

RESEARCH MONOGRAPH . COMPOUND PROFILE

ACD856

A first-in-class triazinetriene pan-Trk positive allosteric modulator developed by AlzeCure Pharma that enhances BDNF and NGF signaling for the treatment of cognitive dysfunction in Alzheimer's disease, with additional preclinical support for depression, traumatic brain injury, and sleep disorders.

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ABSTRACT

ACD856 is a novel, orally bioavailable triazinetrione compound functioning as a positive allosteric modulator (PAM) of the tropomyosin receptor kinases TrkA, TrkB, and TrkC, the principal signal-transducing receptors for the neurotrophins nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), and neurotrophin-3 (NT-3), respectively [1, 2]. The compound was identified through a high-throughput screening campaign of approximately 25,000 compounds and structurally optimized from the veterinary antiparasitic triazinetrione scaffold shared by toltrazuril and ponazuril (ACD855), with the critical improvement of a substantially shortened elimination half-life suitable for once-daily human dosing [3, 4]. ACD856 potentiates the tropomyosin receptor kinases with EC₅₀ values of 382 nM (TrkA), 295 nM (TrkB), and approximately 330 nM (TrkC), and exhibits additional positive allosteric modulation of the insulin-like growth factor 1 receptor (IGF1R) and fibroblast growth factor receptor 1 (FGFR1) [1, 5]. The mechanism of action is distinct from orthosteric Trk agonism: ACD856 binds the intracellular kinase domain of Trk receptors and increases the maximal catalytic velocity (V_{max}) of the kinase, thereby amplifying endogenous neurotrophin signaling rather than substituting for it [2, 6]. This allosteric mechanism preserves the spatiotemporal specificity of native neurotrophin activity, a property expected to confer a more favorable safety profile than direct agonist approaches that have historically been limited by pain, hyperalgesia, and off-target proliferative effects.

In preclinical pharmacology, ACD856 has demonstrated reversal of scopolamine-induced and dizocilpine (MK-801)-induced memory impairment in passive avoidance and novel object recognition tasks in mice, restoration of age-related memory deficits in 21-month-old mice to the performance level of young animals following single-dose administration, neuroprotection against amyloid-beta(1-42)-induced synaptotoxicity in primary cortical neurons, enhancement of NGF-stimulated neurite outgrowth in PC12 cells, elevation of BDNF protein levels in the brains of aged mice following repeated dosing, and sustained antidepressant-like effects in the forced swim test persisting up to seven days after the last dose [5, 7, 8]. The compound also enhanced mitochondrial ATP production under energy-deprived conditions, increased phosphorylation of TrkB and ERK1/2 in cortical neurons, elevated hippocampal concentrations of serotonin, noradrenaline, and dopamine by in vivo microdialysis, and increased expression of the presynaptic protein SNAP25, collectively indicating a broad neuroprotective and neuroplasticity-promoting pharmacological profile [5, 7].

ACD856 has completed two Phase 1 clinical studies in healthy volunteers. The single ascending dose (SAD) study (1 to 150 mg oral, n = 56) demonstrated rapid absorption (median t_{max} 0.33 to 1.0 hours), linear dose-proportional pharmacokinetics, near-complete oral bioavailability (approximately 93 percent relative bioavailability), a terminal elimination half-life of approximately 20 hours supporting once-daily dosing, and an acceptable safety profile with no serious adverse events and no dose-related safety signals [9]. The multiple ascending dose (MAD) study (10, 30, and 90 mg daily for seven days, n = 24) confirmed dose-dependent increases in cerebrospinal fluid concentrations (geometric mean 3.98 to 100 ng/mL), CSF-to-unbound-plasma ratios of 0.37 to 1.20

indicating substantial blood-brain barrier penetration, dose-dependent changes on quantitative electroencephalography (increased theta power and theta/beta ratio) consistent with central target engagement, and continued safety and tolerability with no serious adverse events [10, 11]. AlzeCure Pharma has received a EUR 2.5 million grant from the European Innovation Council to conduct a Phase IIa clinical study of ACD856 in Alzheimer's disease, with higher doses to be evaluated based on the favorable Phase 1 safety profile [12]. Additional indications under preclinical investigation include depressive disorders, traumatic brain injury, sleep disorders, and postoperative cognitive dysfunction.

1. Compound Identification

1.1 Names, synonyms, and registry identifiers

Development code: ACD856 (AlzeCure Pharma AB). The development code is the canonical identifier in all published preclinical and clinical literature. The compound is also referred to as ACD-856 in some sources.

Platform designation: NeuroRestore (AlzeCure Pharma proprietary platform name for Trk-PAM drug candidates). ACD856 is the lead clinical candidate within the NeuroRestore platform; ACD857 is a follow-on compound in the research phase [12].

Chemical Abstracts Service registry number: Not publicly assigned or disclosed as of the most recent monograph revision.

International Union of Pure and Applied Chemistry name: Not publicly disclosed. The exact chemical structure of ACD856 remains proprietary to AlzeCure Pharma AB. The compound is described in the scientific literature as a triazinetrione derivative [5, 7].

1.2 Structural class and chemistry

ACD856 belongs to the triazinetrione (1,3,5-triazine-2,4,6-trione) chemical class, a six-membered heterocyclic ring system containing three nitrogen atoms and three carbonyl groups [5]. The triazinetrione scaffold is shared with the veterinary antiparasitic agents toltrazuril and ponazuril (the latter also designated ACD855), from which ACD856 was derived through medicinal chemistry optimization [3, 4].

Molecular formula: Not publicly disclosed.

Molecular weight: Not publicly disclosed.

Physical properties: White to off-white solid powder. Soluble in dimethyl sulfoxide (DMSO) at concentrations up to 10 mM. Research-grade material is supplied as a solid powder with storage at minus 20 degrees Celsius (12-month stability) or 2 to 8 degrees Celsius (6-month stability) [13].

Structural relationship to predecessor compounds: ACD855 (ponazuril), the immediate structural predecessor, is an approved veterinary coccidiostat with demonstrated Trk-potentiating activity first identified in the 2013 screening campaign [3, 4]. ACD855 was unsuitable for human clinical development owing to an elimination half-life of approximately 68 days. ACD856 was optimized from this scaffold to achieve approximately 70-fold higher oral clearance while retaining Trk-PAM activity, yielding a human elimination half-life of approximately 20 hours suitable for once-daily oral dosing [9].

1.3 Synthesis

The synthesis of ACD856 has not been disclosed in the peer-reviewed literature. The compound was identified through a high-throughput screen of approximately 25,000 compounds for potentiation of neurotrophin-stimulated Trk receptor phosphorylation [3]. Structural optimization from the toltrazuril/ponazuril triazinetrione scaffold was conducted at AlzeCure Pharma with the goals of shortening the elimination half-life, improving oral bioavailability, and maintaining pan-Trk PAM potency. The manufacturing process, synthetic route, and scale-up chemistry remain proprietary. Research-grade ACD856 is available from chemical suppliers (Probechem Biochemicals, catalog PC-23114; Everychem) at greater than 98 percent purity by HPLC [13].

2. Abstract

ACD856 is a first-in-class positive allosteric modulator of the tropomyosin receptor kinases (TrkA, TrkB, TrkC), the high-affinity signal-transducing receptors for the neurotrophins NGF, BDNF, and NT-3 [1, 2]. The compound was developed by AlzeCure Pharma AB (Stockholm, Sweden) as the lead clinical candidate in the NeuroRestore platform, a drug discovery program targeting cognitive dysfunction and neurodegeneration through enhancement of endogenous neurotrophin signaling.

The rationale for Trk-PAM pharmacology in Alzheimer's disease rests on several converging lines of evidence. BDNF levels are reduced in the hippocampus and cortex of Alzheimer's disease patients, and the reduction correlates with cognitive decline [14, 15]. The BDNF Val66Met polymorphism, which reduces activity-dependent BDNF secretion, is associated with accelerated cognitive decline and increased Alzheimer's disease risk [16]. NGF signaling through TrkA is required for the survival and function of basal forebrain cholinergic neurons, the population that degenerates earliest and most severely in Alzheimer's disease [17, 18]. Direct administration of NGF or BDNF protein has demonstrated neuroprotective and procognitive effects in animal models but is not feasible as a therapeutic strategy owing to the inability of the proteins to cross the blood-brain barrier, short plasma half-life, and pain and hyperalgesia mediated by TrkA activation on nociceptive neurons [6, 19].

ACD856 addresses these limitations through allosteric potentiation rather than orthosteric agonism: the compound amplifies the activity of endogenous neurotrophins at their receptors without activating the receptors in the absence of ligand, preserving the physiological spatial and temporal pattern of neurotrophin signaling [2, 5, 6]. This mechanism is expected to avoid the pain and hyperalgesia that have historically limited direct neurotrophin agonist approaches.

The compound has completed Phase 1 clinical development (single and multiple ascending dose studies in healthy volunteers) with favorable safety, tolerability, and pharmacokinetic profiles, and is advancing toward Phase IIa evaluation in Alzheimer's disease patients supported by a EUR 2.5 million European Innovation Council grant [9, 10, 12].

3. Discovery and Development History

3.1 Origin

The NeuroRestore program originated in 2013 at AlzeCure Pharma AB (then operating under the auspices of the Alzheimer's Research Foundation at the Karolinska Institutet) through a high-throughput phenotypic screen of approximately 25,000 compounds for the ability to potentiate NGF-induced Trk receptor phosphorylation in cell-based assays [3, 4]. The screen identified the veterinary antiparasitic agents toltrazuril and its active sulfone metabolite ponazuril as possessing Trk-potentiating activity. Ponazuril was designated ACD855 and characterized as a pan-Trk positive allosteric modulator with EC50 values in the low-micromolar range [3].

3.2 Lead optimization

ACD855 (ponazuril), despite demonstrating Trk-PAM activity and favorable oral bioavailability in rodent species, was unsuitable for human clinical development owing to an elimination half-life of approximately 68 days in preclinical species, a property reflecting the extreme metabolic stability of the triazinetrione core and extensive tissue sequestration [4, 9]. AlzeCure Pharma conducted a medicinal chemistry campaign to identify analogs retaining the Trk-PAM pharmacology while substantially increasing oral clearance. ACD856 emerged from this optimization as the lead clinical candidate, demonstrating approximately 70-fold higher oral clearance than ponazuril while maintaining pan-Trk PAM potency at submicromolar concentrations [9].

3.3 Preclinical characterization

ACD856 was characterized in extensive in vitro and in vivo pharmacology studies between 2018 and 2022, establishing the compound's mechanism of action, neuroprotective properties, cognitive enhancement profile, and antidepressant-like activity [5, 7, 8]. The preclinical package was published principally in Parrado Fernandez et al. (2023) in the International Journal of Molecular Sciences [5] and in the Nordvall et al. (2024) review in Pharmaceuticals [6].

3.4 Clinical development

The first-in-human clinical study was initiated in late 2019 as a Phase 0 intravenous microdose study (0.1 mg, n = 6) to establish human pharmacokinetic parameters [9]. The Phase 1 single ascending dose study (1 to 150 mg oral, n = 56 healthy volunteers) was initiated in late 2020 and completed in the second quarter of 2021 [9]. The Phase 1 multiple ascending dose study (10, 30, and 90 mg oral daily for seven days, n = 24 healthy volunteers) was initiated in the third quarter of 2021 and completed in June 2022 [10, 11]. Results from both studies were published in peer-reviewed journals (Ohrn et al. 2024, *European Journal of Clinical Pharmacology*; Onnestam et al. 2024, *Journal of Prevention of Alzheimer's Disease*) [9, 10].

In February 2025, AlzeCure Pharma received a EUR 2.5 million grant from the European Innovation Council (EIC) to fund a Phase IIa clinical study of ACD856 in Alzheimer's disease patients [12]. The first payment of the grant was received in December 2025. The Phase IIa study is expected to evaluate higher doses of ACD856 in patients with mild cognitive impairment or early Alzheimer's disease.

In March 2026, AlzeCure Pharma presented new preclinical data at the AD/PD 2026 conference in Copenhagen, demonstrating dose- and time-dependent effects of ACD856 on Trk receptor-mediated signaling pathways and significant positive effects on cognition and depression endpoints in rodent models [20].

4. Mechanism of Action

ACD856 is a positive allosteric modulator of the tropomyosin receptor kinases, a family of receptor tyrosine kinases that serve as the high-affinity signal-transducing receptors for the neurotrophin family of growth factors. The mechanism is distinct from orthosteric agonism, competitive antagonism, and negative allosteric modulation: ACD856 binds the intracellular kinase domain of the Trk receptor and enhances the catalytic efficiency of the kinase without competing with or substituting for the neurotrophin ligand at the extracellular binding site [2, 6].

4.1 Trk receptor biology

The tropomyosin receptor kinase family comprises three members: TrkA (the high-affinity receptor for NGF), TrkB (the high-affinity receptor for BDNF and NT-4/5), and TrkC (the high-affinity receptor for NT-3) [14, 17]. Each receptor is a single-pass transmembrane glycoprotein with an extracellular domain containing leucine-rich repeats, two Ig-like domains (the neurotrophin-binding site), a transmembrane helix, and an intracellular tyrosine kinase domain. Neurotrophin binding induces receptor dimerization, transphosphorylation of the intracellular kinase domains, and activation of downstream signaling cascades including the SHC1-RAS-MAPK/ERK pathway (supporting neuronal differentiation and synaptic plasticity), the PI3K-AKT pathway (supporting neuronal survival), and the PLCgamma1-IP3-calcium-PKC pathway (supporting synaptic transmission) [6, 14].

TrkA-NGF signaling is essential for the survival and function of basal forebrain cholinergic neurons, the population most severely affected in Alzheimer's disease [17, 18]. TrkB-BDNF signaling is the principal neurotrophin pathway supporting hippocampal synaptic plasticity, long-term potentiation, and memory formation [14, 15]. TrkC-NT3 signaling contributes to proprioceptive neuron survival and to hippocampal neurogenesis.

4.2 Positive allosteric modulation of Trk kinase activity

ACD856 interacts with the intracellular domain of Trk receptors and increases the V_{max} (maximal velocity) of the TrkA kinase catalytic cycle without altering the affinity of NGF for the TrkA extracellular domain [2, 5, 6]. This mechanism was demonstrated in kinase assays showing that ACD856 enhances TrkA phosphorylation in the presence of NGF but produces minimal activation (approximately 60 percent of maximum) in the absence of neurotrophin ligand [5]. The allosteric nature of the modulation means that ACD856 activity is dependent on endogenous neurotrophin release, preserving the spatial selectivity of neurotrophin signaling (active only where and when neurotrophins are released) and the temporal dynamics of Trk receptor activation and deactivation.

Potency values (EC_{50}) for Trk potentiation are 382 nM for TrkA, 295 nM for TrkB, and approximately 330 nM for TrkC, indicating pan-Trk activity without marked subtype selectivity [1, 5]. ACD856 also demonstrates positive allosteric modulation of the insulin-like growth factor 1 receptor (IGF1R) and the fibroblast growth factor receptor 1 (FGFR1) at similar concentrations, broadening the receptor tyrosine kinase pharmacology beyond the Trk family [1].

4.3 Downstream signaling and neuroprotective mechanisms

In primary cortical neurons, ACD856 at 100 to 1000 nM produced increased phosphorylation of TrkB and of ERK1/2 (specifically in neurites rather than cell bodies, suggesting synapse-targeted effects), increased expression of the presynaptic protein SNAP25, and increased BDNF protein levels (approximately 30 percent increase at 100 nM) [5, 7]. In PC12 cells (a pheochromocytoma line expressing TrkA), ACD856 enhanced NGF-stimulated neurite outgrowth in a dose-dependent manner across multiple morphometric parameters including neurite length per neuron, total neurite length per well, and neurite count per cell [5].

The neuroprotective mechanism involves protection against amyloid-beta(1-42)-induced synaptotoxicity: ACD856 at concentrations beginning at 1 micromolar provided almost complete protection against 10 micromolar amyloid-beta(1-42)-induced loss of SNAP25-positive neurites in primary cortical neurons, with efficacy comparable to exogenous BDNF and NGF [5]. Under energy-deprived conditions

(glutamine as sole energy substrate), ACD856 at 1 to 10 micromolar produced dose-dependent increases in ATP levels, preserved metabolic activity, and maintained cell membrane integrity, indicating mitochondrial protective activity [5].

4.4 Neurochemical effects

In vivo microdialysis studies in rodent hippocampus demonstrated that ACD856 administration increased extracellular concentrations of serotonin, noradrenaline, and dopamine [6, 7]. This monoamine-elevating activity, likely secondary to enhanced BDNF-TrkB signaling and downstream effects on monoaminergic neuron function, provides a mechanistic basis for the observed antidepressant-like effects and distinguishes the pharmacological profile from cholinesterase inhibitors, which primarily elevate acetylcholine.

4.5 Composite pharmacology

The composite pharmacological profile of ACD856 therefore encompasses neurotrophin signal amplification (pan-Trk PAM), neuroprotection (anti-amyloid, mitochondrial support), neuroplasticity promotion (neurite outgrowth, SNAP25 elevation, BDNF induction), and monoamine modulation. This profile is consistent with both symptomatic cognitive enhancement (through acute neuroplasticity and neurotransmitter effects) and potential disease modification (through chronic neuroprotection, BDNF elevation, and synaptic maintenance) [5, 6, 7].

5. Pharmacokinetics and Routes of Administration

5.1 Preclinical pharmacokinetics

In rodent species, ACD856 demonstrates oral bioavailability with rapid absorption. Key preclinical pharmacokinetic parameters following subcutaneous administration at 1 mg/kg include: peak plasma concentration of 3550 nM, peak brain concentration of 402 nM, and plasma elimination half-life of approximately 1.4 hours [5]. Following oral administration at 5 mg/kg: peak plasma concentration of 65,960 nM, peak brain concentration of 1350 nM, and plasma elimination half-life of approximately 3.3 hours [5]. Plasma protein binding is 96.2 to 98.2 percent, yielding estimated unbound plasma concentrations of 65 to 134 nM at the 1 mg/kg subcutaneous dose [5]. The short rodent half-life contrasts with the substantially longer human half-life (approximately 20 hours), reflecting species differences in hepatic clearance.

5.2 Human pharmacokinetics: intravenous microdose

A Phase 0 intravenous microdose study (0.1 mg, n = 6 healthy male volunteers) established baseline human pharmacokinetic parameters: elimination half-life of approximately 19.4 hours, volume of distribution of 17.3 to 17.6 liters (approximately 0.25 L/kg), plasma clearance of 0.64 L/h, and AUC(0-infinity) of 160.9 h*ng/mL [9].

5.3 Human pharmacokinetics: single ascending dose

The Phase 1 SAD study enrolled 56 healthy volunteers (48 males, 8 females) across seven ascending oral dose cohorts (1, 3, 10, 20, 40, 75, and 150 mg) [9]. Key findings:

Absorption was rapid, with median time to peak plasma concentration (t_{max}) of 0.33 to 1.0 hours across all dose levels. The elimination half-life was approximately 20 hours, consistent across the entire dose range and supporting once-daily oral dosing. Dose proportionality was linear across the 1 to 150 mg range. Relative oral

bioavailability was approximately 93 percent (near-complete). Renal elimination was negligible (less than 0.2 percent of the administered dose excreted unchanged in urine), indicating predominantly hepatic metabolism [9].

A food effect assessment demonstrated that a high-fat breakfast reduced C_{max} by approximately 40 percent and delayed t_{max} considerably, but the overall AUC and bioavailability were minimally affected (93 percent relative bioavailability under fed conditions) [9].

5.4 Human pharmacokinetics: multiple ascending dose

The Phase 1 MAD study enrolled 24 healthy volunteers receiving 10, 30, or 90 mg of ACD856 orally once daily for seven days [10, 11]. ACD856 was rapidly absorbed, reaching maximum plasma concentrations 30 to 45 minutes after administration on both day 1 and day 7. Steady state was reached before day 6, consistent with the approximately 20-hour half-life. At steady state, accumulation ratios were approximately 1.6 for C_{max} and approximately 1.9 for AUC [10, 11].

Cerebrospinal fluid (CSF) concentrations measured on day 6 demonstrated dose-dependent blood-brain barrier penetration: geometric mean CSF concentrations were 3.98 ng/mL (10 mg), 13.8 ng/mL (30 mg), and 100 ng/mL (90 mg) [10, 11]. The CSF-to-unbound-plasma concentration ratios ranged from 0.37 to 1.20, indicating that ACD856 achieves central nervous system exposure approximating or exceeding unbound plasma concentrations, a property essential for a centrally acting neurotrophin modulator [10].

5.5 Estimated human efficacious dose

Based on preclinical efficacy data and pharmacokinetic bridging, a single oral dose of 30 mg in humans was estimated to generate an unbound plasma concentration of approximately 32 ng/mL, aligning with the concentrations producing cognitive enhancement in rodent models [5]. The Phase IIa study is expected to evaluate doses at or above this level.

5.6 Routes of administration

ACD856 is formulated for oral administration. The near-complete oral bioavailability and approximately 20-hour half-life support once-daily oral dosing as the primary route for clinical development. Intravenous administration was used only in the Phase 0 microdose study for absolute bioavailability determination [9]. Subcutaneous administration has been used in preclinical rodent studies [5, 7].

6. Preclinical Pharmacology

6.1 Cognitive enhancement

ACD856 reversed scopolamine-induced memory impairment in mouse passive avoidance tasks at a single-dose minimum effective concentration of 0.3 mg/kg [5]. With repeated dosing over four days, the threshold was reduced to 0.1 mg/kg, suggesting neuroplastic adaptation independent of compound accumulation (given the short rodent half-life of approximately 1.4 hours) [5]. ACD856 also reversed MK-801 (dizocilpine)-induced memory impairment, demonstrating efficacy against both cholinergic and glutamatergic deficit models [1, 7].

In aged mice (21 months), a single administration of ACD856 restored memory performance in the passive avoidance task to the level of young (3-month) animals [6, 7]. Repeated dosing (4 weeks, 5 mg/kg subcutaneous) in aged mice produced a significant increase in BDNF levels across the brain hemisphere, an effect not observed in young mice after shorter dosing (5 days, 3 mg/kg oral), suggesting that the BDNF-elevating effect may be more pronounced in the context of age-related neurotrophin deficiency [5].

6.2 Neuroprotection

In primary cortical neuron cultures, ACD856 provided almost complete protection against amyloid-beta(1-42)-induced synaptotoxicity at concentrations of 1 to 10 micromolar, as assessed by preservation of SNAP25-positive neurite networks [5]. The neuroprotective efficacy was comparable to exogenous BDNF and NGF at equivalent concentrations.

Under energy-deprived conditions (neurons cultured with glutamine as the sole energy substrate), ACD856 at 1 to 10 micromolar produced dose-dependent increases in cellular ATP content, preserved metabolic activity as measured by resazurin reduction, and maintained cell membrane integrity [5]. These findings indicate that ACD856 supports mitochondrial function and cellular energy metabolism under stress conditions relevant to neurodegenerative pathology.

6.3 Neurite outgrowth and synaptic markers

In PC12 cells, ACD856 enhanced NGF-stimulated neurite outgrowth in a dose-dependent manner, increasing neurite length per neuron, total neurite length per well, and neurite number per cell [5]. The compound also increased expression of the presynaptic protein SNAP25, with particularly prominent expression in neuritic buddings resembling immature dendritic spines [5].

In SH-SY5Y neuroblastoma cells, ACD856 at 300 nM produced a significant increase in phosphorylation of TrkB receptors, confirming the mechanism of action in a human-derived neuronal cell line [5].

6.4 Antidepressant-like effects

Five daily subcutaneous injections of ACD856 at 1 mg/kg produced a significant reduction in immobility time in the mouse forced swim test, an established model of antidepressant-like activity [5, 7]. The effect persisted for up to seven days after the last dose, indicating sustained neuroplastic changes rather than merely symptomatic pharmacological effects [5]. The sustained duration of the antidepressant-like effect is comparable to that observed with ketamine (used at 10 mg/kg as a benchmark in the same studies), suggesting mechanistic overlap through neuroplasticity-promoting pathways [5, 7].

In vivo microdialysis demonstrated that ACD856 increased hippocampal concentrations of serotonin, noradrenaline, and dopamine, providing a neurochemical basis for the antidepressant-like behavioral profile [6, 7].

6.5 Enhancement of cholinesterase inhibitor efficacy

Preclinical studies demonstrated that ACD856 enhanced the cognitive effects of existing acetylcholinesterase inhibitors, suggesting potential for combination therapy in Alzheimer's disease [12]. The mechanistic basis for this synergy is plausible: acetylcholinesterase inhibitors increase cholinergic transmission at surviving cholinergic neurons, while ACD856 enhances NGF-TrkA signaling to support the survival and function of those neurons.

7. Clinical Evidence Base

7.1 Phase 0 intravenous microdose study

The first-in-human study administered a single intravenous microdose of 0.1 mg ACD856 to six healthy male volunteers to establish human pharmacokinetic parameters [9]. The study confirmed the predicted elimination half-life (approximately 19.4 hours), volume of distribution (17.3 to 17.6 L), and clearance (0.64 L/h). No adverse events were reported.

7.2 Phase 1 single ascending dose study

The Phase 1 SAD study was a randomized, double-blind, placebo-controlled study in 56 healthy volunteers (48 males, 8 females) at seven ascending dose levels (1, 3, 10, 20, 40, 75, and 150 mg oral) [9]. The study demonstrated:

Safety and tolerability: No serious adverse events were reported. No dose-related trends were observed in vital signs, physical examinations, electrocardiographic parameters, or laboratory values. The most common adverse event was headache, reported in 8 subjects at mild intensity. No treatment-emergent liver enzyme elevations were observed [9].

Pharmacokinetics: Rapid absorption (median t_{max} 0.33 to 1.0 hours), linear dose-proportional exposure across the 1 to 150 mg range, approximately 20-hour elimination half-life, and approximately 93 percent oral bioavailability [9].

Food effect: High-fat meal reduced C_{max} by approximately 40 percent and delayed t_{max} but did not materially affect overall bioavailability [9].

7.3 Phase 1 multiple ascending dose study

The Phase 1 MAD study was a randomized, double-blind, placebo-controlled study in 24 healthy volunteers receiving ACD856 at 10, 30, or 90 mg orally once daily for seven days [10, 11]. Key findings:

Safety and tolerability: No serious adverse events were reported. The compound was well tolerated across all dose levels. Two participants showed elevated pancreatic enzymes that normalized without intervention [10]. No dose-dependent adverse event patterns were identified.

Pharmacokinetics: Rapid absorption (C_{max} at 30 to 45 minutes on both day 1 and day 7), steady state before day 6, accumulation ratios of approximately 1.6 (C_{max}) and 1.9 (AUC), and dose-dependent CSF concentrations of 3.98 to 100 ng/mL confirming blood-brain barrier penetration [10, 11].

Target engagement: Quantitative EEG analysis demonstrated that ACD856 significantly increased theta power and the theta/beta ratio compared to baseline and placebo, consistent with central nervous system target engagement and modulation of cortical neuronal activity [10, 11]. These changes are consistent with neurotrophin-mediated effects on cortical and hippocampal neuronal function.

7.4 Phase IIa planning

AlzeCure Pharma received a EUR 2.5 million European Innovation Council grant in February 2025 to fund a Phase IIa clinical study of ACD856 in Alzheimer's disease patients [12]. The grant payment was confirmed in December 2025. The Phase IIa study is expected to evaluate higher doses based on the favorable safety profile observed in Phase 1, with endpoints including cognitive assessments, biomarkers of neurotrophin signaling, and additional safety and pharmacokinetic characterization. As of the monograph revision date, the Phase IIa study had not reported results.

7.5 Additional indications under investigation

ACD856 is in preclinical development for depressive disorders (supported by the sustained antidepressant-like effects in rodent models), traumatic brain injury, sleep disorders, and postoperative cognitive dysfunction [1, 7, 12]. Preclinical data presented at the AD/PD 2026 conference in March 2026 demonstrated dose- and time-dependent effects on Trk receptor-mediated signaling pathways with significant positive effects on cognition and depression endpoints [20]. No clinical trials for these indications have been initiated as of the monograph revision date.

8. Sourcing and Quality Verification

ACD856 is not a registered pharmaceutical product in any jurisdiction. The compound is available exclusively as a research-grade preparation from chemical suppliers.

Research-grade ACD856 is supplied by Probechem Biochemicals (catalog PC-23114), Everychem, and other specialized research chemical vendors at greater than 98 percent purity by HPLC [13]. Supply is available as a solid powder in milligram quantities and as pre-dissolved solutions (10 mg/mL in DMSO).

Pricing and availability should be confirmed directly with suppliers, as ACD856 is a relatively new research compound and supply chains may be limited compared to established reference compounds.

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

- High-performance liquid chromatography area-percent purity, ideally greater than 98 percent
- Mass spectrometry confirmation of molecular weight (exact value not publicly disclosed; investigators should confirm against the supplier certificate of analysis and, where available, against patent literature describing the tri-azinetriene scaffold)
- Nuclear magnetic resonance spectroscopy for structural confirmation
- Solubility verification in DMSO (expected 10 mM)
- Residual solvent and water content analysis

The proprietary nature of the chemical structure presents a limitation for independent analytical verification. Investigators relying on ACD856 for dose-response or mechanism-of-action studies should obtain multiple independent lots and confirm lot-to-lot consistency through functional assays (Trk phosphorylation potentiation) in addition to analytical chemistry.

9. Reconstitution and Handling

ACD856 is supplied as a solid powder. Storage conditions for the solid are minus 20 degrees Celsius (stable for 12 months) or 2 to 8 degrees Celsius (stable for 6 months) [13].

For in vitro research applications, stock solutions are prepared at 10 mM in DMSO. Aliquoting of stock solutions into single-use volumes is recommended to avoid freeze-thaw degradation. Solutions in DMSO are stable for 6 months at minus 80 degrees Celsius or 6 months at minus 20 degrees Celsius [13].

For in vivo research applications, the compound has been administered subcutaneously and orally in rodent studies. Subcutaneous formulations have typically been prepared in standard pharmaceutical vehicles; oral formulations have been administered by gavage. Specific vehicle compositions for in vivo use are described in the preclinical publications [5, 7].

Light protection is reasonable practice for stock solutions, consistent with general handling recommendations for heterocyclic compounds. The compound should be equilibrated to room temperature before opening to prevent moisture condensation on the solid material.

For clinical formulations, ACD856 has been administered as oral tablets or capsules in the Phase 1 studies [9, 10]. The clinical formulation details have not been publicly disclosed.

10. Stack Interactions and Combinations

ACD856 interacts with several drug classes through its neurotrophin-potentiating mechanism and through pharmacokinetic considerations. Investigators conducting research with ACD856, especially in combination protocols, should consider:

Acetylcholinesterase inhibitors (donepezil, rivastigmine, galantamine): Preclinical data suggest that ACD856 enhances the cognitive effects of acetylcholinesterase inhibitors [12]. The mechanistic basis is complementary: acetylcholinesterase inhibitors increase cholinergic transmission at surviving neurons, while ACD856 enhances NGF-TrkA signaling to support the survival and function of those neurons. The combination is pharmacologically rational and is likely to be explored in the Phase IIa study in Alzheimer's disease patients already receiving standard-of-care cholinesterase inhibitor therapy.

Anti-amyloid monoclonal antibodies (lecanemab, aducanumab, donanemab): The combination of ACD856 with anti-amyloid therapies has been proposed as a strategy for addressing both the symptomatic (cognitive) and pathological (amyloid, neurodegeneration) dimensions of Alzheimer's disease [6]. The anti-amyloid antibodies reduce amyloid burden, while ACD856 supports neurotrophin signaling and neuroprotection. No preclinical or clinical data on the combination are available.

CYP enzyme considerations: The specific cytochrome P450 isoforms responsible for ACD856 metabolism have not been publicly disclosed. The negligible renal elimination (less than 0.2 percent) indicates predominantly hepatic metabolism [9]. Until the metabolic pathway is characterized, caution is warranted with strong CYP inhibitors and inducers.

Other neurotrophin-targeting agents: Concurrent administration with other Trk-targeting compounds (E2511, 7,8-dihydroxyflavone, LM22A-4) would produce additive or potentially synergistic effects on Trk signaling. The combination has not been studied and may exceed physiological neurotrophin signaling levels, with unknown consequences for receptor desensitization and downstream pathway adaptation.

Serotonergic and noradrenergic agents: Given that ACD856 increases hippocampal serotonin, noradrenaline, and dopamine via microdialysis [6, 7], concurrent use with antidepressants (SSRIs, SNRIs, MAOIs) may produce additive monoaminergic effects. The clinical significance of this interaction has not been characterized.

Insulin and IGF1R-targeting agents: ACD856 demonstrates positive allosteric modulation of IGF1R at concentrations similar to Trk potentiation [1]. Concurrent use with insulin, insulin analogs, or IGF1R-targeting agents may produce additive effects on IGF1R signaling pathways. The clinical relevance is uncertain but should be considered in research protocols involving diabetic or metabolically compromised subjects.

11. Adverse Events and Safety

11.1 Preclinical safety

Preclinical safety studies have not identified dose-limiting toxicities at the studied dose ranges. The compound was well tolerated in rodent species at doses substantially exceeding the pharmacologically effective range [5, 7]. Importantly, ACD856 did not produce the pain, hyperalgesia, or allodynia that have historically limited direct neurotrophin agonist approaches (such as NGF protein administration), consistent with the allosteric modulation mechanism that requires endogenous ligand for receptor activation [5, 6].

11.2 Phase 1 safety: single ascending dose

In the SAD study (n = 56, doses 1 to 150 mg), no serious adverse events were reported [9]. No dose-related trends were observed in safety parameters including vital signs, electrocardiographic intervals (including QTc), physical examinations, or clinical laboratory values. The most common adverse event was headache, reported in 8 subjects at mild intensity and without a clear dose-response relationship. No treatment-emergent liver enzyme elevations were observed on follow-up [9].

11.3 Phase 1 safety: multiple ascending dose

In the MAD study (n = 24, doses 10 to 90 mg daily for seven days), no serious adverse events were reported [10, 11]. The most common adverse events were headache and nausea, both mild in intensity. Two participants showed elevated pancreatic enzymes (amylase and/or lipase) that normalized without intervention and were not associated with clinical symptoms of pancreatitis [10]. No dose-dependent adverse event patterns were identified across the 10 to 90 mg range.

11.4 Theoretical safety considerations

The pan-Trk PAM mechanism raises theoretical considerations regarding proliferative signaling. Trk receptors, particularly TrkA and TrkB, have been implicated in the biology of certain malignancies (neuroblastoma, medulloblastoma, certain carcinomas) [6]. The allosteric modulation mechanism, which amplifies existing neurotrophin signaling rather than constitutively activating the receptor, may mitigate this concern relative to direct agonist approaches, but long-term safety monitoring for proliferative endpoints will be appropriate in extended clinical studies.

The IGF1R and FGFR1 positive allosteric modulation observed at concentrations similar to Trk potentiation [1] broadens the receptor tyrosine kinase pharmacology and introduces additional theoretical considerations regarding metabolic and proliferative effects that should be monitored in longer-duration clinical studies.

11.5 Comparison to other neurotrophin approaches

The safety profile of ACD856 in Phase 1 studies stands in favorable contrast to the historical experience with direct neurotrophin administration. Recombinant NGF protein administered intracerebroventricularly in Alzheimer's disease patients produced pain as a dose-limiting adverse event [19]. The allosteric modulation strategy circumvents this limitation by preserving the spatial selectivity of neurotrophin signaling [6].

12. Comparable Compounds Assessment

This section presents a structured comparative assessment of five neurotrophin-targeting candidates against ACD856, evaluated against five competency standards: novelty, effect size, promising potential (current clinical state and trajectory), side-effect profile, and overall validation. The five candidates were selected as the principal Trk-targeting or neurotrophin-mimetic compounds with substantive research programs in cognitive or neurodegenerative applications.

12.1 E2511 (Eisai)

Mechanism: Selective TrkA-biased positive allosteric modulator. Unlike the pan-Trk activity of ACD856, E2511 is biased toward TrkA, the NGF receptor, with the goal of selectively supporting cholinergic neuron survival and reinnervation [21, 22].

Development trajectory: Eisai initiated a Phase 1 single ascending dose study in September 2020 in 40 healthy adults and 5 elderly participants, followed by a Phase 1 multiple ascending dose study with 14-day dosing in healthy subjects [21]. Results presented at the 2023 CTAD conference demonstrated CSF-to-plasma ratios of 15 to 32 percent and CSF proteomic changes in axonal and synaptic markers consistent with TrkA-mediated cholinergic reinnervation [21]. One Japanese participant at the highest dose experienced a serious event of mania and was withdrawn. A Phase 1b dose-finding trial is planned.

Novelty: Moderate. TrkA-selective PAM represents a mechanistically related but subtype-selective variant of the approach embodied by ACD856.

Effect size: Preclinical studies demonstrated cholinergic reinnervation effects; no clinical cognitive efficacy data are available.

Promising potential: Moderate. The compound is in early Phase 1 development with a large-company sponsor (Eisai) and complementary positioning alongside lecanemab (Eisai's anti-amyloid antibody).

Side-effect profile: Generally favorable in Phase 1, but the mania event at the highest dose is a safety signal requiring monitoring. The shorter half-life (3.2 hours) relative to ACD856 (approximately 20 hours) may limit steady-state brain exposure but may also reduce accumulation-related risks.

Overall validation: Low to moderate. Phase 1 only, with biomarker but not cognitive efficacy data.

Comparison to ACD856: E2511 is a subtype-selective TrkA PAM with a shorter half-life and more focused cholinergic mechanism. ACD856 has the advantage of pan-Trk activity (supporting both cholinergic and hippocampal BDNF pathways), a longer half-life enabling once-daily dosing, and more advanced preclinical cognitive and antidepressant characterization. E2511 has the advantage of a major pharmaceutical company sponsor and strategic complementarity with lecanemab.

12.2 7,8-Dihydroxyflavone (7,8-DHF)

Mechanism: Reported TrkB agonist. 7,8-DHF is a naturally occurring flavone identified as binding the extracellular domain of TrkB and inducing receptor dimerization and downstream signaling [23, 24]. The compound crosses the blood-brain barrier and is orally bioavailable, though with modest pharmacokinetic properties.

Development trajectory: 7,8-DHF has been extensively characterized in preclinical models over more than a decade. It reversed memory deficits in 5XFAD transgenic Alzheimer's mice, prevented synaptic loss and memory deficits in multiple Alzheimer's models, and reduced BACE1 elevation [23, 24]. A prodrug (R13) with improved oral bioavailability and brain exposure has been developed [25]. No human clinical trials have been conducted.

Novelty: Low. The compound has been in the research literature since 2010 and is now the historical reference compound for small-molecule TrkB agonism.

Effect size: Substantial in preclinical models. Effect sizes in Alzheimer's transgenic mice are moderate to large on synaptic preservation and memory endpoints.

Promising potential: Low. No clinical development. The compound is limited by modest oral bioavailability, a moderate pharmacokinetic profile, and controversy regarding whether it truly activates TrkB directly (some reports suggest failure to activate TrkB or downstream signaling in certain assay systems) [6, 26].

Side-effect profile: Preclinical only; no human safety data. Rodent tolerability has been acceptable.

Overall validation: Moderate as a preclinical research tool; low as a clinical candidate.

Comparison to ACD856: 7,8-DHF operates through orthosteric TrkB agonism (if confirmed), which lacks the spatial selectivity of the allosteric approach of ACD856. ACD856 has the advantages of pan-Trk activity, more favorable pharmacokinetics (approximately 20-hour half-life, near-complete bioavailability), Phase 1 clinical data, and confirmed human CNS penetration. 7,8-DHF has the advantage of a larger preclinical literature and availability as an inexpensive research tool, but reproducibility concerns and absent clinical development limit its translational positioning.

12.3 LM22A-4

Mechanism: Originally described as a selective TrkB agonist; subsequent analysis suggests indirect transactivation of Trk receptors rather than direct TrkB binding [27, 28]. The compound is a small peptide mimetic (98 percent smaller than BDNF) that activates TrkB, AKT, and ERK signaling in vivo following intranasal administration.

Development trajectory: LM22A-4 has been characterized in preclinical models of Alzheimer's disease, traumatic brain injury, stroke, Huntington's disease, and Rett syndrome [27, 28, 29]. The compound prevented neuronal cell death induced by amyloid-beta, MDD+ (Parkinson's model), and quinolinic acid (Huntington's model) with efficacy comparable to BDNF. In vivo, LM22A-4 reduced cholinergic neuron atrophy in Alzheimer's disease transgenic models [29]. No clinical trials have been conducted.

Novelty: Moderate. The peptide mimetic approach to TrkB activation is distinct from both the small-molecule PAM approach of ACD856 and the flavone agonism of 7,8-DHF.

Effect size: Moderate to substantial in preclinical models across multiple neurodegenerative indications.

Promising potential: Low to moderate. No clinical development. The intranasal route of administration in preclinical studies may present translational challenges.

Side-effect profile: Preclinical only. No human safety data.

Overall validation: Low. Preclinical research tool with broad neuroprotective characterization but no clinical translation.

Comparison to ACD856: LM22A-4 operates through a distinct mechanism (indirect Trk transactivation rather than positive allosteric modulation of the kinase domain). ACD856 has the advantages of oral bioavailability, confirmed human pharmacokinetics and CNS penetration, and Phase 1 clinical data. LM22A-4 has the advantage of broad preclinical characterization across multiple neurodegenerative models and a more established research literature.

12.4 ACD855 (Ponazuril)

Mechanism: Pan-Trk positive allosteric modulator, the direct structural predecessor to ACD856, sharing the triazinetrione scaffold and the Trk-PAM mechanism [3, 4]. ACD855 is the sulfone metabolite of the veterinary antiparasitic toltrazuril and is an approved coccidiostat in veterinary medicine.

Development trajectory: ACD855 was the first Trk-PAM identified in the AlzeCure 2013 screen and was the initial research compound that validated the Trk-PAM concept [3, 4]. Preclinical cognitive enhancement was demonstrated. The compound was not advanced to human clinical development owing to an elimination half-life of approximately 68 days, rendering it unsuitable for dose titration and steady-state management in humans.

Novelty: Moderate at the time of identification (2013); the concept has since been superseded by ACD856.

Effect size: Comparable to ACD856 in preclinical Trk-PAM activity assays, given the shared mechanism.

Promising potential: Low. Development was discontinued in favor of ACD856. The compound persists as a research tool and as a veterinary medicine.

Side-effect profile: The compound has an established veterinary safety database. The 68-day half-life is the principal limitation for human use.

Overall validation: Low as a clinical candidate. The compound served its purpose as a proof-of-concept tool for the Trk-PAM mechanism and as the structural starting point for ACD856.

Comparison to ACD856: ACD856 is the direct successor compound with a 70-fold improvement in oral clearance while retaining the Trk-PAM mechanism. ACD856 is superior on all clinical translation parameters.

12.5 BNN27

Mechanism: Synthetic dehydroepiandrosterone derivative acting as a TrkA agonist and p75NTR antagonist [30]. BNN27 binds the extracellular domain of TrkA and activates downstream signaling, while simultaneously antagonizing the p75 neurotrophin receptor (which mediates pro-apoptotic signaling).

Development trajectory: BNN27 has been characterized in preclinical models of neurodegeneration, including Alzheimer's disease, diabetic retinopathy, and cerebellar degeneration [30]. The dual TrkA agonist/p75NTR antagonist mechanism is pharmacologically distinctive. No clinical trials have been conducted.

Novelty: High. The dual agonist/antagonist mechanism targeting both the pro-survival (TrkA) and pro-apoptotic (p75NTR) arms of neurotrophin signaling is mechanistically distinctive.

Effect size: Moderate in preclinical models.

Promising potential: Low. No clinical development. Limited research literature compared to the other comparators.

Side-effect profile: Preclinical only. No human safety data.

Overall validation: Low. Early-stage preclinical compound.

Comparison to ACD856: BNN27 operates through orthosteric TrkA agonism and p75NTR antagonism, a fundamentally different mechanism from the allosteric Trk kinase potentiation of ACD856. ACD856 has the advantages of pan-Trk activity, oral bioavailability, Phase 1 clinical data, and confirmed human CNS penetration. BNN27 has the theoretical advantage of dual pathway modulation (pro-survival and anti-apoptotic) but lacks clinical translation data.

12.6 Comparator summary

The five compounds occupy distinct positions in the neurotrophin therapeutics landscape. **E2511** represents the most closely related clinical-stage compound, with TrkA-selective PAM pharmacology and early Phase 1 data from a major pharmaceutical sponsor. **7,8-Dihydroxyflavone** is the historical reference compound for small-molecule TrkB agonism, with extensive preclinical but no clinical data and unresolved mechanism-of-action questions. **LM22A-4** is a broadly characterized peptide mimetic neuroprotectant with preclinical evidence across multiple indications but no clinical translation. **ACD855** is the direct structural predecessor that validated the Trk-PAM concept but was unsuitable for clinical development owing to extreme half-life. **BNN27** is a mechanistically novel dual TrkA agonist/p75NTR antagonist at an early preclinical stage.

ACD856 occupies a distinctive position among these comparators as the only pan-Trk PAM with Phase 1 clinical data, confirmed human blood-brain barrier penetration, a pharmacokinetic profile suitable for once-daily oral dosing, and demonstrated central target engagement by quantitative EEG. The allosteric mechanism distinguishes ACD856 from the orthosteric agonist approaches (7,8-DHF, LM22A-4, BNN27) by preserving the spatiotemporal specificity of endogenous neurotrophin signaling, an advantage reflected in the absence of pain and hyperalgesia in clinical studies. The pan-Trk activity distinguishes ACD856 from the TrkA-selective E2511 by providing simultaneous support for both cholinergic (TrkA-NGF) and hippocampal plasticity (TrkB-BDNF) pathways.

The principal uncertainty in the ACD856 development trajectory is the absence of Phase 2 efficacy data in Alzheimer's disease patients. The Phase 1 safety, pharmacokinetic, and target engagement data are favorable, and the preclinical cognitive enhancement and neuroprotection data are substantial, but the clinical translation gap between Phase 1 healthy volunteer data and Phase 2 patient efficacy remains to be bridged. The EUR 2.5 million EIC grant provides funding for the Phase IIa study, and the outcome of that study will be the critical determinant of the compound's clinical trajectory.

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