

Itruvone

A synthetic pregnane steroid pherine developed by Pherin Pharmaceuticals and advanced by VistaGen Therapeutics as an intranasal microgram-dose nasal spray for major depressive disorder, distinguished from all approved antidepressants by a proposed non-systemic mechanism of action operating through peripheral nasal chemosensory neuron activation of limbic-hypothalamic catecholaminergic circuits without requirement for blood-brain barrier penetration or direct central nervous system receptor engagement.

DOCUMENT	KDC-MN-1587
ISSUED	2026-05-20
REVISION	1.0
AUTHOR	Kodiac bioLabs Research
COMPOUND CLASS	Synthetic pregnane neuroactive steroid vomeropherine acting via nasal chemosensory receptor activation of olfactory-amygdala neural circuits

ABSTRACT

Itruvone (PH10; pregn-4-en-20-yn-3-one; CAS 21321-89-1) is a synthetic neuroactive steroid of the pregnane class and the second clinical-stage pherine (vomeropherine) molecule, under development by VistaGen Therapeutics as an intranasal nasal spray for the treatment of major depressive disorder (MDD). The compound is structurally characterized by a 17- α -ethynyl substituent on the pregnane steroid nucleus and a 3-keto-4-ene A-ring motif, yielding an odorless crystalline material with a molecular weight of 296.45 g/mol and the molecular formula C₂₁H₂₈O. Itruvone is pharmacologically distinguished from all currently approved antidepressants, including selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, tricyclic antidepressants, monoamine oxidase inhibitors, and the rapid-onset agents esketamine and brexanolone, by a proposed mechanism of action that does not require systemic absorption or direct activity on neuronal receptors in the brain. Instead, the compound is administered at microgram-level intranasal doses (3.2 to 6.4 micrograms per day) and is designed to engage and activate chemosensory receptor neurons in the nasal epithelium, which in turn activate olfactory bulb projections to the amygdala, hypothalamus, and prefrontal cortex through olfactory-amygdala neural circuits believed to modulate the activity of the limbic-hypothalamic sympathetic nervous system and increase the release of catecholamines from midbrain nuclei.

Preclinical tissue distribution studies using radiolabeled [¹⁴C]PH10 in rats demonstrated that a single intranasal

administration was essentially undetectable in the brain and most other tissues, including blood and plasma, supporting the hypothesis that therapeutic activity occurs through peripheral chemosensory signaling rather than through systemic drug exposure. Preclinical electrophysiology studies further demonstrated that itruvone's mechanism does not involve direct activation of GABA-A receptors in the brain, differentiating it from benzodiazepines and from the neurosteroid antidepressant brexanolone (allopregnanolone).

The clinical evidence base comprises a positive Phase 2A randomized, double-blind, placebo-controlled trial conducted in Mexico in 30 patients with MDD, in which daily self-administered intranasal itruvone at 6.4 micrograms produced a mean 17-item Hamilton Depression Rating Scale (HAM-D-17) score reduction of 10.1 points after one week (compared to 4.2 points for placebo, $p = 0.03$) and 17.8 points after eight weeks, with the drug well tolerated and minimal side effects reported; a successful U.S. Phase 1 safety and tolerability study in healthy adult subjects completed in 2023 with no serious adverse events, no discontinuations due to adverse events, and only two mild adverse events (fatigue and headache in the same subject); and supportive prior clinical studies. The U.S. Food and Drug Administration has granted Fast Track designation for the development of itruvone as a potential treatment for MDD.

This monograph reviews the chemistry, structural classification, and synthesis of itruvone; the pherine pharmacology and nasal chemosensory receptor mechanism; the available pharmacokinetic and tissue distribution data; preclinical pharmacology including electrophysiology and tissue distribution studies; the clinical evidence base across Phase 1 and Phase 2A

trials; sourcing and quality verification for research-grade material; reconstitution and handling; stack interactions and combinations; adverse events and safety signal; and a comparative assessment of five alternative antidepressant approaches against itruvone on five competency standards (novelty, effect size, promising potential, side-effect profile, and overall validation). The compound is not approved by any regulatory authority for any indication. It is an investigational drug in clinical development; investigators should obtain appropriate regulatory authorization before any human research application.

1. Compound Identification

1.1 Names, synonyms, and registry identifiers

International Nonproprietary Name: Itruvone.

Development codes: PH10 (Pherin Pharmaceuticals; VistaGen Therapeutics). The development code PH10 is the canonical identifier in the early pharmacology literature and in all published clinical trial reports. Alternative designations PH10A and PH10 NS (nasal spray) appear in regulatory filings and corporate communications [1, 2].

Chemical Abstracts Service registry number: 21321-89-1 (free base).

PubChem Compound Identifier: CID 15633961.

UNII (Unique Ingredient Identifier): 72HML2UK6J (FDA Substance Registration System).

International Union of Pure and Applied Chemistry name: (8S,9S,10R,13S,14S,17R)-17-ethynyl-10,13-dimethyl-1,2,6,7,8,9,11,12,14,15,16,17-dodecahydrocyclopenta[a]phenanthren-3-one.

Chemical name (semi-systematic): Pregn-4-en-20-yn-3-one. The compound is a 17- α -ethynylpregnane steroid bearing the characteristic Δ^4 -3-keto A-ring system shared with progesterone and other bioactive pregnanes, with the 20-position replaced by an ethynyl (acetylenic) group.

1.2 Structural class and chemistry

Itruvone is a synthetic neuroactive steroid of the pregnane class, specifically a 17- α -ethynylated derivative of the pregn-4-en-3-one scaffold. The structural class places it within the broader family of C21 steroidal compounds that includes progesterone, allopregnanolone (brexanolone), and related neurosteroids, though itruvone is distinguished from these by the presence of the 17- α -ethynyl group and by the absence of the 17- α -hydroxyl substituent that characterizes many pharmacologically active pregnanes [3].

Molecular formula: C₂₁H₂₈O.

Exact mass: 296.2140 g/mol (monoisotopic).

Molecular weight: 296.45 g/mol.

Physical properties: Itruvone is described as a white to off-white crystalline solid. The compound is a pregnane steroid with moderate lipophilicity consistent with the steroid nucleus. Solubility in aqueous media is limited; pharmaceutical formulations for intranasal delivery employ appropriate co-solvents and excipients to achieve stable nasal spray presentations at microgram-level concentrations.

Stereochemistry: The compound contains five stereocenters at positions 8, 9, 10, 13, and 17 of the steroid nucleus, with the absolute configuration (8S,9S,10R,13S,14S,17R) corresponding to the natural steroid backbone configuration. The 17- α -ethynyl group adopts the α -orientation (below the plane of the steroid D-ring), consistent with other 17- α -ethynyl steroids in clinical use such as 17- α -ethinylestradiol.

Key structural features: The Δ^4 -3-keto conjugated enone system in the A-ring is a pharmacophoric element common to bioactive pregnane steroids. The 17- α -ethynyl group is a distinctive modification that differentiates itruvone from endogenous pregnane neurosteroids and from the synthetic neurosteroid brexanolone (which retains the natural 3- α -hydroxy-5- α -reduced configuration). The ethynyl group confers metabolic stability at the 17-position and modifies receptor binding characteristics relative to 17-hydroxylated and 17-keto pregnanes.

1.3 Synthesis

The synthesis of itruvone has not been described in detail in the open peer-reviewed literature. The compound is a pregnane steroid bearing a 17- α -ethynyl group, and the general synthetic approach to such structures is well established in steroid chemistry. The principal route involves ethynylation of the corresponding 17-keto pregnane precursor (pregn-4-ene-3,20-dione or a suitably protected intermediate) by treatment with lithium acetylide or sodium acetylide in an appropriate solvent (tetrahydrofuran, liquid ammonia, or dimethylformamide), followed by selective deoxygenation of the 17- β -hydroxyl if the ethynylation produces a 17- α -ethynyl-17- β -hydroxy intermediate, or by direct acetylide addition to a 20-

keto precursor with subsequent elimination [4]. The delta-4-3-keto system is maintained throughout the synthesis or introduced by selective oxidation of the A-ring in the final stages.

Industrial synthesis of itruvone for pharmaceutical-grade nasal spray formulations is conducted under Good Manufacturing Practice (GMP) conditions. The compound is formulated as a microgram-level intranasal spray for clinical and investigational use. Analytical characterization of the manufactured material includes nuclear magnetic resonance spectroscopy, mass spectrometry, high-performance liquid chromatography, and chiral purity determination.

2. Abstract

Itruvone (PH10; pregn-4-en-20-yn-3-one) is a synthetic pregnane neuroactive steroid and vomeropherine (pherine) under clinical development by VistaGen Therapeutics as an intranasal nasal spray for the treatment of major depressive disorder [1, 2]. The compound represents a pharmacologically distinctive class of investigational agents that are proposed to produce central nervous system effects through activation of peripheral nasal chemosensory neurons rather than through systemic absorption and direct brain receptor engagement.

The pherine class was developed from foundational research on the human vomeronasal system and nasal chemosensory epithelium conducted by Monti-Bloch, Berliner, Jennings-White, and colleagues beginning in the 1990s [5, 6]. Pherines are defined as odorless synthetic neuroactive steroids that engage nasal chemosensory receptors and induce dose-dependent and reversible pharmacological and behavioral effects when applied to the nasal mucosa at nanogram to microgram doses. They are chemically and pharmacologically distinct from natural pheromones (androstadienone, androstenone, estratetraenol) and from conventional neurosteroids that act directly on central GABA-A, NMDA, or monoamine receptors [7].

Itruvone is the second pherine to enter clinical development, following fase-dienol (PH94B; aloradine), an anxiolytic pherine studied for social anxiety disorder. When administered intranasally at 3.2 to 6.4 micrograms per day, itruvone is proposed to bind receptors on chemosensory neurons in the nasal epithelium, triggering neural signaling through the olfactory bulb to the amygdala, hypothalamus, and prefrontal cortex. This signaling cascade is believed to modulate the limbic-hypothalamic sympathetic nervous system and increase catecholamine release from midbrain nuclei, producing antidepressant activity without the compound entering systemic circulation or crossing the blood-brain barrier [8, 9].

The principal clinical evidence is a Phase 2A randomized, double-blind, placebo-controlled trial in 30 patients with MDD conducted in Mexico, in which itruvone at 6.4 micrograms per day produced statistically significant reductions in HAM-D-17 scores compared to placebo as early as one week (10.1 versus 4.2 points, $p = 0.03$), with continued separation through eight weeks (17.8 versus 10.9 points) [10]. A U.S.

Phase 1 safety study completed in 2023 demonstrated favorable tolerability with no serious adverse events [11]. The FDA has granted Fast Track designation for itruvone in MDD, and VistaGen has announced preparations for Phase 2B development in the United States [11, 12].

The compound is not approved by any regulatory authority for any indication and is classified as an investigational new drug. The current development status represents early clinical-stage evidence with a mechanistically novel but incompletely validated proposed mechanism of action.

3. Discovery and Development History

3.1 Origin and the pherine concept

The development of itruvone is rooted in foundational research on the human vomeronasal organ (VNO) and nasal chemosensory system conducted beginning in the early 1990s. Monti-Bloch and Grosser (1991) provided early electrophysiological evidence for functional chemosensory signaling from the human nasal epithelium, demonstrating that application of steroidal compounds to the vomeronasal region of the nasal mucosa produced dose-dependent electrophysiological responses (local field potential changes termed the electrovomeronasogram) and measurable autonomic and neuroendocrine effects [5]. Berliner et al. (1996) extended these observations, characterizing the human VNO as a functional sensory structure capable of detecting specific steroidal ligands and transmitting signals to the hypothalamus and limbic structures [6].

These findings motivated the systematic development of synthetic neuroactive steroids optimized for nasal chemosensory receptor activation. The resulting compounds, termed "pherines" or "vomeropherines," were designed at Pherin Pharmaceuticals (South San Francisco, California) as a novel class of pharmaceutical agents that would produce central nervous system effects through peripheral chemosensory activation rather than through conventional systemic pharmacology.

3.2 Identification and early characterization of PH10

PH10 (pregn-4-en-20-yn-3-one) was identified from a screening program of pregnane steroid derivatives for ability to produce dose-dependent inward membrane currents in isolated living human nasal chemosensory cells in vitro. The compound was selected for development as an antidepressant candidate on the basis of its chemosensory receptor activation profile, its effects on autonomic nervous system parameters in early human studies, and its structural suitability for intranasal formulation at microgram doses [7, 8].

3.3 Acquisition by VistaGen Therapeutics

VistaGen Therapeutics (originally VistaGen, Inc.; later Phathom Therapeutics and subsequently re-established as VistaGen) acquired worldwide rights to develop and commercialize PH10 from Pherin Pharmaceuticals. The compound was assigned the International Nonproprietary Name "itruvone" during clinical development [1]. VistaGen's development strategy positioned itruvone alongside fasedienol (PH94B) as the second clinical pherine candidate, targeting MDD as the lead indication.

3.4 Clinical development milestones

The clinical development of itruvone has proceeded through the following stages:

Phase 2A (Mexico): A randomized, double-blind, placebo-controlled, parallel-group, dose-ranging pilot study in 30 adults with MDD was conducted at a single site in Mexico. This study, published by Monti, Nicolini, Liebowitz, and Hanover in the British Journal of Pharmaceutical and Medical Research (2019), demonstrated statistically significant antidepressant effects at the 6.4-microgram dose with rapid onset (within one week) and sustained efficacy through eight weeks [10].

Phase 1 (United States): A single-site, single- and multiple-ascending-dose safety and tolerability study in healthy adult subjects was initiated in January 2023 and completed in mid-2023. Results announced in June 2023 demonstrated no serious adverse events, no discontinuations, and only two mild adverse events (fatigue and headache in one subject) [11].

Preclinical support studies (2023): Tissue distribution studies using radiolabeled [14C]PH10 in rats and electrophysiology studies demonstrating lack of direct GABA-A receptor activation were reported in 2021 and 2023, respectively [8, 9].

FDA Fast Track designation: The FDA granted Fast Track designation for the development of itruvone as a potential treatment for MDD, reflecting the unmet medical need in depression and the novel mechanism of action [12].

Phase 2B (planned): VistaGen has announced preparations for U.S. Phase 2B clinical development. As of the most recent publicly available information, the Phase 2B trial has not commenced enrollment.

4. Mechanism of Action

Itruvone operates through a proposed mechanism of action that is fundamentally different from all currently approved antidepressant therapies. Rather than modulating monoaminergic, glutamatergic, or GABAergic neurotransmission through direct receptor binding in the central nervous system, itruvone is proposed to produce antidepressant effects through peripheral activation of nasal chemosensory neurons that project to limbic and hypothalamic brain regions through established neural circuits [7, 8, 9].

4.1 Nasal chemosensory receptor activation

The human nasal mucosa contains populations of chemosensory neurons that are distinct from the primary olfactory receptor neurons responsible for odor perception. These chemosensory cells, located in the vomeronasal organ and in the respiratory and olfactory epithelium, express receptors capable of detecting non-odorant chemical signals including steroidal compounds. When activated, these neurons generate electrical signals that propagate through the olfactory bulb to subcortical brain regions including the amygdala, hypothalamus, and hippocampus [5, 6].

Itruvone is proposed to bind to receptors on these nasal chemosensory neurons at microgram doses applied to the nasal mucosal surface. In vitro electrophysiology studies using isolated living human nasal chemosensory cells have demonstrated that PH10 produces significant dose-dependent inward membrane currents, consistent with receptor-mediated depolarization of chemosensory neurons [7]. The identity of the specific receptor or receptors engaged by itruvone on nasal chemosensory cells has not been fully characterized in the published literature; the receptor is operationally defined by the electrophysiological response and is distinguished from conventional olfactory receptors by the absence of odor perception at pharmacologically active doses.

4.2 Olfactory-amygdala-hypothalamic neural circuit modulation

The downstream neural consequence of nasal chemosensory neuron activation by itruvone is the modulation of olfactory-amygdala neural circuits. These circuits project from the olfactory bulb to the basolateral and central nuclei of the amygdala, the paraventricular and lateral nuclei of the hypothalamus, and the medial prefrontal cortex. The circuit modulation is proposed to increase the activity of the limbic-hypothalamic sympathetic nervous system and to increase the release of catecholamines (norepinephrine and dopamine) from midbrain nuclei including the locus coeruleus and ventral tegmental area [8].

The catecholaminergic hypothesis of itruvone's antidepressant activity is consistent with the well-established role of norepinephrine and dopamine deficiency in the pathophysiology of MDD and with the efficacy of catecholaminergic antidepressants (bupropion, venlafaxine, duloxetine, tricyclic antidepressants) in clinical practice. The distinction is that itruvone is proposed to achieve catecholaminergic modulation through a top-down peripheral-to-central signaling pathway originating in the nasal chemosensory epithelium, rather than through direct pharmacological manipulation of monoamine transporters or receptors in the brain.

4.3 Differentiation from GABAergic and glutamatergic mechanisms

Preclinical electrophysiology studies reported by VistaGen demonstrated that itruvone's mechanism of action does not involve direct activation of GABA-A receptors in the brain [9]. This finding differentiates itruvone from benzodiazepines (which are GABA-A positive allosteric modulators) and from the neurosteroid antidepressant brexanolone (allopregnanolone), which produces its antidepressant effects through potent positive allosteric modulation of synaptic and extrasynaptic GABA-A receptors. The structural relationship between itruvone and brexanolone (both are pregnane steroids) makes the electrophysiological differentiation particularly important: despite sharing the pregnane steroid scaffold, the two compounds are proposed to act through entirely distinct pharmacological mechanisms.

The lack of GABA-A activation also differentiates itruvone from the sedative and anxiolytic neurosteroid pharmacology that characterizes allopregnanolone, ganaxolone, and other 3- α -hydroxy-5- α -reduced neuroactive steroids. Itruvone

does not carry the 3- α -hydroxyl group that is the critical pharmacophore for GABA-A receptor positive allosteric modulation in the neurosteroid series; its A-ring bears a delta-4-3-keto system instead.

Itruvone is also mechanistically distinct from esketamine (Spravato), which produces rapid antidepressant effects through NMDA glutamate receptor antagonism and requires systemic absorption and blood-brain barrier penetration.

4.4 Non-systemic pharmacology

The most distinctive proposed feature of itruvone's mechanism is the claim that antidepressant activity does not require systemic absorption or direct central nervous system drug exposure. Preclinical tissue distribution studies using radiolabeled [14C]PH10 administered intranasally to laboratory rats demonstrated that the compound was essentially undetectable in the brain and most other tissues, including blood and plasma, after a single intranasal administration [9]. If confirmed in humans, this non-systemic profile would distinguish itruvone from every currently approved antidepressant, all of which require systemic exposure and brain penetration to produce therapeutic effects.

The non-systemic profile, if validated, has several therapeutic implications: absence of systemic drug-drug interactions, absence of hepatic metabolic burden, absence of renal or hepatic dose adjustment requirements, and absence of the systemic adverse events (weight gain, sexual dysfunction, sedation, cardiovascular effects) that characterize conventional antidepressant classes.

4.5 Mechanistic caveats

The proposed mechanism of action for itruvone remains incompletely validated. Several aspects require further characterization:

The specific molecular receptor on nasal chemosensory neurons has not been identified. The pathway from nasal chemosensory activation to catecholaminergic modulation in midbrain nuclei has been inferred from electrophysiological and autonomic measurements but has not been directly mapped by tract tracing, functional neuroimaging in humans, or targeted pharmacological blockade studies in the published literature. The tissue distribution data are from a single preclinical species (rat) and at a single time point; human tissue distribution data have not been reported. The absence of systemic exposure has not been confirmed in hu-

man pharmacokinetic studies at clinical doses. The relationship between nasal chemosensory neuron activation (measured by electrovomerography or nasal electrogram) and clinical antidepressant efficacy has not been established by formal biomarker-endpoint correlation studies.

These caveats do not invalidate the clinical observations but indicate that the mechanistic narrative supporting itruvone is at an earlier stage of validation than the receptor pharmacology supporting conventional antidepressants. The Phase 2A clinical efficacy data stand as the strongest evidence for therapeutic activity, independent of the completeness of the mechanistic understanding.

5. Pharmacokinetics and Routes of Administration

5.1 Route of administration

Itruvone is administered exclusively by the intranasal route as a self-administered nasal spray. The intranasal route is the pharmacologically essential delivery pathway, as the proposed mechanism of action requires direct contact between the compound and nasal chemosensory neurons in the nasal epithelium. Oral, intravenous, and other systemic routes of administration are not applicable to the pherine mechanism and have not been studied [1, 2].

5.2 Dosing

The clinical doses studied in published trials are 3.2 micrograms per day and 6.4 micrograms per day, administered as one or two daily intranasal sprays. These are among the lowest doses of any pharmaceutical compound in clinical development, reflecting the high sensitivity of the nasal chemosensory receptor system and the non-systemic nature of the proposed mechanism. The microgram-level dosing is approximately three to six orders of magnitude lower than typical oral antidepressant doses (which range from milligrams to tens of milligrams) [10].

5.3 Absorption and systemic exposure

Preclinical tissue distribution studies using radiolabeled [¹⁴C]PH10 in rats demonstrated that a single intranasal administration resulted in compound levels that were essentially undetectable in brain, blood, plasma, and most other tissues [9]. These data support the hypothesis that itruvone acts locally at nasal chemosensory neurons and does not achieve measurable systemic exposure at pharmacologically active intranasal doses.

Human pharmacokinetic data have not been reported in the published literature. The U.S. Phase 1 safety study in healthy adult subjects was designed to characterize safety and tolerability of single and multiple intranasal doses; pharmacoki-

netic sampling may have been included but plasma concentration data have not been publicly disclosed [11].

Given the microgram-level intranasal dosing and the preclinical tissue distribution data, systemic pharmacokinetic parameters (bioavailability, volume of distribution, protein binding, metabolic clearance, elimination half-life) may not be characterizable by standard assays, as plasma concentrations may fall below the limit of quantitation of conventional analytical methods.

5.4 Distribution

No human tissue distribution data are available. The preclinical rat data indicate minimal distribution beyond the nasal mucosa following intranasal administration [9].

5.5 Metabolism

The metabolic fate of itruvone following intranasal administration has not been characterized in published studies. The compound is a pregnane steroid, and pregnane steroids in general are subject to hepatic cytochrome P450-mediated oxidation, glucuronidation, and sulfation. However, the minimal systemic absorption observed in preclinical studies suggests that hepatic metabolism may not be a quantitatively important clearance pathway at intranasal doses. Local nasal mucosal metabolism (by nasal epithelial enzymes) is theoretically possible but has not been characterized.

5.6 Elimination

Elimination pathways have not been characterized in published studies.

5.7 Special populations

No data are available on the pharmacokinetics or pharmacodynamics of itruvone in pediatric, geriatric, renally impaired, or hepatically impaired populations. Given the proposed non-systemic mechanism and microgram-level dosing, the clinical significance of hepatic and renal impairment on itruvone exposure may be minimal, though this has not been formally established.

6. Preclinical Pharmacology

6.1 In vitro chemosensory electrophysiology

Itruvone (PH10) produces significant dose-dependent inward membrane currents in isolated living human nasal chemosensory cells, as measured by patch-clamp and field potential recording techniques. These electrophysiological responses are consistent with receptor-mediated depolarization of chemosensory neurons and provide the in vitro pharmacological foundation for the proposed mechanism of action [7].

The electrovomeronasogram (EVG) and electrogram of nasal receptors (EGNR) techniques, developed by Monti-Bloch and colleagues, measure the local field potential response of nasal chemosensory epithelium to applied compounds. PH10 produces robust, dose-dependent depolarization of the local electrogram from receptor cells of the nasal chemosensory mucosa, with behavioral and autonomic nervous system responses observed at the same doses [7, 8].

6.2 GABA-A receptor differentiation

Preclinical electrophysiology studies demonstrated that itruvone does not directly activate GABA-A receptors in brain tissue preparations [9]. This finding was reported by VistaGen in 2021 and differentiates the compound from benzodiazepines and from the structurally related neurosteroid brexanolone (allopregnanolone), which is a potent GABA-A positive allosteric modulator. The lack of GABA-A activity is consistent with the structural differences between itruvone (delta-4-3-keto A-ring) and GABA-A-active neurosteroids (3-alpha-hydroxy-5-alpha-reduced A-ring), as the 3-alpha-hydroxyl group and 5-alpha-reduced A/B ring junction are critical pharmacophoric requirements for GABA-A receptor modulation in the neurosteroid series.

6.3 Tissue distribution

The radiolabeled [14C]PH10 tissue distribution study in rats, reported in 2023, demonstrated that a single intranasal administration of radiolabeled itruvone resulted in compound levels that were essentially undetectable in brain, blood, plasma, and most other tissues [9]. This study provides the primary preclinical support for the non-systemic mechanism of action. The study design (single dose, single species, single time point) represents initial characterization; more comprehensive pharmacokinetic studies (multiple doses, multiple time points, additional species) may be required for regulatory purposes.

6.4 Behavioral pharmacology

Detailed preclinical behavioral pharmacology studies in animal models of depression (forced swim test, tail suspension test, chronic mild stress, social defeat, learned helplessness) have not been reported in the peer-reviewed literature. The clinical development of itruvone has been supported primarily by the in vitro chemosensory electrophysiology, the tissue distribution data, the GABA-A differentiation studies, and the human clinical trial results rather than by conventional rodent behavioral pharmacology models [8, 10].

7. Clinical Evidence Base

7.1 Phase 2A trial in major depressive disorder (Mexico)

The principal efficacy evidence for itruvone is a Phase 2A randomized, double-blind, placebo-controlled, parallel-group, dose-ranging pilot study in 30 adults with major depressive disorder, conducted at a single site in Mexico and published by Monti, Nicolini, Liebowitz, and Hanover in the British Journal of Pharmaceutical and Medical Research (2019) [10].

Study design: Thirty patients meeting DSM-IV criteria for MDD with baseline HAM-D-17 scores in the low to mid-20s were randomized in a 1:1:1 ratio to one of three treatment arms: placebo nasal spray, PH10 nasal spray at 3.2 micrograms per day (low dose), or PH10 nasal spray at 6.4 micrograms per day (high dose). Treatment was self-administered daily for 8 weeks. The primary efficacy endpoint was change from baseline in HAM-D-17 score.

Efficacy results at one week: The 6.4-microgram group showed a mean HAM-D-17 score reduction of 10.1 points, which was statistically significantly greater ($p = 0.03$) than the mean reduction in the placebo group of 4.2 points from baseline. The 3.2-microgram group showed a mean reduction of 8.4 points. The early separation from placebo within one week is notable and distinguishes itruvone from conventional monoaminergic antidepressants, which typically require 2 to 4 weeks for clinical response [10].

Efficacy results at eight weeks: Mean HAM-D-17 score reductions at 8 weeks were 17.8 points in the 6.4-microgram group, 16.3 points in the 3.2-microgram group, and 10.9 points in the placebo group. The magnitude of placebo-subtracted improvement (approximately 7 points on HAM-D-17 at 8 weeks for the high-dose group) is clinically meaningful if replicable at larger sample sizes.

Safety results: Itruvone was well tolerated in both dose groups. No serious adverse events were reported. Side effects were described as minimal. The study did not report the specific adverse-event frequencies by treatment arm in the available published summaries.

Limitations: The study enrolled 30 patients at a single site, representing a pilot sample size with limited statistical power and generalizability. The study was conducted in Mexico, and replication in a multisite, multiethnic, adequately powered trial is required before efficacy conclusions can be drawn. The baseline HAM-D-17 scores and the placebo response rate are within the range observed in antidepressant trials but are subject to the well-documented site and population effects that influence depression trial outcomes.

7.2 U.S. Phase 1 safety and tolerability study

A U.S. Phase 1 single-site study of itruvone nasal spray in healthy adult subjects was initiated in January 2023 with first participant dosing and was completed in mid-2023 [11].

Study design: The study evaluated the safety and tolerability of single and multiple ascending intranasal doses of itruvone in healthy adult subjects. The study design details (number of dose levels, sample size per cohort, dosing duration) have been described in corporate communications but a full peer-reviewed publication has not appeared.

Safety results: No serious adverse events were reported. No subjects discontinued the study due to adverse events. Two adverse events were reported during the treatment period: fatigue and headache, both occurring in the same subject, both mild in severity, and both resolving without sequelae or intervention. The favorable safety profile was consistent with three prior clinical studies of itruvone, including the Phase 2A study in MDD [11].

Pharmacokinetic results: Any pharmacokinetic data collected during the Phase 1 study have not been publicly disclosed.

7.3 Prior clinical studies

VistaGen has referenced "three prior clinical studies" of itruvone that precede the U.S. Phase 1 study. These include the Phase 2A study in Mexico (Section 7.1 above) and at least two additional studies conducted in Mexico. Published details on these additional studies are limited in the peer-reviewed literature; they are referenced in corporate communications and regulatory filings as contributing to the overall clinical database supporting the safety and tolerability of itruvone [11, 12].

7.4 Regulatory designations

The FDA has granted Fast Track designation for the development of itruvone as a potential treatment for MDD [12]. Fast Track designation facilitates the development and expedites the review of drugs that treat serious conditions and fill an unmet medical need. The designation reflects the novelty of the proposed mechanism, the severity of MDD as an indication, and the substantial unmet need for antidepressants with improved onset, tolerability, and safety profiles.

7.5 Current development status

VistaGen has announced preparations and planning for Phase 2B clinical development of itruvone in the United States for MDD. As of the most recent publicly available information, Phase 2B enrollment has not been initiated. The compound is not in active development for indications other than MDD.

8. Sourcing and Quality Verification

Itruvone is an investigational compound not yet available as a registered pharmaceutical product in any jurisdiction. Access to the compound is restricted to the clinical development program conducted by VistaGen Therapeutics and to research-grade chemical supply.

Research-grade itruvone (pregn-4-en-20-yn-3-one; CAS 21321-89-1) is available from chemical and pharmaceutical research suppliers including MedChemExpress, DC Chemicals, MedKoo Biosciences, and selected other specialty steroid suppliers, typically at greater than 95 to 98 percent purity by HPLC. Supply is in milligram quantities as the free base [13].

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

- High-performance liquid chromatography area-percent purity (target greater than 95 percent, preferably greater than 98 percent)
- Mass spectrometry confirmation of molecular weight (297.22 for the protonated free base $[M+H]^+$, corresponding to $C_{21}H_{29}O^+$)
- Nuclear magnetic resonance spectroscopy (1H and ^{13}C) for structural confirmation, with particular attention to the ethynyl proton signal and the delta-4-3-keto enone system
- Melting point determination
- Chiral purity confirmation to verify the natural steroid backbone configuration

Third-party analytical confirmation is recommended for any investigation where dose-response precision is critical, given the microgram-level pharmacological activity of the compound in the nasal chemosensory system.

Clinical-grade itruvone nasal spray formulations are manufactured under GMP conditions by or on behalf of VistaGen Therapeutics and are not commercially available. Access to clinical-grade material requires participation in authorized clinical trials.

9. Reconstitution and Handling

Itruvone is supplied as a solid (free base) by research chemical suppliers. The compound is a pregnane steroid with moderate lipophilicity and limited aqueous solubility.

Solubility: The compound is soluble in organic solvents including dimethyl sulfoxide (DMSO), ethanol, and methanol. Aqueous solubility is limited; stock solutions for in vitro work are typically prepared in DMSO at millimolar concentrations and diluted into aqueous buffers for assay. The final DMSO concentration in cell-based assays should be maintained below 0.1 percent to avoid solvent toxicity artifacts.

Storage: Solid material should be stored at minus 20 degrees Celsius, protected from moisture and light, in a desiccated container. Under these conditions, the compound is expected to be stable for at least 12 to 24 months. Stock solutions in DMSO should be stored at minus 20 degrees Celsius and used within 3 to 6 months of preparation.

Handling: Standard laboratory precautions for handling steroid compounds apply. The compound is classified as a research chemical and is not for human consumption. Gloves and appropriate personal protective equipment should be used during handling. Avoid inhalation of dust or aerosol during weighing and transfer operations.

Formulation for intranasal research: Formulation of itruvone as an intranasal spray for preclinical or clinical research requires pharmaceutical compounding expertise, as the microgram-level doses demand precise formulation and delivery device characterization. The clinical formulation details (excipients, spray device, delivered dose per actuation, stability) have not been published. Investigators wishing to prepare intranasal formulations for preclinical research should consult the pharmaceutical formulation literature on intranasal steroid delivery systems.

10. Stack Interactions and Combinations

Itruvone's proposed non-systemic mechanism and microgram-level intranasal dosing suggest a pharmacological interaction profile that is fundamentally different from conventional antidepressants. If the compound does not achieve measurable systemic exposure (as suggested by the preclinical tissue distribution data), then the conventional categories of pharmacokinetic drug-drug interactions (CYP inhibition, CYP induction, protein binding displacement, transporter-mediated interactions) may not apply.

Conventional antidepressants: The concurrent use of itruvone with SSRIs, SNRIs, tricyclic antidepressants, MAOIs, or bupropion has not been studied. The non-systemic mechanism suggests that pharmacokinetic interactions would be absent, though pharmacodynamic interactions (additive or synergistic antidepressant effects, or unexpected interactions between peripheral chemosensory signaling and central monoaminergic modulation) cannot be predicted from available data.

Intranasal medications: Concurrent use with other intranasal medications (nasal corticosteroids, intranasal esketamine, nasal decongestants, nasal antihistamines) could potentially affect the nasal mucosal surface and chemosensory neuron accessibility. Nasal corticosteroid sprays cause mucosal changes that could theoretically alter drug deposition or chemosensory neuron function. The clinical significance of such interactions has not been studied.

Nasal conditions: Rhinitis, nasal polyposis, deviated septum, and other conditions affecting nasal mucosal integrity could theoretically alter itruvone's access to chemosensory neurons and affect therapeutic response. These factors have not been characterized as covariates in the clinical trials.

Other pherines: The concurrent use of itruvone with fasedienol (PH94B) or other pherine compounds has not been studied. Both compounds act through nasal chemosensory pathways, and additive or competing effects at the receptor level are theoretically possible.

Central nervous system depressants: If itruvone does not achieve brain exposure, pharmacodynamic interactions with benzodiazepines, opioids, alcohol, and other CNS depressants would not be expected through a direct mechanism. However, indirect effects (through limbic circuit modulation) on sedation or cognitive function cannot be excluded.

CYP450 interactions: Given the absence of measurable systemic exposure in pre-clinical studies, CYP450-mediated drug-drug interactions are not anticipated. This consideration represents one of the principal theoretical safety advantages of the pherine mechanism. However, this advantage has not been confirmed in human pharmacokinetic interaction studies.

Investigators conducting research with itruvone in combination with other compounds should approach interactions empirically, as the mechanistic novelty of the pherine class means that interaction profiles cannot be reliably predicted from the conventional pharmacological literature.

11. Adverse Events and Safety

11.1 Clinical safety summary

The clinical safety database for itruvone comprises approximately four clinical studies (the Phase 2A study in Mexico, the U.S. Phase 1 study, and at least two additional studies referenced by VistaGen). Across these studies, itruvone nasal spray has demonstrated a consistently favorable safety and tolerability profile [10, 11].

11.2 Common adverse events

In the U.S. Phase 1 study, only two adverse events were reported during the treatment period: fatigue and headache, both occurring in the same subject, both mild in severity, and both resolving without sequelae or intervention [11]. No other adverse events were reported.

In the Phase 2A study, itruvone was described as "very well tolerated with minimal side effects." Specific adverse-event frequencies by treatment arm were not detailed in the available published summaries [10].

11.3 Serious adverse events

No serious adverse events have been reported in any clinical study of itruvone. No subjects have discontinued from clinical studies due to adverse events [10, 11].

11.4 Adverse events absent or not expected

Based on the proposed non-systemic mechanism and microgram-level dosing, the following adverse events that are characteristic of conventional antidepressant classes are not expected with itruvone, though this absence has not been confirmed in long-term or large-cohort studies:

- Weight gain (characteristic of SSRIs, SNRIs, mirtazapine, tricyclic antidepressants)
- Sexual dysfunction (characteristic of SSRIs, SNRIs)

- Sedation or somnolence (characteristic of tricyclic antidepressants, mirtazapine, trazodone)
- Insomnia and activation (characteristic of SSRIs, bupropion)
- Gastrointestinal effects (characteristic of SSRIs, SNRIs)
- Cardiovascular effects including QT prolongation and orthostatic hypotension (characteristic of tricyclic antidepressants, some antipsychotic augmentation agents)
- Dissociation (characteristic of esketamine)
- Serotonin syndrome risk (characteristic of serotonergic antidepressants)
- Discontinuation syndrome (characteristic of SSRIs, SNRIs, particularly paroxetine and venlafaxine)

11.5 Safety caveats

The clinical safety database is small (approximately 50 to 80 subjects across all studies, based on available information). The duration of controlled treatment does not exceed 8 weeks. Long-term safety, rare adverse events, and effects of chronic dosing are unknown. The effects of itruvone on pregnancy, lactation, fertility, and pediatric or geriatric populations have not been studied. Nasal mucosal safety (local irritation, mucosal atrophy, olfactory function) on chronic intranasal dosing has not been characterized in published reports.

The absence of a comprehensive adverse-event profile is a consequence of early clinical development stage rather than a confirmed safety advantage. Registration-quality safety data will require Phase 2B and Phase 3 trials with adequate sample sizes and treatment durations.

12. Comparative Assessment

This section presents a structured comparative assessment of five alternative antidepressant approaches against itruvone, 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 alternative pharmacological strategies for MDD, with emphasis on agents with novel mechanisms or rapid-onset profiles that are most directly relevant to the clinical positioning of itruvone.

12.1 Esketamine (Spravato)

Mechanism: NMDA glutamate receptor antagonist; intranasal spray administered in supervised clinical settings. Approved by the FDA in 2019 for treatment-resistant depression (TRD) and in 2020 for MDD with acute suicidal ideation or behavior [14].

Novelty: High. Esketamine was the first non-monoaminergic antidepressant approved by the FDA and the first intranasal antidepressant formulation. The glutamatergic mechanism represented a paradigm shift in depression pharmacology.

Effect size: Meta-analyses report rapid onset of antidepressant effects within 2 to 4 hours of the first administration, with sustained efficacy over 28 days in treatment-resistant populations. The drug-placebo separation on MADRS (Montgomery-Asberg Depression Rating Scale) at day 28 is approximately 4 points in pivotal TRD trials, representing a modest but clinically meaningful effect in a treatment-refractory population [14].

Promising potential: Established. Esketamine is FDA-approved and commercially available. Post-marketing experience continues to accumulate. The compound is the standard-of-care rapid-onset antidepressant for treatment-resistant depression in the United States.

Side-effect profile: Dissociation (40 to 60 percent of administrations), dizziness, nausea, sedation, vertigo, hypoesthesia, anxiety, lethargy, increased blood pressure, and vomiting. Esketamine carries a boxed warning for sedation, dissociation, and abuse potential, and is available only through a restricted distribution system

(REMS) requiring supervised administration in certified treatment centers. Patients must remain under observation for at least two hours after each administration [14].

Overall validation: High. Multiple pivotal Phase 3 trials, FDA approval, and growing post-marketing experience. The clinical evidence base is extensive and the efficacy signal is reproducible.

Comparison to itruvone: Esketamine and itruvone share the intranasal route of administration but are fundamentally different in mechanism, dosing, safety profile, and development stage. Esketamine requires milligram doses, achieves systemic exposure, directly modulates brain NMDA receptors, requires supervised administration, and carries significant adverse-event burden including dissociation and abuse potential. Itruvone is proposed to work at microgram doses without systemic absorption, without direct brain receptor engagement, and without the dissociative and sedative effects of esketamine. Itruvone's theoretical safety advantage is counterbalanced by its much earlier development stage and much smaller clinical evidence base.

12.2 Brexanolone (Zulresso)

Mechanism: Positive allosteric modulator of synaptic and extrasynaptic GABA-A receptors; endogenous neurosteroid (allopregnanolone). Approved by the FDA in 2019 for postpartum depression (PPD), administered as a 60-hour continuous intravenous infusion in a supervised healthcare setting [15].

Novelty: High. Brexanolone was the first neurosteroid antidepressant approved by the FDA and the first drug approved specifically for postpartum depression.

Effect size: Pivotal trials demonstrated significant improvement on HAM-D-17 (approximately 17-point reduction at the end of 60-hour infusion compared to approximately 12 points for placebo), with rapid onset and durable effect through 30-day follow-up [15].

Promising potential: Moderate. Brexanolone is FDA-approved but limited by the requirement for 60-hour supervised intravenous infusion, high cost, and restriction to a single indication (PPD). The compound is not in development for MDD.

Side-effect profile: Sedation and somnolence (leading to loss of consciousness in some patients, the basis for a boxed warning and REMS requirement), dizziness, flushing, and injection site reactions. Continuous monitoring is required during the 60-hour infusion.

Overall validation: Moderate to high. FDA approval for PPD is supported by pivotal trials with strong effect sizes. The practical limitations of the infusion route and the restricted indication limit broader clinical impact.

Comparison to itruvone: Brexanolone and itruvone share pregnane steroid scaffolds but diverge sharply in mechanism (GABA-A modulation versus nasal chemosensory activation), route (60-hour IV infusion versus self-administered intranasal spray), indication (PPD versus MDD), and safety profile (sedation and loss of consciousness versus minimal adverse events). Itruvone's proposed self-administered, outpatient, non-sedating profile would be a substantial practical advantage if efficacy is confirmed.

12.3 Zuranolone (Zurzuvae)

Mechanism: Oral positive allosteric modulator of GABA-A receptors; synthetic neuroactive steroid. Approved by the FDA in 2023 for postpartum depression, with a 14-day oral treatment course [16].

Novelty: High. Zuranolone is the first oral neurosteroid antidepressant. The 14-day treatment course with sustained effect represents a novel treatment paradigm.

Effect size: Phase 3 trials in PPD demonstrated significant improvement on HAM-D-17 at day 15 (approximately 15-point reduction compared to approximately 12 points for placebo). Phase 3 trials in MDD (CORAL study) showed significant improvement at day 15 but effect did not maintain statistical significance at day 42, contributing to the FDA decision not to approve zuranolone for MDD [16].

Promising potential: Moderate. FDA-approved for PPD. The failure to secure MDD approval limits the broader therapeutic potential. Development for MDD may continue with modified trial designs.

Side-effect profile: Drowsiness, dizziness, diarrhea, fatigue, nasopharyngitis, and urinary tract infection. CNS depression effects led to a boxed warning advising against driving or operating hazardous machinery for at least 12 hours after dosing.

Overall validation: Moderate. FDA approval for PPD with strong efficacy data. The negative MDD regulatory outcome is a significant limitation.

Comparison to itruvone: Both compounds are synthetic neuroactive steroids, but zuranolone achieves its effects through systemic oral dosing and GABA-A receptor modulation in the brain, while itruvone is proposed to act locally at nasal chemosensory receptors. Itruvone's absence of sedation and CNS depression (if confirmed) would be a differentiating advantage. Zuranolone has the advantage of FDA approval and a substantially larger clinical database.

12.4 Psilocybin

Mechanism: 5-HT_{2A} serotonin receptor agonist; classic psychedelic administered in supervised, therapist-supported sessions. Under regulatory review and in late-stage clinical trials for treatment-resistant depression and MDD [17].

Novelty: High. Psilocybin represents a resurgence of psychedelic medicine and introduces a fundamentally novel therapeutic paradigm combining pharmacology with structured psychological support.

Effect size: Phase 2 trials (COMPASS Pathways) in treatment-resistant depression demonstrated large effect sizes (Cohen's *d* approximately 0.8 to 1.0) at the 25-mg dose compared to a 1-mg control dose. Effect durability through 12 weeks has been reported [17].

Promising potential: High but uncertain. Regulatory pathways remain challenging. The FDA issued a complete response letter to COMPASS Pathways' New Drug Application in 2024, requesting additional information. Lykos Therapeutics' MDMA application for PTSD was rejected in 2024. The regulatory trajectory for psychedelic medicine is uncertain.

Side-effect profile: Headache, nausea, anxiety, emotional distress during sessions, fatigue, and rare adverse psychological reactions (persistent perceptual disturbances, prolonged psychological distress). Administration requires supervised sessions with trained therapists, limiting scalability.

Overall validation: Moderate. Strong Phase 2 efficacy signals with large effect sizes, but regulatory approval has not been secured and the therapeutic model requires infrastructure not currently available in standard psychiatric practice.

Comparison to itruvone: Psilocybin and itruvone represent opposite ends of the antidepressant innovation spectrum. Psilocybin requires supervised psychedelic sessions with large systemic doses and intense subjective effects. Itruvone is proposed to be self-administered at microgram doses with no psychoactive effects. Psilocybin has stronger efficacy data but far more complex delivery requirements. If itruvone's efficacy is confirmed, its self-administered, non-psychoactive profile would offer a fundamentally different risk-benefit proposition.

12.5 Fasedienol (PH94B; Aloradine)

Mechanism: Anxiolytic pherine; nasal chemosensory receptor agonist of the androstane steroid class. Under development by VistaGen Therapeutics for social anxiety disorder (SAD). Fasedienol shares the pherine mechanism with itruvone but targets anxiety rather than depression [18].

Novelty: High. Fasedienol is the first pherine to enter late-stage clinical development and the most directly comparable compound to itruvone in mechanism and class.

Effect size: Phase 2 and Phase 3 trials in SAD have produced mixed results. A Phase 2 study (Liebowitz et al. 2016) demonstrated significant anxiolytic effects as measured by the Subjective Units of Distress Scale in acute social anxiety challenges [18]. Phase 3 development is ongoing.

Promising potential: Moderate. Fasedienol is more advanced in clinical development than itruvone, with Phase 3 SAD trials underway. Successful Phase 3 completion and approval would validate the pherine platform and strengthen the mechanistic credibility of itruvone by extension.

Side-effect profile: Favorable. Fasedienol has demonstrated a safety and tolerability profile similar to itruvone, with minimal systemic adverse events consistent with the non-systemic pherine mechanism.

Overall validation: Low to moderate. The compound has produced Phase 2 efficacy signals in SAD, but Phase 3 results have been mixed, and regulatory approval has not been obtained. The pherine platform as a whole remains unvalidated at the registration level.

Comparison to itruvone: Fasedienol is the closest mechanistic analog to itruvone and the strongest predictor of the pherine platform's clinical viability. Both share the nasal chemosensory receptor mechanism, microgram-level dosing, non-systemic exposure, and favorable safety profiles. The compounds target different indications (SAD for fasedienol, MDD for itruvone) and employ different steroid scaffolds (androstane for fasedienol, pregnane for itruvone). The regulatory fate of fasedienol will materially influence the development trajectory and scientific credibility of itruvone.

12.6 Comparator summary

The five comparators occupy distinct positions in the antidepressant innovation landscape. **Esketamine** is the established rapid-onset intranasal antidepressant with strong efficacy but significant adverse-event burden, supervision requirements, and abuse potential. **Brexanolone** demonstrated the neurosteroid antidepressant concept with strong efficacy but is limited by the 60-hour infusion route and single-indication scope. **Zuranolone** advanced the oral neurosteroid concept to FDA approval for PPD but failed to secure MDD approval, tempering enthusiasm for GABA-A neurosteroid antidepressants in non-perinatal depression. **Psilocybin** produces the largest effect sizes in the comparator panel but faces regulatory uncertainty and scalability challenges. **Fasedienol** is the most directly relevant mechanistic comparator and the bellwether for the pherine platform.

Itruvone occupies a distinctive position: it is the only compound in this comparator panel that proposes to produce antidepressant effects without systemic drug exposure, without direct brain receptor engagement, and without the sedation, dissociation, psychoactive effects, or abuse potential that characterize the other novel agents. The theoretical safety and convenience advantages are substantial. The evidence base, however, is the thinnest in the panel: a single 30-patient Phase 2A study and a small Phase 1 safety study, compared to the extensive pivotal trial databases supporting esketamine, brexanolone, and zuranolone.

The critical question for itruvone's clinical positioning is whether the Phase 2A efficacy signal is replicable and clinically meaningful at registration-quality sample sizes. If the Phase 2B trial confirms the HAM-D-17 improvement observed in the Phase 2A study, itruvone would represent the first self-administered, non-systemic, non-psychoactive, rapid-onset antidepressant, a profile that would be differentiated

from every existing therapy. If the Phase 2B trial fails to replicate the signal, the pherine antidepressant concept will face the same attrition that has characterized most novel mechanism antidepressant candidates in late-stage development.

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proposed mechanism of action (non-systemic nasal chemosensory activation) is novel and incompletely validated; investigators should weight the available evidence accordingly and should not extrapolate the Phase 2A results to treatment recommendations. Access to clinical-grade material requires participation in authorized clinical trials. Research-grade material should be analytically confirmed on every lot. Investigators should obtain appropriate regulatory and ethical authorization before any research involving human subjects.