acute toxicity (oral LD50 > 6000 mg/kg in rodents), a short plasma elimination half-life (approximately 1.0 hour in humans), and does not produce tolerance, dependence, or withdrawal phenomena in preclinical or clinical evaluation [1, 3]. GB-115 represents the first peptide-based CCK-1 receptor antagonist to complete Phase 3 clinical evaluation for an anxiety indication.

3. Discovery and Development History

3.1 Origin

GB-115 was conceived and synthesized at the V.V. Zakusov Research Institute of Pharmacology of the Russian Academy of Medical Sciences in Moscow as part of a systematic program of dipeptide drug design led by T.A. Gudasheva and S.B. Seredenin. The program applied the topochemical Shemyakin-Ovchinnikov-Ivanov principle to the design of orally active, metabolically stable dipeptide analogues of endogenous neuropeptides, with the objective of producing pharmacological agents that retain the receptor specificity of the parent peptide while overcoming the pharmacokinetic limitations (rapid proteolysis, poor oral bioavailability, poor blood-brain barrier penetration) that prevent endogenous peptides from serving as drug candidates [1].

3.2 Selection of the CCK-4 template

The selection of cholecystokinin-4 as the design template was motivated by the well-established role of cholecystokinin in anxiety and panic. CCK-4, the C-terminal tetrapeptide of cholecystokinin, is the most potent endogenous anxiogenic peptide identified in mammalian brain. Intravenous administration of CCK-4 to healthy human volunteers reliably produces panic attacks indistinguishable from spontaneous panic disorder episodes [16]. The cholecystokinin hypothesis of anxiety posited that antagonism of the CCK receptors mediating this anxiogenic signal would produce anxiolytic activity. Earlier CCK receptor antagonists (devazepide, lorglumide, proglumide, and the CCK-2 selective antagonists L-365,260 and CI-988) had demonstrated mixed or negative results in clinical anxiety trials, and none had achieved registration for a psychiatric indication [17].

3.3 Design and lead optimization

The Gudasheva laboratory designed a series of retrodipeptide analogues based on the CCK-4 pharmacophore map, identifying the phenyl and indolyl aromatic groups as essential for receptor interaction and systematically varying the inter-pharmacophore spacer length. The lead compound GB-115, with the optimal five-methyl-

ene spacer and glycine linker, was selected from this series on the basis of maximal anxiolytic potency (0.05 to 0.2 mg/kg oral), absence of sedation, and metabolic stability conferred by the amide terminus and the retro-peptide bond arrangement [1].

3.4 Preclinical development

Preclinical pharmacology studies spanning approximately 2005 to 2015 characterized the anxiolytic, analgesic, anti-inflammatory, and immunomodulatory activities of GB-115 in rodent and primate models. The compound was evaluated in rhesus monkeys under isolation stress conditions, where it decreased stress-related behaviors comparably to phenazepam (a benzodiazepine registered in several post-Soviet jurisdictions) without producing the sedation characteristic of benzodiazepine treatment [18]. Pharmacokinetic studies established the oral bioavailability, plasma half-life, and interspecies scaling parameters required for human dose selection [3, 19].

3.5 Clinical development

Phase 1 healthy volunteer studies established the safety and pharmacokinetic profile of GB-115 in humans, confirming a plasma half-life of approximately 1.0 hour and the absence of clinically significant adverse events at doses up to and including the effective range. Phase 2 clinical trials in patients with generalized anxiety disorder (25 patients, open-label, 6 mg daily for 21 days) demonstrated significant anxiolytic efficacy and cognitive enhancement without sedation or stimulation-related adverse events [12, 13]. A Phase 2 study of 2 mg tablet formulations confirmed anti-anxiety action without side effects [1].

The Phase 3 pivotal trial (NCT05586789) was a double-blind, randomized, placebo-controlled, multicenter study in 220 patients with anxiety associated with neurasthenia and adjustment disorders. Patients received Ranquilon 1 mg tablets at a total dose of 6 mg daily or placebo for 28 days. The trial demonstrated superiority of Ranquilon over placebo on the primary endpoint with a favorable safety profile [14]. A Phase 4 open-label comparative trial (NCT06843044) comparing Ranquilon 6 mg daily to fabomotizole (Afobazole) 30 mg daily in the same patient population is currently recruiting as of 2025 [15].

4. Mechanism of Action

GB-115 is a selective antagonist of the central cholecystokinin type 1 (CCK-1, formerly CCK-A) receptor. The mechanism of action is understood at the receptor, systems, and behavioral levels and distinguishes GB-115 from both the benzodiazepine class of anxiolytics and from the CCK-2 receptor antagonists that were the principal CCK-targeted anxiolytic candidates in earlier drug development programs.

4.1 Cholecystokinin receptor system

The cholecystokinin receptor system comprises two G-protein-coupled receptor subtypes: CCK-1 (CCK-A) and CCK-2 (CCK-B). CCK-1 receptors are expressed predominantly in the gastrointestinal tract (where they regulate pancreatic enzyme secretion, gallbladder contraction, intestinal motility, and satiety signaling) but are also expressed at significant density in discrete central nervous system regions including the nucleus accumbens, ventral tegmental area, hypothalamus, and amygdala. CCK-2 receptors are the predominant central subtype and are widely expressed in cortex, hippocampus, amygdala, brainstem, and dorsal root ganglia, where they mediate anxiety, pain modulation, and memory-related functions [16, 17].

The historical focus of CCK-targeted anxiolytic drug development was on CCK-2 receptor antagonism, based on the rationale that CCK-2 is the dominant central receptor subtype and the primary mediator of CCK-4-induced panic. Multiple selective CCK-2 antagonists (L-365,260, CI-988, LY-262691) advanced through preclinical and early clinical development but failed to demonstrate consistent anxiolytic efficacy in controlled trials, and the class was largely abandoned by the early 2000s [17].

4.2 CCK-1 receptor antagonism

GB-115 acts as an antagonist at the central population of CCK-1 receptors. The selectivity for CCK-1 over CCK-2 has been inferred from the pharmacological profile: GB-115 produces mutual antagonism with CCK-4 in behavioral paradigms, the anxiolytic effect is abolished by activation of CCK-4 type 2 receptors in certain models,

and the compound produces effects distinct from CCK-2-selective antagonists in head-to-head preclinical comparisons [5, 6]. The role of central CCK-1 receptors in anxiety regulation was recognized through studies demonstrating that selective CCK-A receptor antagonists such as IQM-95,333 reduced anxiety in animal models through blockade of the central (rather than peripheral) CCK-1 receptor population [20].

The mechanism by which central CCK-1 antagonism produces anxiolysis is understood to involve modulation of mesolimbic dopaminergic and GABAergic circuits. CCK-1 receptors in the nucleus accumbens and ventral tegmental area modulate dopamine release, and their antagonism reduces the anxiogenic component of CCK signaling in these circuits. Unlike benzodiazepines, which act directly on GABA-A receptor chloride channels to produce sedation, muscle relaxation, and dependence, CCK-1 antagonism modulates the upstream peptidergic input to these circuits without directly altering inhibitory chloride conductance [5, 6].

4.3 Opioidergic interaction

GB-115 potentiates morphine-induced analgesia through a mechanism that is naloxone-reversible and localized to supraspinal circuits [7]. This interaction is consistent with the established role of cholecystokinin as an endogenous anti-opioid peptide. Cholecystokinin acting through CCK-1 and CCK-2 receptors opposes opioid-mediated analgesia and contributes to the development of analgesic tolerance. Antagonism of CCK-1 receptors by GB-115 disinhibits the opioid system, potentiating the analgesic effect of exogenous opioids and reversing the development of antinociceptive tolerance on sub-chronic co-administration [7, 9].

The independent antinociceptive activity of GB-115 (in the acetic acid writhing test and in thermal pain models) includes a significant non-opioid component, as the analgesic effect is only partially blocked by naloxone [8]. The non-opioid component is consistent with modulation of visceral pain processing through CCK-1 receptor antagonism in peripheral and central pain circuits.

4.4 Anti-inflammatory and immunomodulatory mechanisms

The anti-inflammatory activity of GB-115 in experimental autoimmune encephalomyelitis involves suppression of neutrophil infiltration, reduction of perivascular edema, and inhibition of reactive oxygen species generation by activated neutrophils [10]. The immunomodulatory effects (stimulation of macrophage phagocytic activity and humoral immune response) suggest a dual role in which CCK-1 antagonism modulates both the innate and adaptive arms of the immune response [11]. The molecular basis for these immunological effects is not fully characterized but is consistent with the expression of CCK-1 receptors on immune cells and the known immunoregulatory role of cholecystokinin signaling.

4.5 Biologically active conformation

Nuclear Overhauser effect ¹H NMR spectroscopy studies of GB-115 in solution identified the biologically active conformation as a type II beta-turn [21]. This conformation positions the phenyl and indolyl pharmacophores at the native spatial separation required for CCK-1 receptor binding. The conformational specificity explains the steep structure-activity relationship observed in the homologous series: even minor changes in spacer length disrupt the beta-turn geometry and substantially reduce anxiolytic potency [1, 21].

5. Pharmacokinetics and Routes of Administration

5.1 Absorption

GB-115 is absorbed from the gastrointestinal tract after oral administration. The absolute bioavailability in preclinical animal models is approximately 4.65 percent, reflecting significant first-pass metabolism consistent with the peptidic character of the molecule [3, 19]. Despite the low bioavailability, the compound produces robust anxiolytic effects at oral doses of 0.05 to 1 mg/kg in rodents and 6 mg daily in humans, indicating that the pharmacologically active concentration at central CCK-1 receptors is achieved at a small fraction of the administered dose.

The relative bioavailability of GB-115 tablet formulations compared to the pure substance was 128.18 +/- 36.07 percent in rabbits, indicating that the tablet formulation does not reduce and may modestly enhance oral absorption, likely through excipient-mediated effects on gastrointestinal transit and dissolution [22].

5.2 Distribution

Distribution studies indicate central nervous system penetration, as the compound produces centrally mediated behavioral effects (anxiolysis, modulation of supraspinal opioidergic function) after systemic administration. Quantitative blood-brain barrier permeability data have not been published in the English-language literature. The volume of distribution and plasma protein binding have not been fully characterized in published studies.

5.3 Metabolism and elimination

GB-115 is metabolized through peptidase-mediated hydrolysis, though the amide terminus and the retro-peptide bond arrangement confer substantially greater peptidase resistance than native peptide bonds, extending the plasma detection time relative to unmodified dipeptides [3]. The principal metabolic pathway is enzymatic cleavage of the peptide bond between the glycine and tryptophan amide residues, with secondary hydrolysis of the phenylhexanoyl-glycine bond.

The elimination half-life varies across species: approximately 0.2 hours in rats (corrected to 0.6 hours on pharmacokinetic time), approximately 1.3 +/- 0.3 hours in rabbits, and approximately 1.0 +/- 0.2 hours in humans [3, 19, 23]. The interspecies scaling follows the order rat > human > rabbit for elimination rate constant, and rat < human < rabbit for half-life. The human half-life of approximately 1 hour supports twice-daily or three-times-daily dosing at the established clinical dose of 6 mg per day (administered as three 2 mg doses or six 1 mg doses).

5.4 Formulations studied

Three peroral dosage forms of GB-115 have been pharmacokinetically characterized: substance (raw active compound), tablets, and capsules [22]. The tablet formulation at 1 mg and 2 mg strengths is the dosage form used in Phase 2, Phase 3, and Phase 4 clinical trials. The clinical dose is 6 mg per day.

5.5 Routes of administration

Two principal routes have been used: oral (clinical and late-stage preclinical) and intraperitoneal (early preclinical rodent studies). The oral route is the registered clinical route for Ranquilon. Intraperitoneal administration at doses of 0.002 to 10 mg/kg has been used extensively in preclinical pharmacology, with the typical effective anxiolytic dose range of 0.05 to 0.2 mg/kg [1, 4].

5.6 Special populations

No published pharmacokinetic data address renal impairment, hepatic impairment, or pediatric populations. The Phase 3 and Phase 4 trials enrolled patients aged 18 to 70 years. Geriatric-specific pharmacokinetic data have not been reported.

6. Preclinical Pharmacology

6.1 Anxiolytic activity in rodents

GB-115 produces dose-dependent anxiolytic activity across multiple validated behavioral paradigms in rats and mice. In the elevated plus maze, GB-115 at intraperitoneal doses of 0.05 to 0.2 mg/kg significantly increased the time spent in open arms and the number of open arm entries, effects consistent with anxiolysis. In the light-dark box, the compound increased the time spent in the light compartment. In the Vogel conflict test (a model of anxiety that measures the suppression of punished drinking), GB-115 increased punished drinking, indicating anti-conflict activity [1, 4, 5].

The anxiolytic dose-response curve spans approximately two orders of magnitude (0.002 to 0.2 mg/kg intraperitoneal; 0.05 to 1 mg/kg oral), with the optimal anxiolytic effect at 0.1 mg/kg intraperitoneal in most paradigms [1, 5]. The anxiolytic activity was confirmed in both rats and mice across multiple behavioral tests, indicating robust cross-species and cross-paradigm consistency.

Critically, GB-115 did not produce sedation, muscle relaxation, or motor incoordination at anxiolytic doses, distinguishing it from benzodiazepines in the same paradigms. No tolerance to the anxiolytic effect developed on sub-chronic administration, and no withdrawal syndrome was observed on cessation [1].

6.2 Behavioral studies in nonhuman primates

GB-115 was evaluated in rhesus monkeys (*Macaca mulatta*) under isolation stress conditions alongside phenazepam (a benzodiazepine) as a comparator [18]. Both compounds reduced isolation-induced stress behaviors (measured by decreased time spent in the upper portion of the cage, an index of agitation). GB-115 produced anxiolytic effects comparable to phenazepam without the sedation characteristic of benzodiazepine treatment, supporting the translational relevance of the rodent anxiolytic findings.

6.3 Analgesic activity

Peroral administration of GB-115 at doses of 0.1 to 20 mg/kg decreased the incidence of abdominal contractions (writhes) induced by intraperitoneal acetic acid in mice, with efficacy comparable to sodium diclofenac [8]. The effect was only partially antagonized by naloxone, indicating that the analgesic mechanism includes a significant non-opioid component in addition to the opioidergic potentiation observed in the hot-plate model [7, 8].

In the hot-plate test, GB-115 potentiated morphine-induced analgesia in a naloxone-dependent manner, localizing the opioidergic interaction to supraspinal circuits. The compound did not modulate pain behavior in the tail-flick test (a spinally mediated reflex), confirming that the opioidergic interaction is supraspinal rather than spinal [7].

6.4 Reversal of morphine tolerance

Concomitant sub-chronic administration of GB-115 reversed the development of antinociceptive tolerance to morphine in rodent models [9]. This effect is consistent with the established role of endogenous cholecystokinin as an anti-opioid peptide that contributes to the development of opioid tolerance: CCK-1 receptor antagonism by GB-115 removes the CCK-mediated opposition to opioid signaling, restoring opioid sensitivity.

6.5 Anti-inflammatory activity

Intraperitoneal injection of GB-115 at 1 mg/kg to C57Bl/6 female mice with experimental autoimmune encephalomyelitis (EAE) significantly alleviated the pathological symptoms of the disease, improved spontaneous locomotor activity, promoted recovery of thymus weight (an index of immune organ integrity), and reduced edema and neutrophil infiltration of the perivascular space of brain tissue [10]. GB-115 also suppressed the generation of reactive oxygen species (active oxygen forms) by neutrophils in the chemiluminescence test. Anti-inflammatory effects were additionally demonstrated in models of concanavalin A-induced and carrageenan-induced inflammation [10].

6.6 Immunomodulatory activity

GB-115 at doses of 0.1 to 10 mg/kg stimulated the phagocytic activity of peritoneal macrophages and the humoral immune response in intact mice [11]. In animals with secondary immunodeficiency, GB-115 exhibited immunocorrecting activity, restoring immune parameters toward normal values. The immunomodulatory profile distinguishes GB-115 from conventional anxiolytics and supports a potential application in conditions where anxiety co-occurs with immune dysregulation.

6.7 Mutual antagonism with CCK-4

The anxiolytic mechanism of GB-115 was confirmed by mutual antagonism experiments. GB-115 prevented the development of CCK-4-induced anxiety when administered before CCK-4 challenge, and CCK-4 abolished the anxiolytic effect of GB-115 when administered concurrently [5, 6]. Activation of CCK-4 type 2 receptors abolished the antianxiety effect of GB-115 in some behavioral paradigms, while in other paradigms GB-115 fully blocked CCK-4-induced anxiety, indicating that the receptor interaction is specific and context-dependent [6].

7. Clinical Evidence Base

7.1 Phase 2: generalized anxiety disorder (open-label pilot)

The first published clinical study of GB-115 was an open-label pilot trial in 25 patients with generalized anxiety disorder (8 males, 17 females; median age 34 years) treated with GB-115 6 mg daily for 21 days [12, 13]. Patients were diagnosed per ICD-10 criteria and were aged 18 to 55 years without significant somatic diseases.

Primary efficacy endpoint (HAM-A total score): Median HAM-A total score decreased progressively from 22 at baseline to 19 at day 3, 13 at day 7, 9 at day 14, and 5 at day 21 (chi-squared = 95.07, $p < 0.001$). The magnitude of reduction from baseline to endpoint (17 points, or a 77 percent reduction) is large by anxiety trial standards and exceeds the typical placebo-subtracted effect size observed with selective serotonin reuptake inhibitors in GAD trials.

Fatigue (MFI-20): Median Multidimensional Fatigue Inventory score decreased from 70 at baseline to 59 at day 3, 52 at day 7, 37 at day 14, and 28 at day 21 (chi-squared = 55.41, $p < 0.001$).

Cognitive function: Reaction time improved significantly by day 7 (418.17 +/- 61.49 msec versus 449.19 +/- 64.91 msec at baseline, $p < 0.01$) and was sustained through day 21 (406.5 +/- 52.79 msec, $p < 0.01$). Attention parameters improved by day 3 (305.95 +/- 45.31 msec versus 316.41 +/- 42.35 msec at baseline, $p < 0.05$). Shulte-Platonov table performance (a measure of cognitive processing speed and attention switching) improved significantly by day 7 (59.40 +/- 13.71 sec versus 68.84 +/- 16.78 sec at baseline, $p < 0.01$) [13].

Onset of action: The anxiolytic effect was detectable by day 3, with the most substantial reductions occurring between day 3 and day 7. This onset profile is faster than that of SSRIs and SNRIs, which typically require 2 to 4 weeks to produce full anxiolytic effect.

Clinical characterization: The investigators characterized the drug action as "anxiolytic action with mild psychostimulant properties," noting favorable effects on sleep disturbances and autonomic symptoms. In contrast to SSRIs and SNRIs

used as first-line GAD treatments, GB-115 did not induce initial overactivation, anxiety, or sleep disturbances [12, 13].

Safety: None of the patients experienced stimulation-related side effects. No serious adverse events were reported.

7.2 Phase 2: tablet formulation study

A separate Phase 2 clinical study evaluated GB-115 in 2 mg tablet formulation and confirmed anxiolytic efficacy without side effects [1]. Detailed results of this study have been reported primarily in the Russian-language literature.

7.3 Phase 3: neurasthenia and adjustment disorders (NCT05586789)

The pivotal Phase 3 trial (NCT05586789) was a double-blind, randomized, placebo-controlled, multicenter study in 220 patients with anxiety associated with neurasthenia (ICD-10 F48.0) and adjustment disorders (ICD-10 F43.2) [14].

Study design: Patients were randomized 1:1 to Ranquilon 1 mg tablets at a total dose of 6 mg per day (n = 110) or matching placebo (n = 110) for 28 days.

Primary endpoint: Superiority of Ranquilon over placebo in reducing anxiety was confirmed on the primary efficacy endpoint.

Safety: A total of 64 adverse events were recorded in 44 patients (20.0 percent): 43 adverse events in 28 patients (25.5 percent) in the Ranquilon group and 21 adverse events in 16 patients (14.6 percent) in the placebo group. The numerical imbalance between groups was not statistically significant. All recorded adverse events were classified as mild. No serious adverse events occurred. No patients discontinued study therapy due to adverse events [14].

7.4 Phase 4: comparative trial against fabomotizole (NCT06843044)

An open-label, randomized, multicenter Phase 4 trial (NCT06843044) is currently recruiting patients to compare the clinical efficacy and safety of Ranquilon 1 mg tablets at 6 mg daily to fabomotizole (Afobazole) 10 mg tablets at 30 mg daily in patients with anxiety disorders due to neurasthenia and adjustment disorders [15].

The inclusion criteria specify males and females aged 18 to 70 years with HAM-A scores of 18 to 24. Fabomotizole is a sigma-1 receptor agonist anxiolytic registered in the Russian Federation, making this trial a head-to-head comparison against an established non-benzodiazepine anxiolytic in the same regulatory jurisdiction.

7.5 Summary of clinical evidence

The clinical evidence base for GB-115 comprises an open-label Phase 2 pilot study demonstrating large-magnitude anxiolytic effects with cognitive enhancement, a positive Phase 3 double-blind placebo-controlled trial confirming superiority over placebo with a favorable safety profile, and an ongoing Phase 4 comparator trial. The evidence base is geographically concentrated in Russia and post-Soviet jurisdictions. No clinical trials have been conducted in Western European, North American, or East Asian populations as of monograph revision. The compound is not approved in any jurisdiction as of monograph revision, though the Phase 3 data support a regulatory filing in the Russian Federation.

8. Sourcing and Quality Verification

Research-grade GB-115 is supplied by multiple chemical and peptide research suppliers (AbMole BioScience, MedChemExpress, Kimera Chems, Umbrella Labs, EveryBiotech, and others) at stated purity of 98 percent or greater by HPLC. Supply is in milligram quantities as the free amide. Pricing is moderate for a research peptide, typically in the range of \$30 to \$100 per 100 mg depending on supplier and quantity.

The compound is also available in liquid formulation (typically 2 to 5 mg/mL in research-grade vehicles) from peptide research suppliers. These liquid formulations are intended for laboratory research use only and are not pharmaceutical-grade preparations.

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 (expected $[M+H]^+ = 435.2$, consistent with $C_{25}H_{30}N_4O_3$)
- Chiral HPLC or optical rotation to confirm L-tryptophan (S) configuration (the D-tryptophan enantiomer is anxiogenic, not anxiolytic, and contamination would compromise pharmacological interpretation)
- Nuclear magnetic resonance spectroscopy (1H NMR) to confirm structural integrity of the retrodipeptide backbone
- Karl Fischer or loss-on-drying analysis for residual water content in lyophilized preparations

Third-party analytical laboratories can provide independent confirmation of vendor certificates of analysis. Given the stereochemical sensitivity of the compound (L-configuration is anxiolytic; D-configuration is anxiogenic), chiral analysis is particularly important for any investigation where dose-response or mechanism-of-action precision is required.

The pharmaceutical-grade material (Ranquilon 1 mg tablets) is manufactured in the Russian Federation and is not commercially available outside of clinical trial contexts as of monograph revision. Investigators seeking pharmaceutical-grade material should contact the V.V. Zakusov Research Institute of Pharmacology or the clinical development sponsor directly.

9. Reconstitution and Handling

GB-115 is supplied as a white to off-white lyophilized powder or crystalline solid. For research applications, the compound is reconstituted as needed in appropriate solvents.

Aqueous reconstitution: GB-115 is soluble in aqueous buffers at moderately acidic to neutral pH. For in vivo research applications, reconstitution in sterile normal saline or phosphate-buffered saline at concentrations of 1 to 10 mg/mL is appropriate. Sonication may be required for complete dissolution at higher concentrations.

Organic solvent reconstitution: For in vitro applications or preparation of concentrated stock solutions, GB-115 is soluble in dimethyl sulfoxide (DMSO) at concentrations of 10 to 50 mg/mL. DMSO stock solutions should be prepared at the highest feasible concentration to minimize the DMSO fraction in final assay buffers.

Storage: Lyophilized powder should be stored at -20 degrees Celsius in a desiccated environment. Reconstituted solutions should be stored at 2 to 8 degrees Celsius for short-term use (within 7 to 14 days) or aliquoted and stored at -20 degrees Celsius for longer-term use. Repeated freeze-thaw cycles should be avoided; single-use aliquots are recommended.

Light protection: Not specifically required based on published data, but reasonable practice for peptide-class compounds. The indole ring of the tryptophan residue is potentially photosensitive; amber vials or foil wrapping are appropriate for long-term storage of solutions.

Handling precautions: The compound should be handled with standard laboratory personal protective equipment (gloves, laboratory coat, eye protection). The very low acute toxicity (LD50 > 6000 mg/kg oral in rodents) indicates minimal acute hazard, but skin and eye contact should be avoided as a standard precaution for any pharmacologically active research compound.

Stability: The amide terminus and retrodipeptide bond arrangement confer substantially greater stability to enzymatic hydrolysis than native peptide bonds [3]. Chemical stability of the lyophilized solid at -20 degrees Celsius is expected to ex-

ceed 24 months based on the general stability profile of protected dipeptide amides. Aqueous solutions at neutral pH and refrigerated temperature are expected to remain stable for at least 7 to 14 days; investigators should confirm stability by HPLC for any extended storage application.

10. Stack Interactions and Combinations

GB-115 interacts with several drug classes through its CCK-1 receptor antagonist mechanism and its effects on opioidergic, immune, and inflammatory signaling. Investigators conducting research with GB-115 in combination with other compounds should consider the following interactions.

Opioid analgesics: GB-115 potentiates morphine-induced analgesia through supraspinal opioidergic mechanisms and reverses opioid tolerance on sub-chronic co-administration [7, 9]. Co-administration with opioids may therefore enhance analgesic effects but could also potentiate opioid-related adverse events (respiratory depression, sedation). The interaction is pharmacodynamic, not pharmacokinetic, and is mediated by removal of the endogenous CCK-mediated anti-opioid signal.

Benzodiazepines: GB-115 produces anxiolytic effects through a mechanism (CCK-1 antagonism) independent of the GABA-A receptor mechanism of benzodiazepines. Co-administration could produce additive anxiolytic effects through complementary mechanisms. The nonhuman primate study compared GB-115 and phenazepam as independent agents; combination effects have not been characterized [18]. The absence of sedation, tolerance, and dependence with GB-115 makes it a mechanistically attractive complement to benzodiazepine dose reduction strategies, though clinical data supporting this combination are not available.

SSRIs and SNRIs: No pharmacokinetic interaction is expected, as GB-115 is metabolized by peptidases rather than cytochrome P450 enzymes. The clinical studies of GB-115 noted that the compound, unlike SSRIs and SNRIs, does not produce initial overactivation, anxiety, or sleep disturbances [12]. Co-administration during the SSRI/SNRI initiation phase could theoretically mitigate the early anxiogenic effects of serotonergic therapy, though this combination has not been studied.

CCK-2 receptor antagonists: GB-115 is selective for CCK-1 receptors. Concurrent administration with CCK-2 receptor antagonists would produce dual CCK receptor blockade, which has not been pharmacologically characterized. The interaction is

theoretically additive for anxiolytic effects but could alter the balance of CCK-mediated signaling in unpredictable ways.

Immunosuppressants: The immunomodulatory effects of GB-115 (stimulation of phagocytic activity and humoral immune response) could be antagonistic to immunosuppressive therapy. Investigators studying GB-115 in the context of autoimmune or transplant research should consider the immunostimulatory potential.

Noopept (GVS-111) and other Zakusov Institute dipeptides: GB-115 and Noopept are both products of the Zakusov Institute dipeptide drug design program but act through different mechanisms (CCK-1 antagonism versus AMPA and NMDA receptor modulation for Noopept). No pharmacological interaction between the two has been characterized. Combination studies could be informative for understanding the additive or synergistic potential of anxiolytic-plus-nootropic dipeptide combinations.

Fabomotizole (Afobazole): The Phase 4 clinical trial (NCT06843044) compares GB-115 and fabomotizole as independent agents; combination effects have not been characterized. Fabomotizole is a sigma-1 receptor agonist anxiolytic with a distinct mechanism from GB-115 [15].

11. Adverse Events and Safety

11.1 Preclinical safety

The acute toxicity of GB-115 is very low. The oral LD50 in rodents exceeds 6000 mg/kg, providing a therapeutic index of approximately 30,000 to 60,000 relative to the effective anxiolytic dose range of 0.1 to 0.2 mg/kg oral [1]. No organ toxicity, teratogenicity, or mutagenicity findings have been reported in the published preclinical literature, though detailed regulatory toxicology data have not been published in the English-language literature.

GB-115 does not produce tolerance to the anxiolytic effect on sub-chronic administration. No dependence or withdrawal syndrome has been observed in preclinical models [1]. This absence of tolerance and dependence distinguishes GB-115 sharply from the benzodiazepine class and is attributed to the CCK-1 receptor antagonist mechanism, which does not directly modulate GABA-A receptor function.

11.2 Clinical adverse events: Phase 2

In the open-label Phase 2 pilot study in 25 GAD patients treated with 6 mg daily for 21 days, no stimulation-related side effects were reported. No patients discontinued treatment due to adverse events. The investigators noted that the drug action included mild psychostimulant properties, but these did not produce adverse effects in the studied population [12, 13].

11.3 Clinical adverse events: Phase 3

In the Phase 3 double-blind, placebo-controlled trial (NCT05586789) in 220 patients treated for 28 days:

- Total adverse events: 64 events in 44 patients (20.0 percent of all patients)
- Ranquilon group: 43 adverse events in 28 patients (25.5 percent)
- Placebo group: 21 adverse events in 16 patients (14.6 percent)
- The difference between groups was not statistically significant
- All adverse events were classified as mild

- No serious adverse events were recorded
- No patients discontinued study therapy due to adverse events [14]

The specific adverse events reported have not been individually enumerated in the published English-language abstracts. The overall adverse event profile is consistent with a well-tolerated compound with a safety margin comparable to or better than placebo in terms of severity.

11.4 Comparative safety assessment

The safety profile of GB-115 compares favorably to both benzodiazepine and serotonergic anxiolytics:

- Unlike benzodiazepines: no sedation, no muscle relaxation, no cognitive impairment, no tolerance, no dependence, no withdrawal syndrome
- Unlike SSRIs/SNRIs: no initial overactivation, no sexual dysfunction reported, no discontinuation syndrome reported, faster onset of action
- Unlike buspirone: comparable non-sedating profile, but with potentially faster onset (3 to 7 days versus 2 to 4 weeks for buspirone)

11.5 Pregnancy and lactation

No published data address the safety of GB-115 in pregnancy or lactation in humans. The compound should be considered investigational in these populations pending availability of reproductive toxicology data.

12. Comparable Compounds Assessment

This section presents a structured comparative assessment of five anxiolytic or CCK-modulating compounds against GB-115, 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 alternatives for non-benzodiazepine anxiolysis and CCK-targeted therapy.

12.1 Fabomotizole (Afobazole)

Mechanism: Sigma-1 receptor agonist with additional activity at melatonin MT1 and MT3 receptors. Modulates GABA-A receptor trafficking and stabilizes the receptor complex through sigma-1-mediated chaperone activity.

Development trajectory: Developed at the V.V. Zakusov Research Institute of Pharmacology (the same institution as GB-115). Registered in the Russian Federation as an over-the-counter anxiolytic at 30 mg daily. Not registered outside post-Soviet jurisdictions. Extensive clinical use in Russia since approximately 2005 [24].

Novelty: Moderate. The sigma-1 receptor agonist mechanism for anxiolysis is distinct from benzodiazepines and SSRIs but is a known pharmacological concept with multiple sigma-1 ligands in preclinical and clinical development.

Effect size: Moderate in Russian clinical trials. Anxiolytic efficacy has been demonstrated in multiple controlled and observational studies in anxiety disorders associated with neurasthenia, adjustment disorders, and somatic diseases. Effect sizes are generally modest by Western clinical trial standards. The compound is the active comparator in the GB-115 Phase 4 trial (NCT06843044) [15].

Promising potential: Moderate. Registered and in extensive clinical use in the Russian Federation but has not been submitted for regulatory approval in Western jurisdictions. The absence of international registration limits the compound's global relevance as a comparator.

Side-effect profile: Favorable. Generally well tolerated with a safety profile comparable to placebo in clinical trials. No sedation, no dependence, no withdrawal syndrome reported.

Overall validation: Moderate. Extensive clinical use in one regulatory jurisdiction with multiple supportive trials, but the evidence base has not been subjected to the systematic scrutiny typical of international regulatory review.

Comparison to GB-115: Fabomotizole and GB-115 share institutional origin and a non-benzodiazepine, non-serotonergic anxiolytic profile. GB-115 has the advantage of a novel mechanism (CCK-1 antagonism) and additional analgesic, anti-inflammatory, and immunomodulatory activities. Fabomotizole has the advantage of established registration and extensive clinical use. The Phase 4 head-to-head trial will provide direct comparative efficacy data.

12.2 Buspirone

Mechanism: Selective serotonin 5-HT_{1A} receptor partial agonist. Modulates serotonergic neurotransmission in the raphe nuclei and in postsynaptic cortical and limbic 5-HT_{1A} receptors.

Development trajectory: Developed by Mead Johnson (now Bristol-Myers Squibb). Approved by the US FDA in 1986 for generalized anxiety disorder. Widely prescribed internationally. Available as a generic medication [25].

Novelty: Low. The 5-HT_{1A} partial agonist mechanism is well established and has been the basis for buspirone clinical use for approximately 40 years.

Effect size: Modest. Meta-analyses of buspirone in GAD demonstrate effect sizes of approximately Cohen's *d* 0.3 to 0.4, which are smaller than benzodiazepine effect sizes and comparable to SSRIs. Onset of action is delayed (2 to 4 weeks), which limits clinical utility in acute anxiety presentations [25].

Promising potential: Low for further development (the compound is off-patent and generic), but high for clinical use as an established, well-characterized non-benzodiazepine anxiolytic.

Side-effect profile: Favorable. Principal adverse events are dizziness, nausea, and headache. No sedation at therapeutic doses, no dependence, no withdrawal syndrome. Does not potentiate alcohol or other central nervous system

depressants.

Overall validation: High. Extensive controlled trial literature, multiple regulatory approvals, decades of postmarketing experience, and established position in clinical practice guidelines for GAD.

Comparison to GB-115: Buspirone has the advantage of established international regulatory approval, extensive clinical experience, and a well-characterized safety profile. GB-115 has the advantage of a novel mechanism, faster onset of action (3 to 7 days versus 2 to 4 weeks), and additional analgesic and anti-inflammatory activities. The Phase 2 GB-115 HAM-A reduction (22 to 5 over 21 days) substantially exceeds the typical buspirone effect size, though this comparison is confounded by the open-label design of the GB-115 study.

12.3 CI-988 (PD 134308)

Mechanism: Selective CCK-2 (CCK-B) receptor antagonist. Designed to block the central CCK-2 receptors mediating the anxiogenic effects of cholecystokinin.

Development trajectory: Developed by Parke-Davis (now Pfizer). Advanced through Phase 2 clinical trials for panic disorder and generalized anxiety in the 1990s. Failed to demonstrate consistent anxiolytic efficacy in controlled clinical trials. Development was discontinued. The compound is available only as a research tool [17].

Novelty: Moderate at the time of development (1990s); now historical. The CCK-2 receptor antagonist mechanism for anxiolysis was the primary CCK-targeted strategy before the recognition of the role of central CCK-1 receptors.

Effect size: Insufficient. Phase 2 trials did not demonstrate consistent superiority over placebo on anxiety endpoints. The failure of CI-988 and other CCK-2 antagonists contributed to the abandonment of the CCK-2-targeted anxiolytic approach.

Promising potential: None. Development is terminated. The compound serves as a historical reference for the limitations of CCK-2-selective antagonism as an anxiolytic strategy.

Side-effect profile: Generally well tolerated in Phase 2 trials. No major safety concerns identified before development discontinuation.

Overall validation: Low. The compound failed clinically and represents a negative data point for the CCK-2 anxiolytic hypothesis.

Comparison to GB-115: CI-988 and GB-115 both target the cholecystokinin system but at different receptor subtypes (CCK-2 versus CCK-1). The clinical failure of CI-988 and other CCK-2 antagonists suggests that CCK-1 antagonism (the GB-115 mechanism) may be the more therapeutically relevant approach to CCK-mediated anxiety. The success of GB-115 through Phase 3, compared to the failure of CI-988 at Phase 2, supports this interpretation.

12.4 Proglumide

Mechanism: Non-selective CCK receptor antagonist (CCK-1 and CCK-2). Originally developed as an anti-ulcer agent for its peripheral CCK-1 antagonism in the gastrointestinal tract.

Development trajectory: Developed in the 1970s and registered in several European jurisdictions for peptic ulcer disease. Subsequently investigated for anxiety, pain modulation, and opioid potentiation. Not registered for psychiatric indications. The compound is available as a research tool and as a generic anti-ulcer agent in limited markets [17, 26].

Novelty: Low. The compound is non-selective and was not designed for central nervous system applications.

Effect size: Variable. Anti-ulcer efficacy is modest by modern standards. Anxiolytic effects in animal models are inconsistent. Opioid-potentiating effects (consistent with CCK antagonism) have been demonstrated in preclinical and limited clinical studies. Clinical anxiolytic efficacy has not been established in controlled trials.

Promising potential: Low for anxiety. The compound is primarily of historical interest as the first non-peptide CCK antagonist.

Side-effect profile: Generally well tolerated. Gastrointestinal effects (diarrhea, nausea) at anti-ulcer doses.

Overall validation: Low for anxiety; moderate for gastrointestinal applications.

Comparison to GB-115: Proglumide is non-selective (CCK-1 and CCK-2 antagonism) and lacks central nervous system optimization. GB-115 is selective for central CCK-1 receptors and has been optimized for brain penetration and oral bioavailability. The superior clinical efficacy of GB-115 in anxiety trials, compared to the inconsistent preclinical anxiolytic effects of proglumide, supports the advantage of selective, centrally targeted CCK-1 antagonism over non-selective peripheral CCK antagonism.

12.5 Noopept (GVS-111)

Mechanism: Dipeptide nootropic designed at the V.V. Zakusov Research Institute of Pharmacology as an analogue of the endogenous neuropeptide cycloprolylglycine. Acts through AMPA and NMDA glutamate receptor modulation, with additional effects on nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF) expression. Primary indication is cognitive enhancement rather than anxiolysis, but the compound also produces anxiolytic effects at certain dose ranges [2].

Development trajectory: Developed at the same institute as GB-115 using the same dipeptide drug design methodology. Registered in the Russian Federation as a nootropic. Available as an over-the-counter preparation in Russia and as a research compound internationally. Extensive clinical use in Russia for cognitive impairment.

Novelty: Moderate. The glutamate receptor-modulating dipeptide nootropic mechanism is distinct from conventional nootropic and anxiolytic classes.

Effect size: Moderate for cognitive endpoints in Russian clinical trials. Anxiolytic effects are secondary and dose-dependent. Effect sizes in international replication studies are limited.

Promising potential: Moderate. Registered in Russia with extensive use. Not registered in Western jurisdictions. The cognitive enhancement indication is the primary application; anxiolytic activity is secondary.

Side-effect profile: Favorable. Generally well tolerated with minimal adverse events. No dependence or withdrawal reported.

Overall validation: Moderate. Extensive clinical use in one regulatory jurisdiction. Limited international validation.

Comparison to GB-115: Noopept and GB-115 are sister compounds from the same institutional dipeptide drug design program but have distinct mechanisms and primary indications (cognitive enhancement for Noopept, anxiolysis for GB-115). GB-115 has the advantage of a completed Phase 3 placebo-controlled trial for its primary indication. Noopept has the advantage of established registration and broader clinical use. The two compounds could be mechanistically complementary (combined anxiolytic and nootropic activity through non-overlapping mechanisms) but combination data are not available.

12.6 Comparator summary

The five comparators span four mechanistic classes: sigma-1 agonism (fabomotizole), 5-HT_{1A} partial agonism (buspirone), CCK-2 antagonism (CI-988), non-selective CCK antagonism (proglumide), and glutamate receptor modulation (Noopept). GB-115 occupies a unique position as the only selective central CCK-1 receptor antagonist with positive Phase 3 data in an anxiety indication.

Buspirone has the strongest overall validation through international regulatory approval and decades of clinical experience, but its modest effect size and delayed onset of action are limitations. **Fabomotizole** is the most directly comparable compound in terms of institutional origin and regulatory trajectory, and the ongoing Phase 4 head-to-head trial will provide the first direct comparative efficacy data against GB-115. **CI-988** represents a historical negative control demonstrating that CCK-2-selective antagonism is insufficient for clinical anxiolysis, supporting the alternative CCK-1-targeted approach of GB-115. **Proglumide** demonstrates that non-selective, peripherally distributed CCK antagonism does not produce reliable anxiolytic effects, supporting the central-selective design optimization of GB-115. **Noopept** is a sister compound that demonstrates the versatility of the Zakusov Institute dipeptide design platform and represents a mechanistically complementary agent.

GB-115 distinguishes itself from all five comparators through the combination of a novel mechanism (selective central CCK-1 antagonism), a favorable safety profile (no sedation, no tolerance, no dependence), positive Phase 3 efficacy data, very low acute toxicity (LD₅₀ > 6000 mg/kg), additional pharmacological activities (analgesia, anti-inflammation, immunomodulation), and the fastest onset of anxiolytic ac-

tion among the non-benzodiazepine comparators. The principal limitation is the geographic concentration of the clinical evidence base in Russia and the absence of international regulatory validation.

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