

RESEARCH MONOGRAPH . COMPOUND PROFILE

Iclepertin

A potent azabicyclo[3.1.0]hexane methanone GlyT1 inhibitor developed by Boehringer Ingelheim to normalize glutamatergic hypofunction in schizophrenia, distinguished by positive Phase II cognitive efficacy signals (standardized effect size 0.34 on MCCB at 10 mg) and subsequent failure to replicate in the 1835-patient Phase III CONNEX programme.

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ABSTRACT

Iclepertin (BI 425809) is a potent and selective inhibitor of glycine transporter type 1 (GlyT1) with an IC₅₀ of 5.0 nanomolar in human SK-N-MC cells, developed by Boehringer Ingelheim for the treatment of cognitive impairment associated with schizophrenia (CIAS). The compound is an orally bioavailable azabicyclo[3.1.0]hexane methanone bearing two trifluoromethyl groups and a methylsulfonyl substituent, with three defined stereocenters and a molecular weight of 512.42 g/mol. By blocking the reuptake of glycine from the synaptic cleft into astrocytes and presynaptic terminals, iclepertin increases synaptic glycine concentration at the glycine-B co-agonist site of the N-methyl-D-aspartate (NMDA) receptor, thereby enhancing glutamatergic neurotransmission. This mechanism addresses the NMDA receptor hypofunction hypothesis of schizophrenia, which posits that reduced glutamatergic signaling contributes to the cognitive deficits observed in the disorder.

Pharmacokinetically, iclepertin exhibits a terminal half-life of 34 to 59 hours, supporting once-daily oral dosing with steady-state conditions achieved by day 6. Oral bioavailability is approximately 72 percent for a 25 mg tablet under fasted conditions. The compound is metabolized predominantly (90 percent or greater) by cytochrome P450 3A4, rendering it sensitive to strong CYP3A4 inhibitors (approximately 6-fold AUC increase with itraconazole) and inducers (approximately 90 percent AUC reduction with rifampicin). In Phase I studies, oral administration of 10 mg produced a dose-dependent approximately 50 percent increase in

cerebrospinal fluid glycine levels, confirming central target engagement.

The Phase II clinical programme produced divergent results across indications. In a 509-patient randomized, double-blind, placebo-controlled trial in schizophrenia (NCT02832037), iclepertin at 10 mg once daily for 12 weeks produced a statistically significant improvement on the MATRICS Consensus Cognitive Battery overall composite T-score, with an adjusted mean difference of 1.98 points and a standardized effect size of 0.34 versus placebo. However, a parallel 610-patient Phase II trial in mild-to-moderate Alzheimer's disease dementia (NCT02788513) failed to demonstrate any dose-response relationship on the ADAS-Cog11 primary endpoint. A subsequent Phase II trial combining iclepertin with computerized cognitive training (NCT03859973, n=200) also failed to meet its primary endpoint. The compound received United States Food and Drug Administration Breakthrough Therapy Designation for CIAS in May 2021. In January 2025, Boehringer Ingelheim reported that the Phase III CONNEX programme, comprising three replicate randomized controlled trials enrolling 1835 patients across 338 sites in 41 countries with 26 weeks of treatment at 10 mg once daily, failed to meet its primary or key secondary endpoints (pooled MCCB adjusted mean difference 0.127, 95 percent confidence interval negative 0.396 to 0.650, $p=0.63$). Iclepertin was well tolerated across all trials, with adverse event rates numerically similar to or lower than placebo. The compound is not approved in any jurisdiction.

This monograph reviews the chemistry and synthesis of iclepertin; the molecular pharmacology of GlyT1 inhibition and the NMDA receptor enhancement mechanism; the comprehensive

pharmacokinetic characterization including CYP3A4 drug-drug interactions; preclinical efficacy in MK-801 deficit and social recognition models; the complete clinical evidence base across schizophrenia, Alzheimer's disease, and cognitive training paradigms; reconstitution, sourcing, and handling considerations; adverse event and safety signals; and a comparative assessment of five alternative NMDA-enhancing or GlyT1-targeting compounds (bitopertin, sarcosine, D-serine, PF-03463275, luvadaxistat) against iclepertin on five competency standards.

1. Compound Identification

1.1 Names, synonyms, and registry identifiers

International Nonproprietary Name: Iclepertin.

Development code: BI 425809 (Boehringer Ingelheim). The development code is the canonical identifier in the early pharmacology and clinical literature and the designation under which all Phase I through Phase III trials were registered [1, 2]. In regulatory filings and congress abstracts, the compound appears exclusively as "BI 425809" prior to the 2023 adoption of the INN "iclepertin" by the World Health Organization.

Chemical Abstracts Service registry number: 1421936-85-7 (free base) [3].

PubChem CID: 155259577.

UNII: M43ZDU10DD.

DrugBank accession: DB19058.

International Union of Pure and Applied Chemistry name: [5-(methylsulfonyl)-2-[(1R)-2,2,2-trifluoro-1-methylethoxy]phenyl][(1R,5R)-1-[5-(trifluoromethyl)-1,2-oxazol-3-yl]-3-azabicyclo[3.1.0]hexan-3-yl]methanone [3].

Salt forms: All published preclinical, clinical, and synthesis literature describes iclepertin as the free base. No salt or co-crystal forms have been reported in the accessible published literature. The compound was administered as a free-base tablet in all Phase II and Phase III clinical trials [4, 5, 15].

The compound has no marketed brand name; it has not been approved in any jurisdiction for any indication as of the present monograph date.

1.2 Structural class and chemistry

Iclepertin is a synthetic small-molecule glycine transporter type 1 (GlyT1) inhibitor characterized by two principal structural fragments connected by a methanone (ketone) bridge: a substituted phenyl ring and a 3-azabicyclo[3.1.0]hexane ring bearing an isoxazole substituent. The phenyl fragment carries a methylsulfonyl

group at the 5-position and a (1R)-2,2,2-trifluoro-1-methylethoxy substituent at the 2-position. The bicyclic fragment is a 3-azabicyclo[3.1.0]hexane (a fused cyclopropane-piperidine ring system) substituted at the 1-position with a 5-(trifluoromethyl)-1,2-oxazolyl group [1, 15].

Molecular formula: C₂₀H₁₈F₆N₂O₅S (free base).

Molecular weight: 512.42 g/mol (free base) [3].

Physical properties: The compound is classified as Biopharmaceutics Classification System (BCS) Class II, exhibiting low aqueous solubility and high membrane permeability [9]. Solubility in fasted-state simulated intestinal fluid (FaSSIF) is approximately 0.54 mg/mL; in fed-state simulated intestinal fluid (FeSSIF) the tablet formulation shows approximately 0.98 mg/mL [9]. Calculated LogP is 2.70 [9]. The compound is orally bioavailable as a solid dosage form (tablet).

Stereochemistry: Iclepertin contains three defined stereocenters: (1R,5R) on the azabicyclo[3.1.0]hexane ring system and (1R) on the trifluoromethylethoxy side chain of the phenyl fragment. All clinical material is supplied as the single stereoisomeric form specified in the IUPAC name. Investigators acquiring research-grade iclepertin should confirm chiral purity by chiral high-performance liquid chromatography or other enantioselective method.

1.3 Synthesis

The industrial synthesis of iclepertin was developed as a scalable asymmetric process and implemented on a multikilogram scale [15]. The synthesis proceeds through two key intermediates that are coupled by amide bond formation (acylation of the azabicyclohexane nitrogen with the activated benzoic acid fragment). The first key intermediate is 3-((1R,5R)-3-azabicyclo[3.1.0]hexan-1-yl)-5-(trifluoromethyl)isoxazole hydrochloride, prepared from readily available bulk starting materials through a stereocontrolled route that establishes the (1R,5R) configuration of the bicyclic ring system [15]. The second key intermediate is (R)-5-(methylsulfonyl)-2-((1,1,1-trifluoropropan-2-yl)oxy)benzoic acid, synthesized through a novel rhodium-catalyzed asymmetric hydrogenation step that establishes the (R) stereocenter on the trifluoroethoxy side chain [15]. The coupling of these two fragments and final elaboration to the drug substance proceeds under standard amide coupling conditions. The process has been validated for reproducibility and stereochemical integrity at manufacturing scale.

3. Discovery and Development History

3.1 Origin and rationale

Iclepertin (BI 425809) was developed by Boehringer Ingelheim as a novel, potent, and selective GlyT1 inhibitor designed to address the glutamate/NMDA receptor hypofunction hypothesis of schizophrenia [1]. The NMDA receptor hypofunction hypothesis, which emerged from the observation that NMDA receptor antagonists such as phencyclidine and ketamine can reproduce the full spectrum of positive, negative, and cognitive symptoms of schizophrenia in healthy subjects, proposes that reduced glutamatergic signaling through NMDA receptors contributes to the cognitive deficits and negative symptoms that are refractory to dopaminergic antipsychotic treatment [17, 18]. GlyT1, the sodium- and chloride-dependent glycine transporter expressed on astrocytes and presynaptic terminals at glutamatergic synapses, maintains subsaturating glycine concentrations at the NMDA receptor glycine-B co-agonist site. Pharmacological inhibition of GlyT1 increases synaptic glycine and thereby enhances NMDA receptor activation, representing an indirect approach to normalizing glutamatergic hypofunction [1, 16].

3.2 Phase I clinical development

Boehringer Ingelheim initiated Phase I clinical trials of BI 425809 in 2014 [1]. The first-in-human single ascending dose trial (NCT02068690) evaluated single oral doses of 0.5 to 150 mg in liquid formulation in healthy male volunteers, establishing safety and tolerability at doses predicted to be clinically relevant (10 to 25 mg) [1]. A multiple ascending dose trial (NCT02337283; Moschetti et al. 2018) evaluated 10, 25, 50, and 75 mg once daily and 75 mg twice daily in young healthy volunteers and 25 and 50 mg once daily in elderly volunteers for 14 days, with each dose group comprising 12 subjects (9 active, 3 placebo) [3]. A pharmacokinetic and pharmacodynamic study (NCT02362516; Rosenbrock et al. 2018) in 25 healthy male volunteers at doses of 5, 10, 25, and 50 mg demonstrated a dose-dependent increase in cerebrospinal fluid glycine levels, with a mean 50 percent increase at doses as low as 10 mg, confirming central target engagement [2]. A single rising dose study in healthy Japanese and Chinese male subjects (NCT02383888) was also completed [1]. Across all Phase I trials, more than 245 healthy subjects received one or more doses of BI

425809, and the compound was safe and well tolerated in single doses up to 25 mg and multiple doses up to 75 mg once daily and twice daily (150 mg per day) [1]. No deaths, serious adverse events, or adverse events of special interest were reported [1].

3.3 Phase II clinical development

The Phase II schizophrenia trial (NCT02832037) was conducted between 2016 and 2019 across 81 centers in 11 countries and randomized 509 adult patients with schizophrenia to iclepertin 2, 5, 10, or 25 mg or placebo once daily for 12 weeks (Fleischhacker et al. 2021) [4]. Five of six dose-response models showed a statistically significant non-flat relationship on the primary endpoint (MATRICS Consensus Cognitive Battery overall composite T-score at week 12), and pairwise comparisons showed significant improvement at 10 mg (adjusted mean difference 1.98, standardized effect size 0.34) and 25 mg (adjusted mean difference 1.73, effect size 0.30) versus placebo [4]. These positive results led the United States Food and Drug Administration to grant Breakthrough Therapy Designation for iclepertin for the treatment of CIAS in May 2021 [1].

A parallel Phase II trial in Alzheimer's disease (NCT02788513; Wunderlich et al. 2023) randomized 610 patients with mild-to-moderate probable Alzheimer's disease dementia across 97 sites in 14 countries to iclepertin 2, 5, 10, or 25 mg or placebo once daily for 12 weeks [6]. The trial failed to demonstrate any dose-response relationship on the primary endpoint (ADAS-Cog11 change from baseline; adjusted p-value greater than 0.76 for all models) [6]. The Alzheimer's disease programme was discontinued.

A Phase II exploratory trial (NCT03859973; Harvey et al. 2024) evaluated iclepertin 10 mg plus computerized cognitive training (CCT) versus placebo plus CCT in 200 patients with schizophrenia for 12 weeks [10]. The primary endpoint (MCCB composite T-score) was not met: adjusted mean difference negative 0.9 (p=0.31) [10]. All secondary endpoints were also negative [10].

3.4 Phase III clinical development and programme termination

The Phase III CONNEX programme comprised three replicate randomized, double-blind, placebo-controlled, parallel-group trials (CONNEX-1, NCT04846868; CONNEX-2, NCT04846881; CONNEX-3, NCT04860830) designed to confirm the Phase II cognitive efficacy of iclepertin in CIAS [5, 12]. Each trial randomized patients 1:1 to iclepertin 10 mg or placebo once daily for 26 weeks, with CONNEX-X as an open-label safety extension study [12]. Between September 2021 and April 2024, the programme enrolled 1835 patients (918 iclepertin, 917 placebo) across 338 specialist psychiatric centers in 41 countries [5, 13].

On January 16, 2025, Boehringer Ingelheim announced that the CONNEX programme had failed: primary and key secondary endpoints were not met in any individual trial or in the pooled analysis [5, 15r]. The pooled primary endpoint (MCCB composite T-score adjusted mean difference) was 0.127 (95 percent confidence interval negative 0.396 to 0.650; $p=0.63$) [5]. The company immediately discontinued the CONNEX-X long-term extension trial [15r]. As of the present monograph date, iclepertin is not approved in any jurisdiction and is not in active commercial clinical development for any indication.

4. Molecular Pharmacology

4.1 Target: glycine transporter type 1

Glycine transporter type 1 (GlyT1, SLC6A9) is a sodium- and chloride-dependent membrane transporter expressed predominantly on astrocytes and presynaptic terminals at glutamatergic synapses throughout the central nervous system [1, 16]. GlyT1 maintains extracellular glycine concentrations at subsaturating levels relative to the glycine-B co-agonist binding site on the NMDA receptor. The receptor requires simultaneous occupancy of two distinct agonist sites for channel activation: the glutamate binding site on GluN2 subunits and the glycine-B (or D-serine) binding site on GluN1 subunits [16, 17]. Because GlyT1 activity holds synaptic glycine below the saturation threshold of the glycine-B site, inhibition of GlyT1 can increase glycine occupancy at NMDA receptors and thereby enhance glutamatergic neurotransmission [1, 16].

Singer and Yee (2024) described GlyT1 as operating bidirectionally: during resting states, GlyT1 removes extracellular glycine via reuptake into astrocytes; during presynaptic activation, GlyT1 on astrocytes can release glycine into the synaptic cleft from astrocytic pools [16]. This bidirectional operation introduces a pharmacological complexity to GlyT1 inhibition: blockade of the transporter during presynaptic activation could in principle curtail the astrocytic glycine contribution rather than augmenting it [16]. The therapeutic consequence of systemic GlyT1 inhibition is therefore dependent on the balance of these two modes in the specific synaptic context, a factor that may contribute to the inverted-U dose-response relationship observed for several GlyT1 inhibitors in clinical development [1, 16].

4.2 Iclepertin binding and selectivity

Iclepertin is a potent and selective inhibitor of GlyT1 with a half-maximal inhibitory concentration (IC₅₀) of 5.0 nanomolar in human SK-N-MC neuroblastoma cells and 5.2 nanomolar in confirmatory assays [1]. The compound is described consistently in the primary literature as selective for GlyT1 [1, 2, 7]. Selectivity over GlyT2 (the sodium- and chloride-dependent glycine transporter expressed predominantly in the spinal cord and brainstem, involved in inhibitory glycinergic neuro-

transmission) has not been reported as a formal selectivity ratio in the accessible published literature, but the consistent designation as "selective" in the Boehringer Ingelheim publications indicates that off-target GlyT2 activity is not pharmacologically significant at therapeutic concentrations [1]. The compound shows a hERG channel IC₅₀ of 30 micromolar [14], approximately 6000-fold above the GlyT1 IC₅₀, indicating a wide margin for cardiac ion channel safety at therapeutic exposures.

4.3 Functional target engagement

In rats, a single oral administration of iclepertin caused a dose-dependent increase in cerebrospinal fluid (CSF) glycine levels, from 30 percent above vehicle at 0.2 mg/kg (not statistically significant) to 78 percent above vehicle at 2 mg/kg (P less than 0.01) [2]. The dose-response relationship was monotonic, and glycine CSF levels at the effective doses corresponded to plasma iclepertin concentrations of 0.7-fold to 7-fold of the GlyT1 IC₅₀ [1].

In healthy human volunteers, oral administration of BI 425809 at steady state produced a dose-dependent increase in CSF glycine levels, with a mean 50 percent increase at doses as low as 10 mg [2]. A 50 to 60 percent increase in CSF glycine was observed at CSF iclepertin concentrations approximating the GlyT1 IC₅₀ [1]. The correlation between plasma and CSF iclepertin concentrations was described as "very good," with CSF concentrations lagging plasma by approximately 2 to 3 hours (CSF T_{max} 5 to 8 hours versus plasma T_{max} 3 to 5 hours) [2].

The functional target engagement data demonstrated that the 10 mg clinical dose, which produced the primary Phase II cognitive efficacy signal, achieves CSF concentrations in the range of the GlyT1 IC₅₀ and produces a glycine elevation of approximately 50 percent [1, 2, 4]. This level of target engagement was considered pharmacologically meaningful on the basis of the preclinical observation that similar degrees of glycine elevation reverse NMDA receptor antagonist-induced cognitive deficits in rodent models [1, 7].

4.4 NMDA receptor enhancement and downstream signaling

The downstream consequence of GlyT1 inhibition is enhanced NMDA receptor activation at glutamatergic synapses. Increased glycine occupancy at the glycine-B co-agonist site permits more effective NMDA receptor channel opening in response to

presynaptically released glutamate, strengthening excitatory postsynaptic currents and supporting synaptic plasticity processes including long-term potentiation (LTP) [1, 16]. In the context of schizophrenia, the therapeutic hypothesis is that enhanced NMDA receptor function normalizes cortical network activity, restores the excitatory-inhibitory balance in prefrontal cortical circuits, and thereby improves cognitive processing [1, 18].

The NMDA receptor hypofunction hypothesis is supported by several converging lines of evidence: NMDA receptor antagonists (phencyclidine, ketamine, MK-801) reproduce the cognitive, negative, and positive symptom domains of schizophrenia in healthy human subjects and in animal models [17]; genetic variants affecting NMDA receptor signaling are associated with schizophrenia risk [18]; and NMDA receptor co-agonists (glycine, D-serine) and GlyT1 inhibitors show cognitive-enhancing effects in preclinical models [1, 7, 16]. The clinical translation of this hypothesis through GlyT1 inhibition has been challenging, however: bitopertin (the first GlyT1 inhibitor to reach Phase III) failed to demonstrate efficacy on negative symptom endpoints [20, 21], and iclepertin itself failed to replicate its Phase II cognitive signal in the Phase III CONNEX programme [5].

4.5 Inverted-U dose-response and optimal occupancy

A recurring pharmacological observation across GlyT1 inhibitors is an inverted-U dose-response relationship, in which moderate GlyT1 occupancy produces cognitive enhancement while higher occupancy attenuates or reverses the benefit [1, 16]. This pattern has been characterized most precisely for PF-03463275, where positron emission tomography-measured GlyT1 occupancy of approximately 75 percent (at 40 mg twice daily) corresponded to peak cognitive and neuroplasticity effects, with reduced effects at approximately 83 percent occupancy [29]. For bitopertin, preclinical studies demonstrated enhanced hippocampal LTP at 100 nanomolar but not at 300 nanomolar [19]. The Fleischhacker et al. (2021) Phase II data for iclepertin were consistent with this pattern: the 25 mg dose did not produce greater cognitive improvement than 10 mg despite presumably higher GlyT1 occupancy [4]. The mechanistic basis of the inverted-U relationship is hypothesized to involve excessive glycine-driven NMDA receptor activation producing desensitization or compensatory inhibitory mechanisms, or disruption of the astrocytic serine shuttle at high GlyT1 inhibitor concentrations [16].

5. Pharmacokinetics and Routes of Administration

5.1 Absorption

Iclepertin is administered orally as a tablet formulation. It is a Biopharmaceutics Classification System (BCS) Class II compound with low solubility and high permeability [9]. Membrane permeability is approximately 1.39 times 10 to the negative 5 centimeters per minute [9]. Absorption is primarily passive, and iclepertin does not appear to be a substrate of any transport protein [9].

Maximum plasma concentrations are achieved approximately 3 to 5 hours after oral administration [2]. Absolute oral bioavailability is 72 percent for a 25 mg tablet under fasted conditions and approximately 71 percent at the 10 mg clinical dose, with a corresponding C_{max} of approximately 222 nanomolar [9, 14]. A food-effect study was conducted; the compound can be administered without regard to meals at the clinical dose [1].

5.2 Distribution

Iclepertin crosses the blood-brain barrier, as demonstrated by the correlation between plasma and CSF concentrations and by the dose-dependent increase in CSF glycine levels in both rats and humans [2]. CSF concentrations lag plasma by approximately 2 to 3 hours, with CSF T_{max} of 5 to 8 hours compared to plasma T_{max} of 3 to 5 hours [2].

Plasma protein binding is approximately 80.4 percent (fraction unbound 0.196) [9]. Specific binding proteins have not been characterized in the accessible published literature. Volume of distribution parameters from the physiologically based pharmacokinetic model have not been explicitly reported as a single value [9].

5.3 Metabolism

Iclepertin is metabolized predominantly in the liver by cytochrome P450 3A4 (CYP3A4). In vitro studies demonstrated that CYP3A4 accounts for 90 percent or greater of the metabolism of BI 425809 [8]. Intrinsic clearance attributed to CYP3A4 was 56.26 mL/min in the physiologically based pharmacokinetic model [9]. Approximately 7.5 percent of the administered dose is excreted unchanged in urine over 336 hours after administration [9].

The CYP3A4 dependence has been characterized by two open-label Phase I drug-drug interaction trials in healthy male volunteers (Desch et al. 2022) [8]. Coadministration with itraconazole (200 mg daily, a strong CYP3A4 inhibitor) produced a 6-fold increase in iclepertin AUC (geometric mean ratio 597.0 percent) and a modest 1.16-fold increase in C_{max} (geometric mean ratio 116.1 percent) [8]. Coadministration with rifampicin (600 mg daily, a strong CYP3A4 inducer) produced a 90 percent reduction in iclepertin AUC (geometric mean ratio 9.8 percent) and a 63 percent reduction in C_{max} (geometric mean ratio 37.4 percent) [8].

Physiologically based pharmacokinetic modeling (Matsson et al. 2025) extended these observations to predict drug-drug interaction potential at the therapeutic 10 mg dose under steady-state conditions [9]. Predicted fold-changes for iclepertin AUC at steady state with coadministered CYP3A4 modulators were: itraconazole (strong inhibitor) 4.91-fold increase; erythromycin (moderate inhibitor) 2.25-fold increase; efavirenz (moderate inducer) 0.34-fold (66 percent reduction) [9]. As a perpetrator, iclepertin at 10 mg produced only a weak effect on midazolam (CYP3A4 substrate) pharmacokinetics: AUC ratio 0.84, C_{max} ratio 0.87 [9]. Iclepertin also induces CYP3A4 at supratherapeutic concentrations [1].

5.4 Elimination

The terminal elimination half-life of iclepertin varies between 34 and 59 hours across the various Phase I studies [9], supporting once-daily oral dosing with the earliest achievement of steady-state conditions on approximately day 6 of once-daily dosing [9]. The long half-life reflects the combination of moderate hepatic metabolic clearance and the high volume of tissue distribution inferred from the extended terminal phase.

Elimination is predominantly metabolic (CYP3A4-mediated hepatic biotransformation) rather than direct renal clearance, with less than 7.5 percent of the dose excreted unchanged in urine [9].

5.5 Special populations

Pharmacokinetic studies in special populations were conducted as part of the clinical development programme. A renal impairment study (NCT05718843) and a hepatic impairment study (NCT05731895) evaluated the pharmacokinetics of icleperitin in subjects with varying degrees of organ dysfunction [1]. Published peer-reviewed results from these studies have not appeared as of the present monograph date. Specific dose adjustment recommendations for renal or hepatic impairment are therefore not available from the peer-reviewed literature.

The multiple ascending dose Phase I trial included both young (18 to 45 years) and elderly (65 to 80 years) healthy volunteers [3]. The elderly cohort showed a similar safety profile, with gastrointestinal disorders and fatigue as the most common adverse events rather than the nervous system disorders predominant in younger subjects [1].

5.6 Routes of administration

Icleperitin has been administered exclusively as an oral tablet in clinical trials, at doses ranging from 2 to 25 mg in Phase II and at 10 mg in Phase III [4, 5]. The Phase I single ascending dose trial employed a liquid formulation at doses of 0.5 to 150 mg [1]. No intravenous, intramuscular, or subcutaneous formulations have been reported in the published clinical literature.

6. Preclinical Pharmacology

6.1 Target engagement in rodents

In rats, single oral administration of iclepertin produced a dose-dependent increase in cerebrospinal fluid glycine levels across a dose range of 0.2 to 2 mg/kg [1, 2]. At 0.2 mg/kg, glycine CSF levels increased by 30 percent relative to vehicle (not statistically significant); at 2 mg/kg, the increase was 78 percent (P less than 0.01) [2]. The dose-dependent glycine elevation confirmed functional GlyT1 inhibition in the central nervous system and established the translational pharmacokinetic-pharmacodynamic relationship that guided human dose selection [1, 2].

At the effective preclinical doses, plasma iclepertin concentrations corresponded to 0.7-fold to 7-fold of the GlyT1 IC₅₀ (5.0 nanomolar), establishing the exposure-target engagement relationship [1]. The 50 percent glycine increase observed at CSF concentrations approximating the IC₅₀ was consistent across species and was subsequently confirmed in healthy human volunteers at the 10 mg dose [1, 2].

6.2 Cognitive models

Iclepertin demonstrated efficacy in two validated rodent cognitive paradigms relevant to schizophrenia (Rosenbrock et al. 2022) [7].

In the T-maze spontaneous alternation task in mice, MK-801 (an uncompetitive NMDA receptor antagonist used to model NMDA receptor hypofunction) produced working memory deficits. Iclepertin reversed the MK-801-induced working memory deficits, restoring spontaneous alternation performance toward vehicle-treated control levels [7]. This reversal of NMDA antagonist-induced cognitive deficit is the standard pharmacological validation paradigm for glutamate-enhancing compounds in schizophrenia models and directly tests the mechanistic hypothesis of GlyT1 inhibition [7].

In the social recognition test in rats, iclepertin improved social recognition memory performance using a 24-hour forgetting paradigm [1, 7]. Improvement in social recognition memory was observed at all tested doses, with CSF iclepertin

concentrations of 0.7-fold to 7-fold of the GlyT1 IC50 during the testing period [1]. Social recognition is considered a translational measure relevant to the social cognitive deficits observed in schizophrenia.

6.3 Electrophysiological biomarkers

Rosenbrock et al. (2022) characterized the effects of iclepertin on MK-801-induced deficits in translatable electroencephalographic (EEG) parameters in rodents [7]. MK-801 administration produced deficits in multiple EEG measures that parallel abnormalities observed in schizophrenia patients. Iclepertin attenuated MK-801-induced deficits in N1 amplitude and N1 gating (auditory event-related potentials), in 40 Hz auditory steady-state response (ASSR) power and intertrial coherence, and in basal gamma power (attenuating the MK-801-induced increase in resting gamma) [7].

These EEG parameters are translatable biomarkers: mismatch negativity (MMN), ASSR, and gamma oscillation abnormalities are well-characterized neurophysiological features of schizophrenia that have been used as pharmacodynamic biomarkers in clinical trials of glutamate-modulating compounds [7, 11]. The authors concluded that "inhibition of GlyT1 is sufficient to attenuate MK-801-induced deficits in translatable EEG parameters relevant to schizophrenia" [7].

6.4 Translational validity assessment

The preclinical package for iclepertin was internally consistent: dose-dependent CSF glycine elevation, reversal of NMDA antagonist-induced cognitive deficits, improvement in social memory, and attenuation of translatable EEG biomarker abnormalities [1, 2, 7]. The exposure-response relationship (glycine increase at IC50-range concentrations) translated from rats to healthy human volunteers [1, 2]. The Phase II cognitive efficacy at 10 mg, which produces approximately 50 percent CSF glycine elevation, was pharmacodynamically concordant with the preclinical predictions [1, 4].

The subsequent failure of the Phase III CONNEX programme to replicate the Phase II cognitive signal, despite adequate target engagement at the same dose, raises fundamental questions about the translational validity of preclinical cogni-

tive models in schizophrenia and about the sufficiency of the GlyT1 inhibition mechanism as a monotherapy for CIAS [5, 16]. These questions are addressed in the comparative assessment (section 12).

7. Clinical Evidence Base

The clinical evidence is presented for research use only. Iclepertin is an investigational compound not approved by any regulatory authority for any indication. Investigators should obtain all applicable regulatory and institutional review board approvals before initiating any human research with this compound.

7.1 Phase I programme

The Phase I programme comprised at least four trials in more than 245 healthy volunteers [1]. The single ascending dose trial (NCT02068690) evaluated doses from 0.5 to 150 mg in liquid formulation, establishing safety and tolerability at predicted therapeutic doses (10 to 25 mg) [1]. The multiple ascending dose trial (NCT02337283; Moschetti et al. 2018) evaluated 10 to 75 mg once daily and 75 mg twice daily for 14 days [3]. The pharmacokinetic-pharmacodynamic trial (NCT02362516; Rosenbrock et al. 2018) confirmed dose-dependent CSF glycine elevation in 25 healthy males at 5, 10, 25, and 50 mg [2]. A single rising dose trial (NCT02383888) was conducted in Japanese and Chinese healthy male subjects [1].

Safety across the Phase I programme was favorable. All treatment-emergent adverse events were mild or moderate in intensity. CNS and visual effects were the most common adverse events, with dose-dependent increases in nervous system disorders, eye disorders, and ear or labyrinth disorders at the 100 and 150 mg dose levels [1]. No deaths, serious adverse events, or adverse events of special interest were reported [1]. No dose-dependent changes in laboratory parameters, hormone levels, hematology, or vital signs were observed [1].

7.2 Phase II in schizophrenia (NCT02832037)

Fleischhacker et al. (2021) reported the pivotal Phase II randomized, double-blind, placebo-controlled, parallel-group trial of iclepertin in schizophrenia cognitive impairment [4]. The trial enrolled 509 adult outpatients (aged 18 to 50 years) with DSM-5-diagnosed schizophrenia on stable antipsychotic treatment across 81 centers in 11 countries, randomized 1:1:1:1:2 to iclepertin 2, 5, 10, or 25 mg or placebo once daily for 12 weeks [4].

The primary endpoint was change from baseline in the MATRICS Consensus Cognitive Battery (MCCB) overall composite T-score at week 12 [4]. Five of six dose-response models showed a statistically significant non-flat relationship [4]. Pairwise comparisons demonstrated greater mean improvement with iclepertin 10 mg versus placebo (adjusted mean difference 1.98 points; 95 percent confidence interval 0.43 to 3.53; standardized effect size 0.34) and with 25 mg versus placebo (adjusted mean difference 1.73 points; 95 percent confidence interval 0.18 to 3.28; standardized effect size 0.30) [4]. The 25 mg dose did not provide additional cognitive benefit beyond 10 mg, consistent with the inverted-U dose-response pattern observed for other GlyT1 inhibitors [4]. The efficacy at 10 mg corresponded to exposure levels achieving approximately 50 percent glycine increase in CSF [1, 4].

The secondary efficacy endpoint (Schizophrenia Cognition Rating Scale interviewer-rated total score change from baseline at week 12) did not show a statistically significant dose-response relationship [1].

Adverse events were balanced across groups and were not dose-dependent: 59 percent (2 mg), 52 percent (5 mg), 41 percent (10 mg), 42 percent (25 mg), and 44 percent (placebo) [4]. The lower adverse event rate at the 10 and 25 mg doses compared to placebo was noted. Treatment completion was 87 percent (444 of 509 patients) [4].

7.3 Phase II in Alzheimer's disease (NCT02788513)

Wunderlich et al. (2023) reported a Phase II randomized, double-blind, placebo-controlled trial in 610 patients with mild-to-moderate probable Alzheimer's disease dementia (MMSE 15 to 26) across 97 sites in 14 countries, with randomization 1:1:1:1:1 to iclepertin 2, 5, 10, or 25 mg or placebo once daily for 12 weeks [6]. The study was conducted between August 2016 and October 2019 [6].

The primary endpoint (ADAS-Cog11 change from baseline at week 12) showed no significant dose-response relationship: adjusted p-values exceeded 0.76 for all dose-response models tested [6]. No significant change from baseline in adjusted mean ADAS-Cog11 scores was observed across any dose group (mean changes between negative 0.08 and 0.69; standard error 0.41) [6]. Secondary endpoints (ADCS-ADL, CIBIC+, NPI) were uniformly negative [6].

The trial concluded that iclepertin "did not demonstrate proof-of-clinical concept for the efficacy of BI 425809 in improving memory, cognitive function, and activities of daily living in patients with probable AD dementia" [6]. Iclepertin was well tolerated in this population, with overall adverse event incidence of 47.9 percent (similar across treatment groups), drug-related adverse event rates of 15.4 to 19.5 percent versus 15.8 percent for placebo, and a completion rate of 94.1 percent [6]. A dose-dependent hemoglobin reduction of up to 5.7 percent was observed at the 25 mg dose, with 6 of 8 affected patients in the 25 mg group [6].

7.4 Phase II with computerized cognitive training (NCT03859973)

Harvey et al. (2024) reported a Phase II randomized, double-blind, placebo-controlled trial evaluating iclepertin 10 mg combined with daily computerized cognitive training (CCT) versus placebo plus CCT in 200 patients with schizophrenia for 12 weeks [10]. The primary endpoint (MCCB composite T-score change from baseline at week 12) was not met: the iclepertin group improved by 1.6 points (SE 0.6) compared to 2.5 points (SE 0.6) for placebo, yielding an adjusted mean difference of negative 0.9 (SE 0.9; $p=0.31$) [10]. All secondary endpoints were negative: SCoRS interviewer total ($p=0.52$), PANSS total ($p=0.64$), and VRFCAT ($p=0.65$) [10].

The safety profile was consistent with prior studies; the iclepertin group had a lower incidence of adverse events (39 percent) compared to placebo (56 percent), with headache as the most common adverse event [10].

7.5 qEEG Phase II substudy

Schultheis et al. (2022) reported an EEG substudy within the Phase II schizophrenia trial, evaluating quantitative EEG parameters as potential neurophysiological biomarkers of iclepertin treatment response [11]. Seventy-nine patients were randomized and 57 completed the substudy across 17 sites in five countries, with EEG measurements at baseline and week 12 [11]. Parameters measured included mismatch negativity (MMN), auditory steady-state response (ASSR) evoked and induced power, and resting-state gamma power [11].

Only slight differences in MMN frequency amplitude and ASSR evoked power were observed between the combined 10 plus 25 mg group and placebo, and these were not deemed clinically meaningful [11]. No significant correlations were found

between changes from baseline in MCCB scores and changes in any EEG parameter [11]. The authors concluded that the measured EEG parameters showed "limited potential as biomarkers of treatment response or as predictors of treatment response to iclepertin in the present study" [11].

7.6 Phase III CONNEX programme (NCT04846868, NCT04846881, NCT04860830)

The CONNEX programme was designed as three replicate randomized, double-blind, placebo-controlled, parallel-group trials, each targeting approximately 586 patients, with randomization 1:1 to iclepertin 10 mg or placebo once daily for 26 weeks [5, 12]. Inclusion criteria required age 18 to 50 years, DSM-5-diagnosed schizophrenia, treatment with one or two stable antipsychotic medications, demonstrated functional impairment, and interaction with a study partner at least one hour weekly [12]. Patients receiving cognitive remediation therapy within 12 weeks of screening were excluded [12].

Keefe et al. (2025) reported the CONNEX programme results in the *Lancet Psychiatry* [5]. Between September 8, 2021, and April 24, 2024, 1835 patients were recruited and received at least one dose (918 iclepertin, 917 placebo) across 338 centers in 41 countries; 1602 patients completed treatment [5]. Baseline characteristics across the three trials were consistent: mean age 34.0 to 35.9 years, 63 to 69 percent male, baseline MCCB composite T-score 27.3 to 29.7, baseline SCoRS total 38.0 to 40.5, and mean illness duration 9.6 to 12.2 years [5, 13].

The primary endpoint (MCCB composite T-score change from baseline at week 26) was not met in any individual trial or in the pooled analysis: pooled adjusted mean difference 0.127 (95 percent CI negative 0.396 to 0.650; $p=0.63$) [5]. The authors concluded: "Iclepertin was not associated with significant improvements in cognition in adults with schizophrenia, but it was well tolerated by patients" [5].

Safety in the Phase III programme was consistent with prior studies. On-treatment adverse events were reported in 604 of 918 patients (66 percent) in the iclepertin group versus 633 of 917 patients (69 percent) in the placebo group [5]. One death occurred in a patient receiving placebo, deemed unrelated to the study [5].

7.7 Regulatory status

Iclepertin received United States Food and Drug Administration Breakthrough Therapy Designation for the treatment of CIAS in May 2021, based on the positive Phase II schizophrenia results [1]. Following the Phase III CONNEX programme failure in January 2025, Boehringer Ingelheim discontinued the CONNEX-X extension study and is not pursuing further clinical development for CIAS with iclepertin [15r]. The compound is not approved for any indication in any jurisdiction as of the present monograph date.

8. Sourcing and Quality Verification

Iclepertin is available exclusively as a research-grade compound; no pharmaceutical-grade commercial product exists because the compound has not received marketing authorization in any jurisdiction.

Research-grade iclepertin (BI 425809) is supplied by multiple chemical and pharmaceutical research suppliers, including MedChemExpress (catalog HY-109580), Selleckchem, Cayman Chemical, and other specialty chemical vendors. The compound is typically supplied as the free base at greater than 98 percent purity by high-performance liquid chromatography (HPLC), in milligram to gram quantities, as a solid (powder or crystalline) material.

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 ion consistent with the molecular formula $C_{20}H_{18}F_6N_2O_5S$ (MW 512.42; expected $[M+H]^+$ at m/z 513.09)
- Nuclear magnetic resonance spectroscopy (1H -NMR and ^{19}F -NMR) for structural confirmation, with particular attention to the trifluoromethyl and methylsulfonyl resonances
- Chiral chromatographic analysis to confirm stereochemical purity of all three stereocenters

Certificate-of-analysis data from suppliers should be verified against the PubChem or ChemSpider reference spectra for CID 155259577 / CAS 1421936-85-7. Third-party analytical confirmation is recommended for investigations where dose-response precision is critical.

9. Reconstitution and Handling

Iclepertin as the free base is a BCS Class II compound with low aqueous solubility (approximately 0.54 mg/mL in fasted-state simulated intestinal fluid) [9]. For in vitro research applications, stock solutions are typically prepared in dimethyl sulfoxide (DMSO) at concentrations of 10 to 50 millimolar, then diluted into aqueous assay buffer at the desired working concentration. Final DMSO concentration in cell-based assays should be maintained below 0.1 percent to avoid solvent-mediated cytotoxicity.

For in vivo rodent studies, the compound has been administered orally in suspension formulations (consistent with published preclinical protocols using dose ranges of 0.2 to 2 mg/kg) [1, 2, 7]. Vehicle formulations suitable for oral gavage in rodents include 0.5 percent methylcellulose in water or polyethylene glycol-based suspensions.

Storage of the solid compound should be at negative 20 degrees Celsius for long-term storage or 2 to 8 degrees Celsius for working stocks, in a desiccated container protected from light and moisture. DMSO stock solutions should be aliquoted for single-use to avoid freeze-thaw degradation; stability data for repeated freeze-thaw cycles have not been published in the accessible literature, and investigators should characterize stability for their specific formulation conditions.

The compound contains no peptide bonds and is not subject to the freeze-thaw and reconstitution considerations that apply to peptide or protein research materials. Standard small-molecule handling precautions (dry storage, light protection, analytical verification of potency after extended storage) are appropriate.

10. Stack Interaction Considerations

Iclepertin interacts with other compounds principally through its CYP3A4-mediated metabolism and, at higher exposures, through its CYP3A4-inducing properties. Investigators conducting research with iclepertin in combination studies or in pre-clinical or clinical contexts where concurrent medications are present should consider:

CYP3A4 inhibitors: Strong CYP3A4 inhibitors (itraconazole, ketoconazole, voriconazole, posaconazole, clarithromycin, ritonavir) produce approximately 5- to 6-fold increases in iclepertin AUC and should be considered contraindicated or require substantial dose reduction [8, 9]. Moderate CYP3A4 inhibitors (erythromycin, fluconazole, verapamil, diltiazem, grapefruit juice) produce approximately 2.25-fold AUC increases [9]. In a real-world data analysis, the most common CYP3A4-interacting medications in the target population included atorvastatin, omeprazole, amlodipine, and simvastatin, all of which are CYP3A4 substrates or weak inhibitors [14].

CYP3A4 inducers: Strong inducers (rifampicin, carbamazepine, phenytoin, phenobarbital, St. John's wort) reduce iclepertin exposure by approximately 90 percent and would be expected to eliminate therapeutic efficacy [8]. Moderate inducers (efavirenz, modafinil) reduce exposure by approximately 66 percent [9]. Given that many schizophrenia patients receive carbamazepine or other enzyme-inducing anticonvulsants as mood stabilizers, this interaction is operationally relevant.

CYP3A4 substrates: Iclepertin at the 10 mg clinical dose is a weak CYP3A4 inhibitor (midazolam AUC ratio 0.84) and at supratherapeutic concentrations induces CYP3A4 [1, 9]. At clinical doses, the effect on CYP3A4 substrate exposure is modest and unlikely to be clinically significant.

Donepezil and memantine: Drug-drug interaction studies between iclepertin and donepezil (NCT03905096) and between iclepertin and memantine (NCT03988803) were conducted in healthy volunteers in anticipation of potential Alzheimer's disease combination therapy [1]. Published peer-reviewed results from these studies have not appeared as of the present monograph date.

Antipsychotics: Iclepertin was designed as adjunctive therapy to stable antipsychotic treatment and was administered concurrently with one or two antipsychotic medications in all Phase II and Phase III trials [4, 5]. No pharmacokinetic or pharmacodynamic interactions with standard antipsychotic agents were identified as safety signals in the clinical programme [4, 5].

NMDA receptor-active compounds: Concurrent administration of iclepertin with other glutamate-modulating agents (D-serine, sarcosine, D-cycloserine, memantine) has not been studied in clinical contexts. The theoretical concern with combinations of NMDA-enhancing agents is excessive glutamatergic activation leading to excitotoxicity; however, the degree of glycine elevation produced by iclepertin at clinical doses (approximately 50 percent above baseline) is modest relative to the total synaptic glycine pool, and the risk of excitotoxicity at therapeutic exposures is considered low [1, 2].

11. Adverse Events and Safety Signal

11.1 Phase I safety

Across more than 245 healthy volunteers receiving single doses of 0.5 to 150 mg and multiple doses of 10 to 75 mg twice daily, iclepertin was safe and well tolerated [1]. All treatment-emergent adverse events were mild or moderate in intensity [1]. The most common adverse events were nervous system disorders (headache, dizziness, somnolence) and, at doses of 100 mg and above, visual disturbances and ear or labyrinth disorders [1]. No deaths, serious adverse events, or adverse events of special interest were reported [1]. No dose-dependent changes in laboratory parameters, vital signs, or electrocardiographic parameters were observed [1].

11.2 Phase II safety in schizophrenia

In the 509-patient Phase II schizophrenia trial, adverse event rates were balanced across treatment groups and were not dose-dependent: 59 percent at 2 mg, 52 percent at 5 mg, 41 percent at 10 mg, 42 percent at 25 mg, and 44 percent on placebo [4]. No significant differences in psychiatric adverse events or suicidal ideation and behavior were observed between treatment groups [4]. The compound was described as "generally well tolerated, with no significant differences in psychiatric adverse events" [4].

11.3 Phase II safety in Alzheimer's disease

In the 610-patient Alzheimer's disease trial, 47.9 percent of patients reported at least one adverse event, with drug-related adverse event frequencies of 15.4 to 19.5 percent across iclepertin dose groups versus 15.8 percent for placebo [6]. The most common adverse events were headache (5.4 percent), diarrhea (3.9 percent), dizziness (3.9 percent), nasopharyngitis (3.1 percent), and nausea (3.1 percent) [6]. Severe adverse events occurred in 2.5 percent; serious adverse events in 3.6 percent (similar across groups) [6]. A hemoglobin reduction was observed dose-dependently, with a maximum relative change from baseline of 5.7 percent in the 25 mg group, affecting 6 of 8 patients in that group [6]. No active suicidal ideation or suicidal behavior was reported on the Columbia Suicide Severity Rating Scale [6].

11.4 Phase III safety

In the 1835-patient Phase III CONNEX programme, on-treatment adverse events were reported in 66 percent of the iclepertin group versus 69 percent of the placebo group [5]. One death occurred in a patient receiving placebo, deemed unrelated to study treatment [5]. The safety profile was described as consistent with all prior studies [5].

11.5 Cardiac safety

The hERG channel IC₅₀ for iclepertin is 30 micromolar [14], approximately 6000-fold above the GlyT1 IC₅₀, providing a wide margin for cardiac ion channel effects. A pre-emptive drug safety evaluation using real-world data from 4.4 million individuals predicted that virtual addition of iclepertin to existing drug regimens would place an additional 0.0032 percent of the population at risk of QT prolongation, with no individuals transitioning to high-risk categories [14]. No clinically significant QT prolongation has been reported in any iclepertin clinical trial.

11.6 Visual adverse events

Visual disturbances at high doses (100 mg and above) in Phase I are a potential class effect of GlyT1 inhibitors; visual adverse events have been noted for PF-03463275 as well [1, 29]. At the clinical dose of 10 mg, visual adverse events have not been reported at rates above placebo in any trial.

12. Comparable Compounds Assessment

This section presents a structured comparative assessment of five alternative compounds in the NMDA receptor enhancement or GlyT1 inhibitor space against iclepertin, evaluated against five competency standards: novelty, effect size, promising potential, side-effect profile, and overall validation. The comparators were selected as the principal compounds with substantive preclinical or clinical data relevant to the GlyT1 inhibition mechanism or the broader NMDA-enhancing approach to cognitive impairment in schizophrenia.

12.1 Bitopertin (RG1678, Roche)

Mechanism: Non-competitive GlyT1 inhibitor with an IC₅₀ of 25 nanomolar for glycine uptake inhibition at human GlyT1 and a K_i of 8.1 nanomolar [19]. Bitopertin enhanced NMDA-dependent long-term potentiation at 100 nanomolar but not at 300 nanomolar in hippocampal preparations, consistent with the inverted-U dose-response pattern characteristic of the GlyT1 inhibitor class [19]. Developers proposed approximately 50 percent GlyT1 occupancy as optimal [20].

Development trajectory: Roche advanced bitopertin through the most extensive Phase III programme ever conducted for a GlyT1 inhibitor. Phase II proof-of-concept (n=323, Umbricht et al. 2014) demonstrated 25 percent reduction in PANSS negative factor score at 10 and 30 mg (p=0.049 and p=0.03, respectively, in per-protocol analysis) [20]. Three Phase III negative symptom trials (FlashLyte NCT01192867 n=594; DayLyte NCT01192906 n=605; SunLyte NCT01192880) tested 5, 10, and 20 mg daily for 24 weeks; none achieved statistical significance on the PANSS negative symptom factor score primary endpoint [21]. Three additional Phase III suboptimal-responder trials (SearchLyte programme: TwiLyte, NightLyte, MoonLyte; total n=1794) tested positive symptom endpoints; only 1 of 6 active treatment arms (NightLyte 10 mg) reached significance [22]. A Phase II/III acute exacerbation trial (CandleLyte, n=301) also failed its primary endpoint [20]. The programme was terminated in its entirety.

Clinical outcome: All Phase III programmes failed their primary endpoints. Bitopertin is the most extensively studied GlyT1 inhibitor in clinical history and provides the most comprehensive negative data set for the mechanism.

Novelty: 3. Non-competitive binding mode differentiates bitopertin from competitive GlyT1 inhibitors (iclepertin, PF-03463275, sarcosine) at the molecular level, but the mechanism does not represent a departure from the GlyT1 inhibition concept.

Effect size: 2. Phase II showed modest negative symptom improvement; Phase III effects were consistently null. No cognitive endpoints were studied as primary outcomes.

Promising potential: 1. Discontinued for all psychiatric indications. Under investigation for non-CNS applications (beta-thalassemia, erythropoietic protoporphyria).

Side-effect profile: 3. Somnolence and dizziness were dose-dependent. In a Japanese Phase III study, adverse drug reaction incidence was 13.3 percent (5 mg), 47.9 percent (10 mg), and 56.2 percent (20 mg) [23]. Four deaths occurred in the SearchLyte programme; one was deemed drug-related (suicide) [22].

Overall validation: 3. Extensive Phase III dataset provides high confidence in the negative conclusion but no path to clinical application.

Comparison to iclepertin: Both compounds inhibit GlyT1 at low-nanomolar IC50 values but through different binding modes (non-competitive for bitopertin, competitive for iclepertin). Bitopertin targeted negative symptoms rather than cognitive endpoints; iclepertin specifically targeted cognitive impairment. The failure of both compounds' Phase III programmes, despite positive Phase II signals, underscores the difficulty of translating GlyT1 inhibition to robust clinical benefit. Iclepertin has the advantage of positive Phase II cognitive data; bitopertin has the larger Phase III dataset but in a different symptom domain.

12.2 Sarcosine (N-methylglycine)

Mechanism: Endogenous amino acid that acts as a competitive GlyT1 inhibitor with an IC50 of approximately 190 micromolar, approximately three to four orders of magnitude less potent than synthetic GlyT1 inhibitors [24]. Also acts as an agonist

at inhibitory glycine receptors at higher concentrations. Available as a dietary supplement.

Development trajectory: No pharmaceutical sponsor; studied exclusively by academic groups (principally in Taiwan and Poland) in small, investigator-initiated trials. Key studies include Tsai et al. (2004, n=38), demonstrating significant improvements in positive, negative, cognitive, and general psychiatric symptoms with adjunctive sarcosine 2 g daily [25]; and Lane et al. (2008, n=20), showing benefit particularly in antipsychotic-naïve patients [26]. A meta-analysis (Singh et al. 2023, 7 trials, n=326) reported a pooled standardized mean difference of 0.51 (95 percent CI 0.26 to 0.76, p less than 0.01) for overall clinical symptoms; cognitive outcomes trended positive but were not statistically significant (SMD 0.27, 95 percent CI negative 0.06 to 0.60, p=0.10) [27]. No benefit was observed when sarcosine was added to clozapine, consistent with clozapine's intrinsic glycinergic properties [25].

Novelty: 2. Endogenous amino acid with well-characterized pharmacology; low potency limits its utility as a pharmacological probe.

Effect size: 3. Consistent modest effects in small academic trials (pooled SMD 0.51 for symptoms); cognitive effects positive but not statistically significant.

Promising potential: 2. No pharmaceutical development programme; research tool and supplement only. The low potency (micromolar range) limits the achievable GlyT1 occupancy at practical oral doses.

Side-effect profile: 5. Excellent tolerability at 1 to 2 g daily across all trials. Rare case reports of hypomania when combined with serotonergic antidepressants [25].

Overall validation: 2. Small academic trials only; no large randomized controlled trial or Phase III data.

Comparison to iclepertin: Sarcosine provides proof-of-concept for the GlyT1 inhibition mechanism in clinical psychiatry but at a potency approximately 38,000-fold lower than iclepertin (IC₅₀ 190 micromolar versus 5 nanomolar). The clinical effect sizes for sarcosine (SMD approximately 0.5) are nominally larger than the iclepertin Phase II effect (d=0.34), but the comparison is confounded by differences in trial design (small vs. large, short vs. long, different endpoints). Iclepertin has the advantage of potency, selectivity, and a rigorous Phase III dataset; sarcosine has the advantages of availability, safety, and consistent positive signals in small trials.

12.3 D-Serine

Mechanism: Endogenous D-amino acid; full agonist at the glycine-B co-agonist site of the NMDA receptor [28]. Acts as a direct co-agonist rather than working indirectly through transporter inhibition. Metabolized by D-amino acid oxidase (DAAO).

Development trajectory: Studied in academic investigator-initiated trials at doses of 30 to 120 mg/kg/day (approximately 2.1 to 8.4 g/day for a 70 kg individual). Tsai et al. (1998, n=31) reported significant improvements in positive, negative, and cognitive symptoms with D-serine 30 mg/kg/day [28]. Heresco-Levy et al. (2005, n=39) demonstrated significant improvements when D-serine was added to risperidone or olanzapine in treatment-refractory patients [30]. Concert Pharmaceuticals developed CTP-692, a deuterated D-serine with improved pharmacokinetics, through Phase 2 (NCT04158687); published peer-reviewed results have not appeared.

Novelty: 2. Endogenous amino acid with direct NMDA receptor agonism; mechanism is well characterized but pharmacologically straightforward.

Effect size: 3. Positive in small trials at 30 mg/kg/day; higher doses (60 to 120 mg/kg/day) showed dose-dependent efficacy. Not replicated in large controlled studies.

Promising potential: 2. Practical limitations include high dose burden (multiple grams daily), short half-life, and potential nephrotoxicity monitoring requirements. CTP-692 (deuterated D-serine) may address some pharmacokinetic limitations but clinical data are unpublished.

Side-effect profile: 3. Nephrotoxicity is the principal safety concern: 2+ proteinuria reported in 1 of 16 patients (0.2 percent) at 120 mg/kg/day (Bearden et al. 2021, review of 490 D-serine-treated subjects across 19 trials) [31]. No nephrotoxicity at doses of 30 mg/kg/day or below. Rat-specific nephrotoxicity at 500 mg/kg or greater does not translate to other species.

Overall validation: 2. Consistent positive signals in small academic trials but not validated in large controlled studies.

Comparison to iclepertin: D-serine addresses the same NMDA receptor target as iclepertin but through a direct agonist mechanism rather than indirect glycine elevation. The clinical effect sizes in small trials are broadly comparable. D-serine has

the conceptual advantage of directness (no dependence on endogenous glycine dynamics) but the practical disadvantages of high dose burden, short half-life, and nephrotoxicity risk at higher doses. Iclepertin has the advantages of low-nanomolar potency, oral tablet convenience, long half-life supporting once-daily dosing, and a comprehensive safety database, offset by the Phase III cognitive efficacy failure.

12.4 PF-03463275 (Pfizer)

Mechanism: Competitive, reversible GlyT1 inhibitor with a K_i of 11.6 nanomolar [29]. Dose-dependent GlyT1 occupancy was characterized by positron emission tomography: approximately 44 percent at 10 mg twice daily, 61 percent at 20 mg twice daily, 76 percent at 40 mg twice daily, and 83 percent at 60 mg twice daily [29]. The compound demonstrated the inverted-U dose-response relationship most precisely: peak cognitive and neuroplasticity effects (enhanced visual long-term potentiation in schizophrenia patients) occurred at approximately 75 percent GlyT1 occupancy (40 mg twice daily), with reduced effects at higher occupancy [29].

Development trajectory: Pfizer advanced PF-03463275 through Phase I/II PET-occupancy and biomarker studies (D'Souza et al. 2018) [29] and a Phase II augmentation trial combining the compound with cognitive training (NCT01911676; D'Souza et al. 2023, n=71) [32]. In the Phase II trial, PF-03463275 at 40 or 60 mg twice daily combined with cognitive training for two 5-week periods did not produce greater MCCB improvement compared to cognitive training alone [32].

Novelty: 3. Competitive GlyT1 inhibitor with the best-characterized PET occupancy-response relationship in the class.

Effect size: 2. Enhanced neuroplasticity biomarker (visual LTP) but failed to improve clinical cognitive outcomes beyond cognitive training alone.

Promising potential: 1. Discontinued. Not in active development for any indication. Available as a research tool.

Side-effect profile: 3. Visual adverse effects reported in healthy volunteers, described as a potential retinal class effect of GlyT1 inhibitors. Otherwise well tolerated [29].

Overall validation: 2. Phase II negative for cognitive endpoints; valuable principally for the PET occupancy data that defined the optimal GlyT1 occupancy range.

Comparison to iclepertin: PF-03463275 and iclepertin are both competitive GlyT1 inhibitors with similar potency (K_i 11.6 nM vs. IC_{50} 5.0 nM). The PF-03463275 PET data (peak effect at approximately 75 percent occupancy) inform the interpretation of iclepertin dosing: the 10 mg iclepertin dose that produced the Phase II cognitive signal achieves CSF concentrations in the IC_{50} range, suggesting moderate GlyT1 occupancy consistent with the optimal window defined by PF-03463275. Both compounds failed to demonstrate cognitive improvement beyond placebo or cognitive training in their respective Phase II trials, reinforcing the pattern of difficulty in translating GlyT1 inhibition to clinical cognitive endpoints.

12.5 Luvadaxistat (TAK-831, NBI-1065844, Takeda/Neurocrine Biosciences)

Mechanism: Selective D-amino acid oxidase (DAAO) inhibitor with an IC_{50} of 14 nanomolar against human recombinant DAAO [33]. Inhibits the oxidative deamination of D-serine, increasing endogenous D-serine levels at NMDA receptor co-agonist sites. Represents an indirect NMDA-enhancing strategy upstream of the direct co-agonist approach (D-serine) and mechanistically orthogonal to GlyT1 inhibition (which increases glycine rather than D-serine) [33].

Development trajectory: Originally developed by Takeda as TAK-831, licensed to Neurocrine Biosciences as NBI-1065844. Phase 1 studies (NCT02566759, NCT03224325) demonstrated dose-dependent D-serine elevation in plasma and CSF with a terminal half-life of 6 to 23 hours [33]. A Phase 2a biomarker study (NCT03359785; Kantrowitz et al. 2023, n=31) evaluated 50 and 500 mg luvadaxistat in a randomized crossover design; the primary eyeblink conditioning endpoint was negative, while mismatch negativity showed nominally significant improvement at 50 mg (effect size negative 0.691, $p=0.050$) but not 500 mg ($p=0.85$), again demonstrating the inverted-U dose-response pattern [34]. The INTERACT Phase 2 trial (NCT03382639; Fleischhacker et al. 2024, n=256) tested 50, 125, and 500 mg daily for 12 weeks; the primary endpoint (PANSS negative symptom factor score) was not met at any dose. Secondary cognitive endpoints at 50 mg showed nominal signals on BACS composite (one-sided $p=0.031$, effect size 0.4) and SCoRS (one-sided $p=0.011$, effect size 0.4) [35]. A confirmatory ERUDITE Phase 2 trial failed to replicate the cognitive signals. Neurocrine halted luvadaxistat development in September 2024 and terminated the Takeda license agreement effective April 2025 [35].

Novelty: 4. DAAO inhibition is mechanistically distinct from GlyT1 inhibition, targeting D-serine rather than glycine. Represents the most novel approach in this comparator panel.

Effect size: 2. INTERACT showed a cognitive signal at 50 mg (effect size 0.4) comparable to the iclepertin Phase II signal ($d=0.34$), but the signal was not replicated in the ERUDITE confirmatory trial.

Promising potential: 1. Discontinued in September 2024 after ERUDITE failure.

Side-effect profile: 4. Well tolerated across all clinical studies; no significant safety signals identified.

Overall validation: 2. Phase II with non-replicated cognitive signals; development terminated.

Comparison to iclepertin: Luvadaxistat and iclepertin both target NMDA receptor hypofunction but through orthogonal mechanisms: iclepertin increases glycine via GlyT1 inhibition while luvadaxistat increases D-serine via DAAO inhibition. Both compounds produced positive Phase II cognitive signals of similar magnitude (effect sizes approximately 0.3 to 0.4) that failed to replicate in confirmatory trials, suggesting that the challenge of treating CIAS extends beyond the choice of NMDA-enhancing mechanism. The inverted-U dose-response pattern was observed for both compounds, reinforcing the general difficulty of optimizing NMDA-enhancing therapy.

12.6 Comparator summary

The five comparator compounds and iclepertin collectively represent the principal NMDA receptor enhancement strategies evaluated in clinical development for schizophrenia-related cognitive and negative symptom endpoints. The consistent finding across this field is a pattern of positive Phase II signals followed by negative Phase III or confirmatory results: bitopertin (Phase III negative for negative symptoms), iclepertin (Phase III negative for cognition), PF-03463275 (Phase II negative for cognition), luvadaxistat (Phase II confirmatory negative for cognition), sarcosine and D-serine (positive only in small academic trials that have not been scaled).

The inverted-U dose-response relationship is a recurring pharmacological observation across GlyT1 inhibitors (bitopertin, iclepertin, PF-03463275) and the DAAO inhibitor (luvadaxistat), suggesting that the optimal window for NMDA receptor en-

hancement is narrow and may not be achievable with systemic administration of a single agent [1, 16, 19, 29, 34]. Singer and Yee (2024) proposed that the bidirectional operation of GlyT1, the role of the astrocytic serine shuttle, and the requirement for cell-type and regional specificity may fundamentally limit the efficacy of systemic GlyT1 inhibitors [16].

Iclepertin occupies a position in this landscape as the most rigorously evaluated GlyT1 inhibitor for cognitive endpoints in schizophrenia, with the largest Phase III cognitive impairment dataset (1835 patients, 26 weeks) and the most comprehensive pharmacokinetic-pharmacodynamic characterization. Its Phase II cognitive signal ($d=0.34$) was the strongest prospective evidence for the GlyT1-NMDA pathway in cognition, and its Phase III failure ($p=0.63$) is correspondingly the most definitive negative result. The compound remains a valuable pharmacological tool for investigating GlyT1 biology in vitro and in preclinical models, and the comprehensive clinical dataset informs the design of future NMDA-enhancing strategies.

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