

RESEARCH MONOGRAPH . COMPOUND PROFILE

J-147

A phenyl hydrazide small molecule developed at the Salk Institute through iterative phenotypic optimization of curcumin, identified as a modulator of mitochondrial ATP synthase alpha subunit (ATP5A), with demonstrated neuroprotective, neurotrophic, and geroprotective activity across multiple rodent models of Alzheimer's disease and accelerated aging, and advanced to Phase 1 clinical evaluation.

DOCUMENT	KDC-MN-1460
ISSUED	2026-05-13
REVISION	1.0
AUTHOR	Kodi ac biolabs Research
COMPOUND CLASS	Phenyl hydrazide neurotrophic compound derived from curcumin optimization; mitochondrial ATP synthase (ATP5A) modulator with geroprotective and neuroprotective activity

ABSTRACT

J-147 (CAS 1146963-51-0; molecular formula C₁₈H₁₇F₃N₂O₂; molecular weight 350.34) is a synthetic phenyl hydrazide small molecule developed at the Salk Institute for Biological Studies by the laboratory of David Schubert through iterative phenotypic optimization of the natural product curcumin. The compound was first reported by Chen et al. in 2011 as the product of a medicinal chemistry campaign that began with curcumin, proceeded through the intermediate hybrid compound CNB-001 (a curcumin and cyclohexyl-bisphenol A fusion), and culminated in J-147, a structurally distinct molecule with substantially improved potency, oral bioavailability, and blood-brain barrier penetration relative to curcumin [1]. J-147 was identified through a cell-based phenotypic screening platform employing six simultaneous assays for age-associated neurotoxicities, including oxidative stress, trophic factor withdrawal, excitotoxicity, and amyloid-beta toxicity, with EC₅₀ values between 10 and 200 nanomolar across the panel [1, 2]. The molecular target of J-147 was identified in 2018 by Goldberg et al. using drug affinity responsive target stability (DARTS) and affinity precipitation with a biotinylated derivative as the alpha subunit of mitochondrial ATP synthase (ATP5A) [3]. J-147 produces a partial (approximately 20 percent) inhibition of ATP synthase activity, leading to a transient increase in intracellular calcium, sustained activation of the calcium/calmodulin-dependent protein kinase kinase beta (CAMKK2) and AMPK/mTOR signaling axis, and elevated cellular levels of ATP, NAD⁺, NADH, and NADPH [3, 4]. This bioenergetic modulation is consistent with a hormetic mitochondrial mechanism and parallels genetic manipulations of ATP synthase

subunits that extend lifespan in *Caenorhabditis elegans* and *Drosophila melanogaster* [3]. Behavioral efficacy has been demonstrated in multiple rodent models. In aged (20-month-old) APP^{swe}/PS1^{deltaE9} transgenic mice, oral J-147 at 10 mg/kg/day reversed cognitive deficits, reduced soluble amyloid-beta levels, elevated brain-derived neurotrophic factor (BDNF) and nerve growth factor (NGF), and reduced neuroinflammatory markers [5]. In SAMP8 (senescence-accelerated mouse prone 8) mice, J-147 at 10 mg/kg/day for seven months reversed age-associated transcriptomic and metabolomic signatures, with treated old animals resembling young controls on multiple molecular indices [6, 7]. Geroprotective effects including lifespan extension were reported in *Drosophila* fed J-147 or structurally related candidates [8]. A Phase 1 clinical trial (NCT03838185), sponsored by Abrexa Pharmaceuticals, was initiated in February 2019 as a randomized, double-blind, placebo-controlled study of single ascending oral doses in healthy young and elderly volunteers. The study completed in February 2020; formal results have not been published in a peer-reviewed forum as of the most recent monograph revision [9]. David Schubert, the principal investigator and inventor of J-147, passed away in August 2020 [10]. The compound is not approved by any regulatory authority. It is available as a research-grade preparation from multiple chemical suppliers at greater than 98 percent purity. Investigators should obtain analytical confirmation of identity and purity on every lot.

1. Compound Identification

1.1 Names, synonyms, and registry identifiers

Chemical name (IUPAC): N-(2,4-dimethylphenyl)-2,2,2-trifluoro-N'-[(E)-(3-methoxyphenyl)methylidene]acetohydrazide.

Common name: J-147. The compound name derives from the internal laboratory designation at the Salk Institute Cellular Neurobiology Laboratory. No International Nonproprietary Name has been assigned.

Development codes: J-147 (Salk Institute); the compound has also been referenced as J147 (without hyphen) in some publications and vendor catalogs.

Chemical Abstracts Service registry number: 1146963-51-0.

PubChem Compound Identifier: CID 25229652.

DrugBank identifier: DB13957.

1.2 Structural class and chemistry

J-147 is a phenyl hydrazide (acetohydrazide) compound bearing a trifluoroacetyl group, a 2,4-dimethylphenyl ring on the hydrazide nitrogen, and a 3-methoxybenzylidene group forming an (E)-configured hydrazone. The compound is structurally unrelated to the polyphenolic curcuminoid scaffold from which its development began; the iterative optimization campaign through CNB-001 eliminated the beta-diketone, the bis-phenol, and the conjugated heptadienone elements of curcumin and replaced them with a compact hydrazide core [1, 2].

Molecular formula: C₁₈H₁₇F₃N₂O₂.

Molecular weight: 350.34 g/mol.

Exact mass: 350.1242 g/mol (monoisotopic).

SMILES: O=C(N(C1=CC=C(C)C=C1C)/N=C/C2=CC=CC(OC)=C2)C(F)(F)F.

Physical properties: Off-white to pale yellow crystalline powder. Soluble in dimethyl sulfoxide (DMSO) to approximately 70 mg/mL (200 mM) and in ethanol to approximately 100 mM. Sparingly soluble in water; aqueous formulations require co-solvent (DMSO, polyethylene glycol, or cyclodextrin complexation). The compound is lipophilic, consistent with favorable blood-brain barrier penetration. Predicted cLogP values from multiple computational platforms fall in the range of 3.5 to 4.5.

Stereochemistry: The benzylidene double bond adopts the (E) configuration as the thermodynamically stable isomer. No additional stereocenters are present.

1.3 Synthesis

The published synthesis of J-147 proceeds through condensation of 2,2,2-trifluoro-N-(2,4-dimethylphenyl)acetohydrazide with 3-methoxybenzaldehyde under acid-catalyzed or thermal conditions to form the (E)-hydrazone product [1, 2]. The acetohydrazide precursor is prepared by acylation of 2,4-dimethylphenylhydrazine with trifluoroacetic anhydride or ethyl trifluoroacetate. The condensation step typically proceeds in ethanol or methanol with catalytic acetic acid at reflux for 2 to 4 hours. The product crystallizes from the reaction mixture or is obtained by concentration and recrystallization from ethanol or ethyl acetate. Yields of 70 to 90 percent are reported for the condensation step. Purity is confirmed by high-performance liquid chromatography (HPLC), nuclear magnetic resonance (NMR) spectroscopy, and mass spectrometry. The synthesis is straightforward and scalable; the compound has been produced at multi-gram quantities for preclinical toxicology and clinical supply.

2. Abstract

J-147 is a phenyl hydrazide neurotrophic compound developed at the Salk Institute for Biological Studies through an iterative phenotypic screening and medicinal chemistry optimization campaign beginning from curcumin [1]. The compound was reported by Chen et al. (2011) and was selected from a library of curcumin and CNB-001 derivatives on the basis of potent neuroprotective activity (EC₅₀ 10 to 200 nM) across six cell-based assays for age-associated neurotoxicities, including oxidative glutathione depletion, trophic factor withdrawal, excitotoxicity, and direct amyloid-beta peptide toxicity [1, 2].

The molecular target was identified in 2018 by Goldberg et al. as the alpha subunit of mitochondrial ATP synthase (ATP5A), using drug affinity responsive target stability (DARTS) and affinity precipitation with biotinylated J-147 [3]. Binding produces partial inhibition of ATP synthase (approximately 20 percent reduction in activity), an increase in intracellular calcium, and sustained activation of the CAMKK2/AMPK/mTOR signaling axis, resulting in elevated ATP, NAD⁺, and NADPH and a broad shift in cellular bioenergetic state [3, 4]. This mechanism parallels genetic knockdown of ATP synthase subunits that extends lifespan in *C. elegans* and *Drosophila* and positions J-147 as a pharmacological modulator of a conserved longevity pathway [3].

Preclinical efficacy has been demonstrated in multiple models. In aged APP^{swe}/PS1^{deltaE9} transgenic Alzheimer's disease mice (20 months of age at treatment initiation), oral J-147 at 10 mg/kg/day for three months reversed cognitive deficits in contextual fear conditioning and the Barnes maze, reduced soluble amyloid-beta 1-40 and 1-42, elevated hippocampal BDNF and NGF, and reduced markers of oxidative stress and neuroinflammation [5]. In the SAMP8 model of accelerated aging, J-147 at 10 mg/kg/day for seven months reversed age-associated transcriptomic, metabolomic, and proteomic signatures, with treated old mice clustering with young controls on principal component analyses of brain gene expression [6, 7]. The compound also reduced cognitive deficits in scopolamine-induced amnesia models, performing comparably to donepezil for short-term memory and superiorly for spatial memory in the same paradigm [5].

Pharmacokinetic studies in mice demonstrate oral bioavailability of approximately 28 percent at 20 mg/kg, with brain concentrations reaching approximately 600 nM at 2 hours post-dose and a brain-to-blood ratio of approximately 0.5, indicating favorable central nervous system penetration [2, 11]. The compound is lipophilic, has high blood-brain barrier permeability confirmed by MDCK-MDR1 cell monolayer assays, and is metabolized predominantly through hepatic pathways [11].

A Phase 1 clinical trial (NCT03838185) was initiated in February 2019 by Abrexa Pharmaceuticals as a randomized, double-blind, placebo-controlled study of single ascending doses in healthy young and elderly volunteers. The study was completed in February 2020; no peer-reviewed publication of results has appeared [9]. Preclinical toxicology studies (CeeTox analysis) estimated a CTox (concentration producing toxicity in a 14-day rat repeat dose study) of approximately 90 micromolar, and the compound was not genotoxic in standard battery assays [12]. No Phase 2 or efficacy trials in patients with Alzheimer's disease have been initiated as of the most recent monograph revision.

J-147 is not approved by any regulatory authority. It is available from multiple research chemical suppliers at greater than 98 percent purity. The compound represents a distinct pharmacological approach to neurodegeneration and aging, operating through mitochondrial bioenergetic modulation rather than amyloid clearance, tau aggregation inhibition, or cholinesterase inhibition.

3. Discovery and Development History

3.1 Origin and design rationale

J-147 was developed at the Salk Institute for Biological Studies in San Diego, California, in the Cellular Neurobiology Laboratory directed by David Schubert. The program originated from the observation that curcumin, the principal polyphenol of turmeric (*Curcuma longa*), demonstrated broad neuroprotective activity in cell culture assays but was not a viable drug candidate owing to negligible oral bioavailability (less than 1 percent in most species), rapid hepatic glucuronidation and sulfation, poor aqueous solubility, and chemical instability at physiological pH [1, 2]. Rather than pursuing incremental modification of the curcumin scaffold, the Schubert laboratory adopted a phenotypic screening strategy: iterative design and testing against multiple cell-based assays for age-associated neurotoxicity, with the screening hit profile rather than a single molecular target driving compound selection.

3.2 Medicinal chemistry progression

The first stage of optimization produced CNB-001, a hybrid molecule combining structural elements of curcumin and cyclohexyl-bisphenol A. CNB-001 was more potent and more stable than curcumin in the screening panel and showed neuroprotective activity in rodent models, but its pharmacokinetic profile and potency were insufficient for clinical candidacy [1, 13]. The second stage produced a large library of CNB-001 derivatives. J-147 was selected from this library as the most potent compound across the six-assay panel, with EC₅₀ values between 10 and 200 nanomolar [1]. Despite its synthetic origin in a curcumin optimization program, J-147 shares no structural similarity with curcumin or CNB-001; the phenyl hydrazide scaffold is a distinct chemotype.

3.3 Publication history

The initial report by Chen et al. (2011) in PLoS ONE described the synthesis, cell-based activity, and in vivo efficacy of J-147 in APP^{swe}/PS1^{deltaE9} transgenic mice [1]. Prior et al. (2013) published the comprehensive in vivo study in aged transgenic

mice in Alzheimer's Research and Therapy [5]. Currais et al. (2015) reported the multiomics analysis in SAMP8 mice in Aging (Albany NY) [6]. Prior et al. (2014) provided a perspective on phenotypic screening for Alzheimer's disease drug discovery in ACS Chemical Neuroscience [2]. Goldberg et al. (2018) identified the ATP5A molecular target in Aging Cell [3]. Kepchia et al. (2021) reported geroprotective effects in *Drosophila* and mice in Aging (Albany NY) [8].

3.4 Clinical translation

The compound was licensed to Abrexa Pharmaceuticals for clinical development. A Phase 1 randomized, double-blind, placebo-controlled study (NCT03838185) was initiated in February 2019 to assess safety, tolerability, and pharmacokinetics of single ascending oral doses of J-147 in healthy young (18 to 55 years) and elderly (65 to 85 years) volunteers. The study was completed in February 2020 [9]. The principal investigator and inventor, David Schubert, passed away on August 6, 2020, at the age of 77 [10]. No peer-reviewed publication of Phase 1 results has appeared. No Phase 2 trials have been registered. The current development status is uncertain; the compound is not in active commercial development as of the most recent monograph revision.

4. Mechanism of Action

J-147 is a multi-pathway modulator whose primary molecular target is the alpha subunit of the mitochondrial F1Fo-ATP synthase complex (ATP5A). The target identification, downstream signaling, and secondary pharmacological activities are described below.

4.1 ATP synthase alpha subunit (ATP5A) binding

The molecular target of J-147 was identified by Goldberg et al. (2018) using two independent chemical biology approaches [3]. Drug affinity responsive target stability (DARTS), an unbiased method in which drug binding protects a protein from protease digestion, identified ATP5A as the most enriched protein in J-147-treated mitochondrial lysates compared to vehicle controls. In parallel, affinity precipitation using a biotinylated analog of J-147 (BJ-147) followed by streptavidin pulldown and mass spectrometry confirmed ATP5A as the principal binding partner [3]. The binding was validated by surface plasmon resonance and by thermal shift assays demonstrating J-147-induced stabilization of purified recombinant ATP5A.

4.2 Downstream signaling through CAMKK2/AMPK/mTOR

J-147 binding to ATP5A produces a partial (approximately 20 percent) inhibition of ATP synthase enzymatic activity [3]. This partial inhibition is sufficient to transiently elevate intracellular calcium through modulation of mitochondrial calcium handling, leading to sustained activation of calcium/calmodulin-dependent protein kinase kinase beta (CAMKK2). CAMKK2 activation phosphorylates and activates AMP-activated protein kinase (AMPK), which in turn modulates the mTOR pathway [3, 4]. The net bioenergetic consequence is an increase in cellular ATP, NAD⁺, NADH, and NADPH, consistent with a hormetic or compensatory upregulation of mitochondrial biogenesis and oxidative phosphorylation in response to partial ATP synthase inhibition [3].

The CAMKK2/AMPK/mTOR axis is a canonical longevity signaling pathway. Genetic manipulations of ATP synthase subunits in *C. elegans* (atp-3 RNA interference) and *Drosophila* (ATP synthase d knockdown) produce lifespan extension through the same signaling axis, providing evolutionary conservation evidence for the mechanism [3].

4.3 Neurotrophic factor induction

J-147 treatment elevates hippocampal brain-derived neurotrophic factor (BDNF) and nerve growth factor (NGF) in aged transgenic Alzheimer's disease mice and in SAMP8 mice [5, 6]. BDNF-responsive proteins, including Homer-1, Egr-3, and the activity-regulated cytoskeleton-associated protein (Arc/Arg3.1), are concurrently up-regulated [5]. The neurotrophic factor induction is likely downstream of AMPK activation and enhanced mitochondrial function, as mitochondrial bioenergetic state is a known regulator of BDNF transcription through PGC-1alpha and CREB signaling [3, 5].

4.4 Anti-amyloid and anti-inflammatory effects

In APPswe/PS1deltaE9 transgenic mice, J-147 reduces soluble amyloid-beta 1-40 and 1-42 levels and reduces the number and area of hippocampal amyloid plaques [5]. The mechanism is indirect: J-147 does not inhibit beta-secretase or gamma-secretase and does not directly bind amyloid-beta peptide. The reduction in amyloid burden is attributed to improved neuronal health, enhanced proteostatic clearance, and reduced neuroinflammation [5, 6]. J-147 also reduces markers of neuroinflammation including GFAP (astrocytic activation), Iba1 (microglial activation), and proinflammatory cytokines (TNF-alpha, IL-1beta) in treated animals [5, 7].

4.5 Synaptic and electrophysiological effects

J-147 preserves synaptic protein levels (synaptophysin, PSD-95, GluR1) in aged transgenic mice, reduces long-term potentiation (LTP) deficits in hippocampal slices from treated animals, and improves spatial and contextual memory performance [5]. These synaptic effects are consistent with the combined neurotrophic factor induction, reduced neuroinflammation, and improved mitochondrial bioenergetics described above.

4.6 Composite pharmacology

The composite pharmacology of J-147 is therefore a primary mitochondrial bioenergetic mechanism (ATP5A binding, CAMKK2/AMPK activation, NAD⁺ elevation) that drives multiple downstream neuroprotective outputs (BDNF/NGF induction, anti-inflammatory signaling, synaptic preservation, amyloid reduction). This multi-output pharmacology from a single molecular target distinguishes J-147 from most Alzheimer's disease drug candidates, which target a single downstream pathway (amyloid clearance, tau aggregation, cholinesterase inhibition, or NMDA receptor modulation).

5. Pharmacokinetics and Routes of Administration

5.1 Absorption

J-147 is absorbed from the gastrointestinal tract after oral administration in rodents. Oral bioavailability in mice was calculated at approximately 28 percent following a single 20 mg/kg dose [2, 11]. The compound is lipophilic (estimated cLogP 3.5 to 4.5) and is absorbed from the small intestine; co-administration with a lipid vehicle (corn oil, sesame oil, or polyethylene glycol) may enhance absorption in research settings, though this has not been systematically characterized.

5.2 Distribution

J-147 distributes extensively to the central nervous system. Following a single 20 mg/kg oral dose in mice, brain concentrations reached approximately 600 nanomolar at 2 hours post-dose, with a brain-to-blood ratio of approximately 0.5 [2, 11]. Blood-brain barrier penetration assessed by MDCK-MDR1 cell monolayer permeability assay demonstrated high permeability [11]. The favorable CNS penetration is consistent with the compound's lipophilicity, low molecular weight (350 Da), and absence of efflux transporter substrate activity at clinically relevant concentrations. Volume of distribution has not been formally reported but is expected to be large based on the lipophilicity and tissue distribution profile.

5.3 Metabolism

Metabolic pathways for J-147 have not been comprehensively characterized in published literature. The compound is expected to undergo hepatic oxidative metabolism (cytochrome P450-mediated) and possible hydrolysis of the hydrazide bond. No published data identify the specific CYP isoforms responsible for J-147 metabolism. The CeeTox in vitro toxicology analysis identified a CTox value of approximately 90 micromolar, suggesting a moderate therapeutic index [12]. Plasma protein binding has not been formally reported in published form.

5.4 Elimination

Elimination half-life and clearance in rodents have not been formally published in the peer-reviewed literature. The brain concentration time-course data from Prior et al. (2014) suggest a brain half-life on the order of several hours, consistent with the chronic dosing regimen of 10 mg/kg/day used in efficacy studies [2, 5].

5.5 Routes of administration

The compound has been administered orally in all published in vivo efficacy studies. In chronic rodent studies, J-147 was incorporated into the diet at concentrations calculated to deliver approximately 10 mg/kg/day [5, 6]. For acute dosing, oral gavage in corn oil or similar lipid vehicle has been used [2]. The Phase 1 clinical trial (NCT03838185) employed oral administration [9]. Parenteral routes (intraperitoneal, intravenous) have been used in selected mechanistic studies; these are research routes and are not relevant to clinical translation.

5.6 Special populations

No data on special populations (hepatic impairment, renal impairment, pediatric, geriatric pharmacokinetics) have been published in peer-reviewed form. The Phase 1 study enrolled both young (18 to 55 years) and elderly (65 to 85 years) healthy volunteers, which would provide comparative pharmacokinetic data across age groups if results are published [9].

6. Preclinical Pharmacology

6.1 Cell-based neuroprotection assays

J-147 was selected from a library of curcumin and CNB-001 derivatives on the basis of potent activity across six cell-based assays for age-associated neurotoxicities [1, 2]. The assays included: (a) MC65 cells undergoing conditional expression of the C-terminal fragment of amyloid precursor protein (APP-CTF toxicity); (b) HT22 hippocampal neuronal cells exposed to oxidative glutathione depletion by glutamate or iodoacetic acid; (c) primary cortical neurons subjected to trophic factor withdrawal; (d) PC12 cells exposed to 6-hydroxydopamine; (e) cortical neurons exposed to NMDA-type excitotoxicity; and (f) cortical neurons exposed to synthetic amyloid-beta 1-42 oligomers. EC50 values ranged from 10 to 200 nanomolar across this panel, with the most potent activity observed in the MC65 and oxidative stress assays [1].

6.2 APP^{swe}/PS1^{deltaE9} transgenic mice (aged)

Prior et al. (2013) treated 20-month-old APP^{swe}/PS1^{deltaE9} transgenic mice (a model of familial Alzheimer's disease expressing Swedish-mutant APP and presenilin 1 with exon 9 deletion) with J-147 at 10 mg/kg/day in the diet for three months [5]. Behavioral testing at the conclusion of treatment demonstrated significant reversal of cognitive deficits: treated transgenic mice performed comparably to wild-type controls on the Barnes maze (spatial memory) and on contextual fear conditioning (associative memory). Hippocampal BDNF was elevated approximately 2-fold and NGF approximately 1.5-fold relative to untreated transgenic controls. Soluble amyloid-beta 1-42 was reduced by approximately 35 percent. Markers of oxidative stress (lipid peroxidation, protein carbonylation) and neuroinflammation (GFAP, CD45 immunoreactivity) were significantly reduced. Synaptic protein markers (synaptophysin, PSD-95, GluR1) were preserved at levels approaching wild-type controls [5].

6.3 SAMP8 accelerated aging model

Currais et al. (2015) treated SAMP8 mice (a model of accelerated aging with spontaneous cognitive decline, elevated oxidative stress, and neuroinflammation) with J-147 at 10 mg/kg/day in the diet for seven months beginning at 3 months of age [6]. A comprehensive multiomics analysis (transcriptomics, proteomics, metabolomics) of hippocampal tissue demonstrated that J-147-treated old SAMP8 mice clustered with young SAMP8 controls on principal component analysis of gene expression, while untreated old SAMP8 mice formed a distinct cluster [6]. The reversal of age-associated gene expression changes was broad, affecting mitochondrial biogenesis, synaptic function, inflammation, and lipid metabolism pathways. Behavioral testing confirmed rescue of spatial memory in the radial arm water maze [6, 7].

6.4 Geroprotective effects

Kepchia et al. (2021) reported that J-147, along with the related compounds CMS121 and CAD31, extended median lifespan in *Drosophila melanogaster* when administered in the diet [8]. In mice, J-147 improved physiological markers of aging in brain and kidney, though the molecular pathways engaged differed between the two organs [8]. These geroprotective effects are consistent with the identification of ATP synthase as the molecular target and with the conservation of the ATP synthase/AMPK longevity mechanism across species [3, 8].

6.5 Additional preclinical models

J-147 has been evaluated in additional preclinical contexts beyond Alzheimer's disease models. Reports include activity in traumatic brain injury (TBI) models, where J-147 treatment reduced neuronal endoplasmic reticulum stress through AMPK/SREBP-1 pathway modulation [14]; in scopolamine-induced amnesia, where J-147 performed comparably to donepezil for short-term memory and superiorly for spatial memory [5]; and in tPA-induced brain hemorrhage models relevant to stroke, where J-147 reduced hemorrhage volume and improved neurological outcomes [15]. These additional models support the broad neuroprotective profile predicted by the mitochondrial bioenergetic mechanism.

7. Clinical Evidence Base

7.1 Phase 1 clinical trial

The sole registered clinical trial for J-147 is NCT03838185, a Phase 1, randomized, double-blind, placebo-controlled, parallel-design study of single ascending oral doses of J-147 in healthy young (18 to 55 years) and elderly (65 to 85 years) volunteers [9]. The study was sponsored by Abrexa Pharmaceuticals and was conducted in the United States. The study was initiated in February 2019 and completed in February 2020.

The primary endpoints were safety and tolerability (adverse event incidence, vital signs, ECG, clinical laboratory parameters). Secondary endpoints included pharmacokinetic parameters (C_{max} , T_{max} , AUC, $t_{1/2}$) of J-147 and its metabolites. Exploratory endpoints included pharmacodynamic biomarkers.

As of the most recent monograph revision, no peer-reviewed publication of Phase 1 results has appeared, and the results have not been posted on ClinicalTrials.gov. No safety signals requiring study termination were reported during the trial conduct period [9].

7.2 Absence of efficacy data in patients

No clinical trial has evaluated J-147 in patients with Alzheimer's disease, mild cognitive impairment, or any other neurological condition. The clinical evidence base is therefore limited to the unpublished Phase 1 safety and pharmacokinetic study in healthy volunteers.

7.3 Translational considerations

The translational path from preclinical to clinical is complicated by several factors. The chronic rodent dosing regimen (10 mg/kg/day for 3 to 7 months) translates by allometric scaling to a human-equivalent dose of approximately 0.8 to 1.6 mg/kg/day, or approximately 50 to 110 mg/day for a 70 kg adult [2]. The Phase 1 study was designed to evaluate single ascending doses, and the specific doses tested

have not been publicly disclosed. The absence of published Phase 1 results limits the ability to assess whether the plasma and brain concentrations associated with preclinical efficacy are achievable at tolerated human doses.

8. Sourcing and Quality Verification

J-147 is not a marketed pharmaceutical product in any jurisdiction. It is available exclusively as a research-grade compound.

Research-grade J-147 is supplied by multiple chemical and pharmaceutical research suppliers (Tocris/Bio-Techne, Selleckchem, MedChemExpress, Cayman Chemical, Sigma-Aldrich/MilliporeSigma, MedKoo Biosciences, Santa Cruz Biotechnology, Aobious, and others) at greater than 98 percent purity by HPLC. Supply is in milligram to gram quantities as the free base (the compound does not form a standard salt). Pricing is moderate, in the range of \$50 to \$300 per 50 mg of research-grade material at the time of monograph preparation.

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 (351.13 for the protonated molecule $[M+H]^+$, consistent with $C_{18}H_{17}F_3N_2O_2$)
- 1H and ^{19}F nuclear magnetic resonance spectroscopy confirming the presence and correct integration of the trifluoromethyl group, the 2,4-dimethylphenyl ring, the 3-methoxyphenyl ring, and the hydrazone linkage
- Assessment of (E)/(Z) isomer ratio by HPLC or NMR, as the (Z) isomer may be present in small amounts in incompletely purified lots

Third-party analytical laboratories (Janoshik Analytical, Anabolic Lab, others) provide independent confirmation of vendor certificates of analysis. The J-147 research chemical market is established but the compound is less widely supplied than well-known research tool compounds, and lot-to-lot variability in purity and isomer composition should be expected.

9. Reconstitution and Handling

J-147 is a lipophilic small molecule with limited aqueous solubility. The compound is supplied as a solid powder and is reconstituted as needed for research applications.

Solubility: J-147 is soluble in DMSO to approximately 70 mg/mL (200 mM) and in ethanol to approximately 35 mg/mL (100 mM). The compound is sparingly soluble in water; aqueous stock solutions require co-solvent (typically 5 to 10 percent DMSO in saline or buffer) or formulation with cyclodextrin (hydroxypropyl-beta-cyclodextrin at 20 to 40 percent w/v produces clear aqueous solutions suitable for in vivo dosing).

Storage (solid): Store at 2 to 8 degrees Celsius, desiccated, protected from light. The solid is stable for at least 2 years under these conditions. Room temperature storage in dry, dark conditions is acceptable for short periods (weeks to months) but refrigerated storage is preferred for long-term stocks.

Storage (solution): DMSO stock solutions should be stored at minus 20 degrees Celsius in single-use aliquots to avoid repeated freeze-thaw cycles. Stability in DMSO at minus 20 degrees Celsius is at least 6 months. Aqueous formulations should be prepared fresh for each experiment; stability in aqueous solution at room temperature or 37 degrees Celsius has not been formally characterized and degradation (hydrazide hydrolysis) should be assumed over days to weeks.

In vivo formulation: For chronic oral dosing in rodent studies, the standard approach has been incorporation into the diet at the appropriate concentration to deliver 10 mg/kg/day based on average food consumption [5, 6]. For acute oral gavage, the compound is dissolved in corn oil, sesame oil, or a PEG-400/Tween-80 vehicle [2]. Parenteral administration requires DMSO-containing vehicles (typically 5 to 10 percent DMSO in saline or PEG-300).

10. Stack Interaction Considerations

J-147 has not been evaluated in formal drug-drug interaction studies in humans. The following interaction considerations are based on the known mechanism of action, the preclinical pharmacology, and structural class reasoning.

Mitochondrial modulators: Concurrent administration with other compounds that modulate mitochondrial function (metformin, rapamycin, NAD⁺ precursors such as nicotinamide riboside or nicotinamide mononucleotide, CoQ10, PQQ, SS-31/elamipretide) produces potential additive or synergistic effects on mitochondrial bioenergetics. The combination of J-147 with metformin is of particular theoretical interest given that both activate AMPK, though through distinct upstream mechanisms (metformin through complex I inhibition, J-147 through ATP synthase modulation). Additive AMPK activation could produce excessive suppression of mTOR signaling; the interaction has not been characterized in vivo.

AMPK activators: Concurrent use with other direct or indirect AMPK activators (AICAR, A-769662, berberine, resveratrol) produces potential additive AMPK activation. Investigators should monitor for excessive metabolic suppression.

Cholinesterase inhibitors: The donepezil comparison in Chen et al. (2011) suggests complementary activity with cholinesterase inhibitors [1]. The combination of J-147 and donepezil produced additive effects on contextual and cued memory in the scopolamine model. No pharmacokinetic interaction is expected. The combination is mechanistically rational (bioenergetic enhancement plus cholinergic augmentation) and has not produced adverse signals in rodent models.

CYP-mediated interactions: The specific CYP isoforms responsible for J-147 metabolism have not been published. Until CYP interaction data are available, investigators should exercise caution with concurrent strong CYP inhibitors or inducers, particularly CYP3A4 inhibitors (ketoconazole, itraconazole, ritonavir, clarithromycin) and inducers (rifampin, carbamazepine, phenytoin, St. John's wort).

Anticoagulants and antiplatelet agents: J-147 has not demonstrated effects on coagulation in published studies, but the compound has not been evaluated in combination with anticoagulants. No specific interaction signal exists.

Serotonergic compounds: J-147 does not have characterized serotonergic activity. No serotonin syndrome risk is anticipated from concurrent serotonergic drug use, though formal evaluation has not been conducted.

11. Adverse Events and Safety

11.1 Preclinical toxicology

The CeeTox in vitro toxicology analysis, published by Prior et al. (2014), evaluated J-147 across a panel of cytotoxicity, mitochondrial function, and cellular health endpoints [12]. The CTox value (estimated sustained plasma concentration expected to produce toxicity in a rat 14-day repeat dose study) was approximately 90 micromolar, approximately 150-fold above the brain concentrations associated with preclinical efficacy (approximately 600 nM) [2, 12]. This indicates a favorable in vitro therapeutic index. At high concentrations (above 30 micromolar), J-147 produced some reduction in mitochondrial membrane potential in the CeeTox panel, consistent with the mechanism of action (partial ATP synthase inhibition) but at concentrations well above those relevant to therapeutic dosing [12].

J-147 was negative in the Ames test (bacterial reverse mutation assay) for genotoxicity, supporting the absence of direct DNA-reactive mutagenicity [12].

11.2 Chronic rodent toxicology

In the chronic efficacy studies (10 mg/kg/day for 3 to 7 months in mice), J-147 was well tolerated with no reported mortality, no significant body weight changes, and no gross organ pathology at necropsy [5, 6]. Formal Good Laboratory Practice (GLP) toxicology studies required for IND (Investigational New Drug) filing were completed prior to the Phase 1 trial; these results have not been published in peer-reviewed form but were presumably acceptable to the FDA given the IND clearance [9].

11.3 Human safety data

No peer-reviewed human safety data are available. The Phase 1 trial (NCT03838185) was completed without reported serious adverse events or early termination signals during the trial conduct period [9]. Specific adverse event frequencies, laboratory abnormalities, and ECG findings have not been disclosed.

11.4 Theoretical safety considerations

Based on the mechanism of action, the following theoretical safety considerations apply:

- **Mitochondrial toxicity at supratherapeutic concentrations:** Partial ATP synthase inhibition at therapeutic concentrations produces hormetic mitochondrial stimulation; excessive inhibition at supratherapeutic concentrations could impair oxidative phosphorylation. This is supported by the in vitro mitochondrial membrane potential findings at high concentrations [12].
- **Metabolic effects:** Sustained AMPK activation can suppress anabolic pathways including lipogenesis and protein synthesis. In chronic dosing, this could theoretically produce metabolic effects, though none were observed in the 7-month SAMP8 study [6].
- **Calcium homeostasis:** The mechanism involves transient elevation of intracellular calcium. In susceptible cell populations (e.g., cardiomyocytes), excessive calcium elevation could produce arrhythmogenic effects. No cardiac safety signals have been reported in preclinical or Phase 1 studies.

11.5 Pregnancy and lactation

No reproductive toxicology data are available. J-147 is a research compound and is not intended for use in pregnant or lactating subjects.

12. Comparable Compounds Assessment

This section presents a structured comparative assessment of five neuroprotective and geroprotective candidates against J-147, 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 compounds with mechanistic overlap, shared development context, or positioning in the same therapeutic space as J-147 for Alzheimer's disease and aging research.

12.1 CMS121

Mechanism: Fatty acid synthase (FASN) inhibitor; fisetin-derived synthetic compound developed at the Salk Institute by the same laboratory that produced J-147. CMS121 reduces lipid peroxidation through FASN inhibition and modulates the Nrf2 antioxidant response pathway [16].

Development trajectory: CMS121 was developed through the same phenotypic screening paradigm used for J-147, beginning from the natural flavonoid fisetin. Preclinical efficacy has been demonstrated in APPswe/PS1deltaE9 transgenic mice and in SAMP8 mice, with geroprotective effects in *Drosophila* [8, 16]. A Phase 1 clinical trial (safety, tolerability, pharmacokinetics, and cardiodynamics in healthy adult volunteers) has been completed, with results posted on medRxiv in 2025 [17].

Novelty: Moderate to high. The FASN-dependent lipid peroxidation mechanism is distinct from amyloid-targeting, cholinergic, or mitochondrial bioenergetic strategies.

Effect size: Preclinical effect sizes in SAMP8 and APPswe/PS1deltaE9 models are comparable to J-147, with rescue of cognitive deficits and reversal of molecular aging signatures [8, 16].

Promising potential: Moderate. Phase 1 completed; further development depends on Phase 2 funding and execution.

Side-effect profile: Phase 1 data suggest acceptable tolerability in healthy volunteers [17]. Preclinical toxicology is favorable.

Overall validation: Moderate. Strong preclinical data; Phase 1 completed; no efficacy data in patients.

Comparison to J-147: CMS121 and J-147 are sister compounds from the same laboratory, developed through the same screening paradigm, but with distinct molecular targets (FASN versus ATP5A) and distinct mechanisms (lipid peroxidation reduction versus mitochondrial bioenergetic modulation). The combination of the two has been studied in geroprotective contexts but not in formal preclinical combination efficacy studies [8]. CMS121 is further advanced in clinical development (Phase 1 results posted) compared to J-147 (Phase 1 results unpublished).

12.2 Fisetin

Mechanism: Naturally occurring flavonoid with multiple reported targets including activation of ERK/CREB/BDNF signaling, inhibition of lipoxygenases, antioxidant activity, and senolytic activity (clearance of senescent cells). The molecular pharmacology is less precisely defined than J-147 or CMS121 [18].

Development trajectory: Fisetin has been studied extensively in preclinical models of aging, neurodegeneration, and cancer. Clinical trials for frailty and osteoarthritis (led by the Mayo Clinic, NCT03675724 and others) have evaluated fisetin as a senolytic agent at doses of 20 mg/kg/day for 2 consecutive days (the "hit-and-run" senolytic protocol) [18]. Fisetin is the parent compound from which CMS121 was derived.

Novelty: Low. Fisetin is a well-characterized natural product with decades of research; the specific pharmacology is broad and non-selective.

Effect size: Preclinical neuroprotective effect sizes are modest and are substantially lower than those of J-147 on a molar basis. The senolytic effect size in the clinical frailty trial (AFFIRM-LITE) was not significant on the primary endpoint [18].

Promising potential: Moderate. Multiple clinical trials ongoing; broad interest in senolytic applications; available over the counter as a dietary supplement.

Side-effect profile: Generally well tolerated at studied doses. Bioavailability is poor (less than 10 percent in most reports), limiting systemic exposure and both efficacy and toxicity [18].

Overall validation: Low to moderate for neuroprotection specifically; moderate for senolytic applications. The poor bioavailability is a fundamental limitation.

Comparison to J-147: Fisetin is the natural-product starting point for the optimization that produced CMS121, analogous to curcumin as the starting point for J-147. J-147 is approximately 100-fold more potent than fisetin in cell-based neuroprotection assays, has superior oral bioavailability and CNS penetration, and has a defined molecular target. Fisetin has the advantage of extensive human safety data, over-the-counter availability, and ongoing clinical trials.

12.3 Curcumin

Mechanism: Polyphenolic diarylheptanoid with broad reported pharmacology including antioxidant, anti-inflammatory (NF-kappaB inhibition), amyloid-beta binding, and multiple kinase modulation. The molecular pharmacology is diffuse and concentration-dependent [19].

Development trajectory: Curcumin has been evaluated in multiple clinical trials for Alzheimer's disease, mild cognitive impairment, and age-associated cognitive decline, including the Ringman et al. (2012) randomized, double-blind, placebo-controlled trial at UCLA (NCT00099710) in 36 patients with mild to moderate Alzheimer's disease [19]. Results were negative: no significant differences from placebo on cognitive endpoints, CSF biomarkers, or neuroimaging endpoints. Additional trials using bioavailability-enhanced formulations (Theracurmin, Longvida) have produced mixed results on peripheral inflammatory markers but no replicable cognitive benefit [19].

Novelty: Low. Curcumin is one of the most extensively studied natural products in history.

Effect size: Negligible to small for cognitive endpoints in Alzheimer's disease clinical trials. Preclinical effect sizes are modest and confounded by extremely poor bioavailability.

Promising potential: Low for Alzheimer's disease as a standalone therapeutic. Continued interest as a dietary supplement and as a scaffold for optimization (as demonstrated by J-147).

Side-effect profile: Excellent at dietary doses. Dose-dependent gastrointestinal effects (nausea, diarrhea) at gram-scale supplementation.

Overall validation: Low for Alzheimer's disease. Multiple negative clinical trials despite extensive preclinical literature.

Comparison to J-147: Curcumin is the structural ancestor of J-147, but the two compounds share no structural similarity and have fundamentally different pharmacokinetic profiles. J-147 was designed to overcome the limitations of curcumin (negligible bioavailability, no defined target, diffuse pharmacology). J-147 is approximately 100 to 1000-fold more potent in cell-based neuroprotection assays, has defined target engagement at ATP5A, and achieves meaningful brain concentrations at tolerated oral doses. Curcumin has the advantage of extensive human safety data and over-the-counter availability.

12.4 Donepezil

Mechanism: Reversible acetylcholinesterase inhibitor. Donepezil increases synaptic acetylcholine concentrations by inhibiting the enzyme responsible for acetylcholine hydrolysis, producing symptomatic improvement in cholinergic-dependent cognitive functions [20].

Development trajectory: Donepezil is an FDA-approved treatment for mild, moderate, and severe Alzheimer's disease, marketed as Aricept (Eisai/Pfizer) since 1996. It is one of four approved cholinesterase inhibitors (with rivastigmine, galantamine, and the combination memantine/donepezil) [20].

Novelty: Low. Cholinesterase inhibition is a well-established, three-decade-old mechanism in Alzheimer's disease.

Effect size: Modest. Typical improvements of 2 to 4 points on the ADAS-Cog 70-point scale over 6 months. The effect is symptomatic and does not modify disease progression [20].

Promising potential: Established but limited. The compound is a standard of care but does not arrest cognitive decline.

Side-effect profile: Dose-dependent cholinergic adverse events: nausea, diarrhea, vomiting, insomnia, muscle cramps, bradycardia. Generally well tolerated at 5 mg; more adverse events at 10 mg and 23 mg extended-release doses [20].

Overall validation: High. FDA-approved, extensive Phase 3 and postmarketing data, standard of care.

Comparison to J-147: Donepezil and J-147 operate through fundamentally different mechanisms (cholinergic augmentation versus mitochondrial bioenergetic modulation). In the Chen et al. (2011) scopolamine model, J-147 was comparable to donepezil for short-term memory and superior for spatial memory, and the combination was superior to either compound alone for contextual and cued memory [1]. Donepezil has the overwhelming advantage of clinical validation, regulatory approval, and decades of safety data. J-147 has the theoretical advantage of addressing upstream disease biology (mitochondrial dysfunction, bioenergetic decline) rather than downstream symptomatology (cholinergic deficit).

12.5 Lecanemab

Mechanism: Humanized IgG1 monoclonal antibody targeting soluble amyloid-beta protofibrils. Lecanemab binds large soluble aggregates of amyloid-beta with higher affinity than monomers or insoluble fibrils, promoting clearance through Fc-receptor-mediated phagocytosis [21].

Development trajectory: Lecanemab (BAN2401, Leqembi; Eisai/Biogen) received accelerated FDA approval in January 2023 and traditional approval in July 2023 based on the CLARITY AD Phase 3 trial in 1795 patients with early Alzheimer's disease [21].

Novelty: Moderate. Anti-amyloid immunotherapy is a well-explored class; lecanemab's protofibril selectivity is a refinement.

Effect size: In CLARITY AD, lecanemab reduced decline on the CDR-SB (Clinical Dementia Rating Sum of Boxes) by 27 percent relative to placebo over 18 months. The absolute difference was 0.45 points on a 18-point scale [21].

Promising potential: High. FDA-approved; the first anti-amyloid antibody to demonstrate statistically significant clinical benefit.

Side-effect profile: Amyloid-related imaging abnormalities (ARIA) including ARIA-E (edema) in approximately 12.6 percent and ARIA-H (hemorrhage) in approximately 17.3 percent of treated patients. Most ARIA events are asymptomatic; symptomatic ARIA occurs in approximately 3 percent. Three deaths potentially related to ARIA were reported during the trial program [21].

Overall validation: High. Phase 3 positive, FDA-approved, replicable benefit.

Comparison to J-147: Lecanemab and J-147 address completely different aspects of Alzheimer's disease biology (amyloid clearance versus mitochondrial bioenergetics). The two mechanisms are complementary rather than competing and could theoretically be combined. Lecanemab has the advantage of Phase 3 validation and regulatory approval. J-147 has the advantage of oral administration (versus bi-weekly intravenous infusion for lecanemab), absence of ARIA risk, low cost, and a mechanism that addresses the bioenergetic decline associated with aging, which may be upstream of amyloid pathology. J-147 is many years behind lecanemab in clinical development.

12.6 Comparator summary

The five comparators span the spectrum from the ancestral natural products that gave rise to J-147 (curcumin, fisetin) through the sister compound from the same laboratory (CMS121), a standard-of-care symptomatic treatment (donepezil), and the most recently approved disease-modifying therapy (lecanemab). J-147 occupies a distinct position: it is more potent and better characterized than its natural-product predecessors, operates through a unique molecular target (ATP5A), and addresses an aspect of disease biology (mitochondrial bioenergetic decline) that is not targeted by any approved therapy. The principal limitation is the early stage of clinical development: no published human efficacy data, no Phase 2 trial, and uncertainty regarding the continuation of the development program following the death of the compound's inventor. Investigators considering J-147 for research applications should recognize it as a well-characterized preclinical tool compound with strong rodent efficacy data and a defined molecular target, but with an incomplete clinical translation record.

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weight the evidence accordingly. J-147 is not approved by any regulatory authority. The compound is available as a research-grade preparation; investigators should obtain analytical confirmation of identity and purity on every lot.