

RESEARCH MONOGRAPH . COMPOUND PROFILE

CMS121

A synthetic quinoline derivative of the flavonoid fisetin, developed at the Salk Institute through phenotypic screening against age-associated neuronal cell death, that inhibits fatty acid synthase and acetyl-CoA carboxylase 1 to protect against ferroptotic lipid peroxidation and cognitive decline in transgenic Alzheimer's disease and accelerated aging mouse models, with Phase 1 human pharmacokinetic data completed in 2022.

DOCUMENT	KDC-MN-1642
ISSUED	2026-05-22
REVISION	1.0
AUTHOR	Kodiac biolabs Research
COMPOUND CLASS	Geroneuroprotective small molecule; synthetic fisetin derivative; fatty acid synthase inhibitor with anti-ferroptotic and anti-inflammatory activity

ABSTRACT

CMS121 (CAS 1353224-53-9) is a synthetic quinoline derivative of the dietary flavonoid fisetin (3,7,3',4'-tetrahydroxyflavone), identified through a phenotypic screening cascade at the Salk Institute for Biological Studies as a potent inhibitor of oxytotic/ferroptotic neuronal cell death with nanomolar protective activity in glutamate toxicity and iodoacetic acid toxicity assays in the HT22 hippocampal cell line. The compound was selected from more than 160 synthetic fisetin derivatives prepared by Chiruta, Schubert, Dargusch, and Maher (Journal of Medicinal Chemistry, 2012) through a multitiered screening approach that evaluated neuroprotective potency, anti-inflammatory activity, and oral pharmacokinetic suitability. The molecular target of CMS121 was subsequently identified as fatty acid synthase (FASN), with dose-dependent enzymatic inhibition demonstrated in cell lysate assays (Ates, Goldberg, Currais, and Maher, Redox Biology, 2020). Downstream of FASN inhibition, CMS121 engages the AMP-activated protein kinase/acetyl-CoA carboxylase 1 (AMPK/ACC1) axis, elevating intracellular acetyl-CoA levels and promoting histone H3 lysine 9 acetylation, a modification linked to memory enhancement in the senescence-accelerated mouse prone 8 (SAMP8) model (Currais et al., eLife, 2019). The anti-ferroptotic mechanism operates through reduction of polyunsaturated fatty acid substrates available for lipid peroxidation, thereby decreasing 4-hydroxynonenal protein adduct accumulation and suppressing downstream neuroinflammatory cascades including inducible nitric oxide synthase, cyclooxygenase-2, and tumor necrosis factor- α expression in activated microglia. Preclinical efficacy has been

demonstrated across multiple disease models: in APPswe/PS1deltaE9 double transgenic Alzheimer's disease mice, dietary CMS121 at 400 parts per million (approximately 34 mg/kg/day) for three months beginning at nine months of age normalized spatial memory, contextual fear conditioning, and hippocampal lipid peroxidation markers to wild-type levels; in SAMP8 accelerated aging mice, four months of treatment preserved cognition and reduced transcriptional markers of brain aging; in R6/2 and YAC128 Huntington's disease models, CMS121 slowed motor dysfunction and extended median lifespan by up to 17 percent; and in db/db leptin receptor deficient mice and wild-type C57BL/6 mice, the compound ameliorated metabolic dysfunction, reduced adiposity, and improved hepatic and renal biomarkers. The compound was advanced to a first-in-human Phase 1 clinical trial (NCT05318040) by Virogenics, Inc. in collaboration with the National Institute on Aging, conducted at Celerion (Lincoln, Nebraska) in 2022. Single ascending doses up to 1800 mg and multiple ascending doses up to 900 mg per day for seven days were generally well tolerated in approximately 88 healthy volunteers, with the majority of treatment-emergent adverse events mild in severity. Pharmacokinetics were dose-proportional or slightly greater than dose-proportional; the CMS121-C2 metabolite was the predominant circulating species; urinary excretion was minimal; systemic exposure was approximately 50 percent higher in the fed state; and elderly subjects exhibited higher exposures and longer terminal elimination half-lives than young adults (Maher, Christopher, Evans, and Raschke, medRxiv, 2025, preprint). This monograph reviews the chemistry and structural relationship to fisetin; the FASN/ACC1/AMPK molecular pharmacology; the preclinical evidence base across Alzheimer's disease, Huntington's disease,

aging, and metabolic models; the Phase 1 human pharmacokinetic and safety data; sourcing and handling considerations for research applications; and a comparative assessment of five related compounds (fisetin, J147, CAD031, denifanstat, and ferrostatin-1) against CMS121 on five competency standards. The compound has not received regulatory approval for any therapeutic indication. It is positioned as a research-grade geroneuroprotector for investigational use.

1. Compound Identification

1.1 Names, synonyms, and registry identifiers

Designation: CMS121.

Synonyms: CMS-121, CMS 121. The compound does not carry an International Nonproprietary Name, a United States Adopted Name, or a marketed brand name; CMS121 is the laboratory designation assigned during the structure-activity relationship campaign at the Salk Institute for Biological Studies.

Chemical Abstracts Service registry number: 1353224-53-9.

International Union of Pure and Applied Chemistry name: 4-(4-(cyclopentyloxy)quinolin-2-yl)benzene-1,2-diol.

The name denotes a quinoline ring bearing a cyclopentyloxy substituent at the 4-position and a catechol (1,2-dihydroxybenzene) group appended at the 2-position of the quinoline through a direct aryl-aryl bond. The catechol moiety preserves a structural echo of the 3',4'-dihydroxyphenyl ring of the parent flavonoid fisetin, while the quinoline core replaces the chromenone (benzopyranone) scaffold of the flavonoid with a nitrogen-containing heterocycle selected for improved metabolic stability and oral pharmacokinetic parameters [1].

1.2 Structural class and chemistry

CMS121 is a substituted 2-arylquinoline. It belongs to a series of synthetic fisetin derivatives prepared through structure-activity relationship-driven iterative chemistry at the Salk Institute by Chiruta, Schubert, Dargusch, and Maher [1]. More than 160 derivatives of fisetin were synthesized in this campaign, exploring four structural motif classes: chalcone derivatives, flavone derivatives, flavonol derivatives, and quinoline derivatives. CMS121 was selected from this series on the basis of substantially enhanced neuroprotective potency (approximately 10-fold to 100-fold improvement over fisetin in glutamate-induced oxytosis assays) while retaining the anti-inflammatory and antioxidant activities of the parent compound [1, 4].

Molecular formula: C₂₀H₁₉NO₃.

Molecular weight: 321.37 g/mol.

Structural features: The compound contains three principal pharmacophoric elements: (a) the quinoline heterocyclic core, which provides metabolic stability relative to the flavonoid chromenone ring of fisetin; (b) the catechol (1,2-dihydroxybenzene) moiety at the 2-position, which is responsible for redox activity and metal chelation capacity; and (c) the cyclopentyloxy ether at the 4-position of the quinoline, which confers lipophilicity and influences pharmacokinetic profile. The compound does not contain a stereocenter and is achiral.

Physical properties: Supplied as a solid powder. Freely soluble in dimethyl sulfoxide (approximately 50 mg/mL, corresponding to approximately 155.6 mM). For in vivo formulation, solubility of at least 2.08 mg/mL has been demonstrated in a vehicle of 10 percent dimethyl sulfoxide, 40 percent polyethylene glycol 300, 5 percent Tween 80, and 45 percent normal saline. Aqueous solubility at physiological pH is limited, consistent with the lipophilic quinoline core.

1.3 Relationship to the parent compound fisetin

Fisetin (3,7,3',4'-tetrahydroxyflavone; CAS 528-48-3; molecular formula C₁₅H₁₀O₆; molecular weight 286.24 g/mol) is a naturally occurring flavonoid found at low concentrations in strawberries, apples, persimmons, grapes, onions, and cucumbers. Fisetin was identified as an orally active neuroprotective and cognition-enhancing molecule through phenotypic screening in the Maher laboratory at the Salk Institute [12, 13]. However, fisetin exhibits a relatively high EC₅₀ in cell-based neuroprotection assays (low micromolar range), low lipophilicity, a high topological polar surface area, and poor oral bioavailability, all of which limit its translational potential as a drug candidate [1]. CMS121 was designed to address these limitations through replacement of the flavonoid scaffold with a quinoline core, yielding a compound with substantially lower EC₅₀ values (7 nanomolar in the iodoacetic acid assay; 200 nanomolar in the glutamate oxytosis assay), improved oral pharmacokinetic parameters, and demonstrated brain penetration at oral doses in mice [1, 2, 4].

1.4 Synthesis

The published synthesis of CMS121 proceeds through standard quinoline construction chemistry. The Chiruta et al. (2012) medicinal chemistry campaign describes the general synthetic schemes employed for the quinoline derivative series, including Friedlander and Doebner-Miller approaches for quinoline ring formation, followed by O-alkylation at the 4-hydroxyl position with cyclopentyl bromide and deprotection of the catechol hydroxyl groups [1]. Specific step-by-step synthetic procedures for CMS121 itself have not been published in detail in the peer-reviewed literature; the synthesis is described at the level of the structural class in the original Journal of Medicinal Chemistry report. Research-grade material is commercially available from multiple suppliers at greater than 98 percent purity.

2. Abstract

CMS121 is a synthetic quinoline derivative of the dietary flavonoid fisetin, developed through a phenotypic screening approach targeting the oxytosis/ferroptosis neuronal cell death pathway. This monograph reviews the chemistry, molecular pharmacology, preclinical efficacy, Phase 1 clinical pharmacokinetic and safety data, and comparative positioning of CMS121 as a research-grade geroneuroprotector. The compound inhibits fatty acid synthase and engages the AMPK/ACC1 metabolic axis, producing neuroprotection through reduction of lipid peroxidation and neuroinflammation. Preclinical efficacy spans Alzheimer's disease, Huntington's disease, accelerated aging, and metabolic dysfunction models. First-in-human data from a completed Phase 1 trial (NCT05318040) demonstrate tolerability at single doses up to 1800 mg and repeat doses up to 900 mg per day for seven days, with dose-proportional pharmacokinetics and a significant food and age effect on systemic exposure. The compound is not approved for any therapeutic indication and is positioned for research use only.

3. Discovery and Development History

3.1 Identification of fisetin as a neuroprotective lead

The development of CMS121 originates in the Cellular Neurobiology Laboratory at the Salk Institute for Biological Studies (La Jolla, California), directed by Pamela Maher and David Schubert. Beginning in the mid-2000s, the laboratory employed a phenotypic screening platform based on age-associated brain toxicities to identify small molecules with neuroprotective potential [10, 11]. The screening cascade comprised six cell-based assays: protection against glutamate-induced oxidative toxicity (oxygenotoxicity) in the HT22 hippocampal cell line, protection against amyloid-beta proteotoxicity, protection against ATP synthesis reduction (modeling ischemia), inhibition of microglial activation (modeling neuroinflammation), protection against trophic factor withdrawal, and induction of neurite outgrowth in PC12 cells [10].

From a screen of approximately 30 flavonoids, fisetin (3,7,3',4'-tetrahydroxyflavone) was identified as an orally active compound that maintained glutathione levels under oxidative stress by inducing the transcription factors Nrf2 and ATF4, facilitated long-term potentiation in hippocampal slices and in mouse brain, and enhanced object recognition memory in healthy mice [12, 13, 29, 38]. However, fisetin's relatively high EC₅₀ in neuroprotection assays, low lipophilicity, high topological polar surface area, and poor oral bioavailability limited its candidacy for clinical development [1].

3.2 Medicinal chemistry optimization

To address fisetin's pharmacokinetic limitations, Chiruta, Schubert, Dargusch, and Maher undertook a structure-activity relationship campaign published in the *Journal of Medicinal Chemistry* in 2012 [1]. More than 160 synthetic fisetin derivatives were prepared, spanning four structural classes: chalcone derivatives, flavone derivatives, flavonol derivatives, and quinoline derivatives. A multitiered screening approach evaluated neuroprotective potency in the glutamate oxygenotoxicity assay (pri-

mary screen), maintenance of anti-inflammatory and antioxidant activities (secondary screens), and oral pharmacokinetic suitability including brain penetration after oral dosing in mice [1].

CMS121 emerged from this campaign as a lead compound on the basis of substantially enhanced neuroprotective potency (EC₅₀ of 200 nanomolar in the glutamate oxytosis assay and 7 nanomolar in the iodoacetic acid assay, compared to low micromolar EC₅₀ for fisetin), maintained anti-inflammatory and antioxidant activities, and oral pharmacokinetic parameters demonstrating peak brain levels after a single oral dose of 20 mg/kg that substantially exceeded the in vitro median effective concentration [1, 2, 4]. The compound was described as "a more potent derivative of the flavonol fisetin that maintains most of its biological properties" [3].

3.3 Target identification and preclinical development

Following selection of CMS121, the Maher laboratory undertook target identification using unbiased proteomic approaches. Fatty acid synthase (FASN) was identified as a direct molecular target of CMS121 through drug affinity responsive target stability (DARTS) analysis, with dose-dependent inhibition of FASN enzymatic activity confirmed in HT22 cell lysate kinetic assays [2]. A second metabolic target, acetyl-CoA carboxylase 1 (ACC1), was characterized in the context of the shared AMPK/ACC1 pathway engaged by both CMS121 and the structurally distinct Alzheimer's disease drug candidate J147, a curcumin derivative from the same laboratory [3, 9].

Preclinical efficacy studies were conducted across multiple disease models between 2017 and 2024, including APP^{swe}/PS1^{deltaE9} transgenic Alzheimer's disease mice [2], senescence-accelerated SAMP8 mice [3, 7], R6/2 and YAC128 Huntington's disease models [6], db/db leptin receptor deficient diabetic mice, and wild-type C57BL/6 aging mice [8]. These studies established CMS121 as a geroneuroprotector, a term coined by Schubert, Currais, and Maher (Trends in Pharmacological Sciences, 2018) to designate compounds that are effective geroprotectors for the brain, extending lifespan and delaying physiological and molecular aspects of aging [10].

3.4 IND-enabling studies and clinical entry

To advance CMS121 toward human testing, Maher partnered with Virogenics, Inc. (San Diego, California), a biotech startup founded by William Raschke. In 2013, Maher and Virogenics obtained a Small Business Technology Transfer Grant from the National Institute of Allergy and Infectious Diseases (NIAID) to support IND-enabling preclinical and toxicology studies [4, 17]. The results of these studies, described comprehensively in the Currais, Raschke, and Maher (2024) review in the Journal of Alzheimer's Disease, provided sufficient safety margins to support an Investigational New Drug application, which was accepted by the United States Food and Drug Administration [4].

In October 2021, the Salk Institute announced the launch of a first-in-human Phase 1 clinical trial of CMS121, funded by a \$4.5 million National Institute on Aging award (R01AG074447) over two years [17]. The Phase 1 study (NCT05318040) was conducted by Celerion at their clinical pharmacology unit in Lincoln, Nebraska, between May and December 2022, enrolling approximately 88 healthy volunteers across single ascending dose, multiple ascending dose, and elderly cohort arms [5, 16]. Results were published as a medRxiv preprint in February 2025 [5].

As of the present monograph date (May 2026), no Phase 2 clinical trial of CMS121 has been registered or publicly announced. The compound is not approved for any therapeutic indication in any jurisdiction.

4. Molecular Pharmacology

CMS121 operates through a convergent multi-target mechanism centered on the inhibition of lipid biosynthetic enzymes, producing downstream reduction in ferroptotic lipid peroxidation, neuroinflammation, and age-associated transcriptional dysregulation. The principal molecular targets are fatty acid synthase (FASN) and, indirectly through the AMPK signaling cascade, acetyl-CoA carboxylase 1 (ACC1). The compound was identified through its phenotypic activity (protection of HT22 hippocampal neurons against oxytotic/ferroptotic cell death) rather than through target-based screening, and the molecular targets were subsequently deconvoluted through proteomic and genetic validation [2, 4].

4.1 Fatty acid synthase inhibition

Fatty acid synthase (FASN, EC 2.3.1.85) is a homodimeric multifunctional enzyme that catalyzes the de novo synthesis of palmitate from acetyl-CoA and malonyl-CoA precursors using NADPH as a reductant [25]. FASN is expressed in all tissues but at highest levels in liver, adipose tissue, and brain, where de novo fatty acid synthesis provides both structural lipids for membrane biogenesis and polyunsaturated fatty acid substrates that are targets of lipid peroxidation [2, 15, 25].

Ates, Goldberg, Currais, and Maher (2020) identified FASN as a direct binding target of CMS121 using drug affinity responsive target stability (DARTS) analysis, in which CMS121 protected FASN against protease digestion in a concentration-dependent manner at 5, 10, 25, 50, and 100 micromolar concentrations [2]. FASN enzymatic activity assays in HT22 cell lysates demonstrated that CMS121 produces a dose-dependent decrease in the maximum velocity (V_{max}) during the linear phase of the NADPH consumption kinetic curve, consistent with direct enzyme inhibition [2]. The study did not report a formal IC_{50} for FASN inhibition; the inhibition was characterized kinetically rather than as a single-point potency value.

Genetic validation was provided by FASN gene silencing experiments: small interfering RNA knockdown of FASN in HT22 cells recapitulated the protective effects of CMS121 against oxytosis/ferroptosis, and a significant correlation was observed between FASN protein levels and 4-hydroxynonenal (4HNE) lipid peroxidation

adduct levels across treatment conditions (Pearson $r = 0.86$, $p < 0.0001$) [2]. Elevated FASN protein levels have been reported in the brains of human Alzheimer's disease patients, providing a disease-relevant context for the target [2, 4].

The mechanistic consequence of FASN inhibition is reduction in de novo polyunsaturated fatty acid (PUFA) synthesis, thereby decreasing the pool of substrates available for lipid peroxidation. In the APP^{swe}/PS1^{deltaE9} transgenic Alzheimer's disease mouse model, CMS121 treatment normalized the elevated levels of several lipid metabolite groups that were increased in untreated transgenic mice relative to wild-type controls [2].

4.2 AMPK/ACC1 pathway and acetyl-CoA metabolism

A second metabolic axis engaged by CMS121 is the AMP-activated protein kinase (AMPK)/acetyl-CoA carboxylase 1 (ACC1) pathway. ACC1 catalyzes the carboxylation of acetyl-CoA to malonyl-CoA, the rate-limiting step in de novo fatty acid synthesis [26]. AMPK phosphorylates ACC1 at serine 79, producing inhibitory phosphorylation that reduces malonyl-CoA production and thereby decreases fatty acid synthesis while elevating intracellular acetyl-CoA levels [3, 9, 27].

Currais, Huang, Goldberg, and colleagues (2019) demonstrated that CMS121 and the structurally distinct Alzheimer's disease drug candidate J147 (a curcumin derivative) both increased acetyl-CoA levels in cell culture and in the brains of SAMP8 mice via inhibition of ACC1, and that the elevated acetyl-CoA resulted in increased acetylation of histone H3 at lysine 9 (H3K9), a chromatin modification previously linked to memory enhancement [3]. The AMPK/ACC1/acetyl-CoA/H3K9 acetylation cascade represents a metabolic mechanism of epigenetic regulation that connects the lipid biosynthetic inhibition to transcriptional effects relevant to cognitive preservation [3].

Dafre and colleagues (2024) extended the AMPK/ACC1 characterization to peripheral tissues, demonstrating increased ACC1 phosphorylation (inhibitory) in adipose tissue and decreased FASN levels in liver in C57BL/6 wild-type mice treated with CMS121, resulting in enhanced acetyl-CoA availability and a metabolic shift toward ketogenic metabolism resembling the metabolic signature of caloric restriction [8].

4.3 Anti-ferroptotic mechanism

The oxytosis/ferroptosis pathway is a regulated cell death mechanism distinct from apoptosis, characterized by glutathione depletion, lipoxygenase activation, reactive oxygen species accumulation, lipid peroxidation, and calcium-dependent mitochondrial dysfunction [11, 18, 21, 22, 28]. The Maher and Schubert laboratory has studied this pathway for over three decades, and the phenotypic screening platform used to discover CMS121 was designed specifically to identify compounds that protect neurons against oxytotic/ferroptotic death [11].

CMS121 prevents glutamate-induced oxytosis in HT22 hippocampal neurons with an EC₅₀ of approximately 200 nanomolar and prevents iodoacetic acid-induced cell death with an EC₅₀ of approximately 7 nanomolar [4]. The compound also prevents cell death induced by the canonical ferroptosis inducers erastin (which inhibits system xc-minus cystine/glutamate antiporter) and RSL3 (which directly inhibits glutathione peroxidase 4) [2]. The protective mechanism operates upstream of lipid peroxidation: by inhibiting FASN and thereby reducing the availability of polyunsaturated fatty acid substrates, CMS121 decreases the lipid pool susceptible to peroxidation [2, 11].

In the BV2 microglial cell line, CMS121 prevented RSL3-induced and LPS-induced lipid peroxidation as measured by the Bodipy 581/591 C11 fluorescent probe, with statistical significance at $p < 0.001$ [2]. In vivo, CMS121 reduced hippocampal 4-hydroxynonenal (4HNE) protein adduct levels (a stable end-product of lipid peroxidation) in APP^{swe}/PS1^{deltaE9} transgenic mice to levels comparable to wild-type controls, from approximately 50 percent elevation in untreated transgenic animals [2].

4.4 Anti-inflammatory activity

The anti-inflammatory activity of CMS121 operates through at least two convergent mechanisms: FASN inhibition-dependent reduction in eicosanoid precursors and direct suppression of proinflammatory signaling in microglia.

In BV2 microglial cells activated by lipopolysaccharide (LPS), both CMS121 treatment and FASN gene silencing prevented the increases in inducible nitric oxide synthase (iNOS), cyclooxygenase-2 (COX-2), and tumor necrosis factor-alpha (TNF-alpha) expression, with statistical significance ranging from $p < 0.05$ to $p < 0.0001$ [2]. In the MC65 neuronal cell line (an intracellular amyloid-beta proteotoxicity model), eicosanoid profiling identified 43 detectable eicosanoids (29 derived from

arachidonic acid, 11 from linoleic acid, and 3 from docosahexaenoic acid); amyloid-beta induction produced a general increase in eicosanoid levels, and CMS121 treatment prevented this increase ($p < 0.0001$) [2].

In vivo, CMS121 reduced glial fibrillary acidic protein (GFAP) expression (a marker of astrocyte activation and neuroinflammation) in the hippocampus of APPswe/PS1deltaE9 transgenic mice ($p < 0.01$ to $p < 0.0001$) and reduced 15-lipoxygenase-2 (15LOX2) levels to those of wild-type controls ($p < 0.05$) [2].

4.5 Mitochondrial and transcriptional effects

In SAMP8 accelerated aging mice, CMS121 treatment preserved mitochondrial homeostasis by maintaining the expression of genes involved in oxidative phosphorylation that were downregulated with aging [3]. Transcriptomic analysis identified 485 differentially expressed genes between 9-month-old and 13-month-old SAMP8 mice; CMS121 treatment modified 684 genes, with substantial overlap in mitochondrial-related pathways including oxidative phosphorylation and pathways annotated to Parkinson's disease, Huntington's disease, and Alzheimer's disease [3].

In the R6/2 Huntington's disease model, CMS121 partially or fully restored the expression of leading-edge genes in the oxidative phosphorylation and proteasome gene sets that were dysregulated in untreated R6/2 mice, with genes downregulated by CMS121 at both tested doses generally reverting toward the expression levels observed in non-carrier controls [6].

5. Pharmacokinetics and Routes of Administration

5.1 Preclinical pharmacokinetics

CMS121 was selected in part for favorable oral pharmacokinetic properties in rodents. Pharmacokinetic studies of the fisetin derivative series demonstrated that several derivatives, including CMS121, achieved peak brain levels following a single oral dose of 20 mg/kg that substantially exceeded their average median effective concentration in *in vitro* neuroprotection assays, indicating good oral bioavailability and brain penetration [1, 4]. Specific quantitative pharmacokinetic parameters (absolute oral bioavailability, volume of distribution, clearance, protein binding) from preclinical species have not been published in the peer-reviewed literature as individual numeric values; the available characterization is presented at the level of brain-to-plasma ratios and EC50 exceedance following oral dosing [4].

In preclinical efficacy studies, CMS121 has been administered chronically via dietary admixture at concentrations of 200 to 400 parts per million (ppm), corresponding to approximate daily oral doses of 9.4 to 34 mg/kg/day depending on food consumption and body weight of the specific mouse strain [2, 3, 6, 8]. This dietary administration route achieves sustained systemic and brain exposure without the stress of daily gavage and is the standard route for chronic neurodegeneration studies in the Maher laboratory.

5.2 Human pharmacokinetics (Phase 1)

The first-in-human Phase 1 study (NCT05318040) evaluated the pharmacokinetics of CMS121 in healthy adult volunteers in three study parts: Part 1, single ascending dose (SAD) in approximately 48 young subjects at doses up to 1800 mg; Part 2, multiple ascending dose (MAD) in approximately 32 young subjects at doses up to 900 mg per day for seven days; and Part 3, MAD in approximately 8 elderly subjects [5, 16].

Key pharmacokinetic findings from the Phase 1 trial (Maher, Christopher, Evans, and Raschke, medRxiv preprint, 2025):

Dose proportionality: The pharmacokinetics of CMS121 and its metabolites increased in a dose-proportional or slightly greater than dose-proportional manner across the range of doses assessed in the SAD and MAD portions of the study [5].

Metabolite profile: Three metabolites were characterized: CMS121-C1, CMS121-C2, and CMS121-C3. The CMS121-C2 metabolite contributed the most to the total molar-equivalent CMS121 in plasma, exceeding the parent compound and the other two metabolites in circulating concentrations [5]. The identity and pharmacological activity of the CMS121-C2 metabolite have not been published.

Elimination route: Urinary excretion of CMS121 metabolites was minimal, indicating that urinary excretion is not a major clearance route and that elimination is predominantly hepatic (metabolic) rather than renal [5].

Age effect: A significant effect of age on the pharmacokinetics of CMS121 and its metabolites was observed, with higher systemic exposures and longer terminal elimination half-lives in elderly subjects compared to young adults [5]. Specific fold-changes and numeric comparisons between age groups have not been published in the available preprint abstract.

Food effect: Systemic exposures to CMS121 were approximately 50 percent higher in the fed state compared to fasted administration [5]. This positive food effect suggests that CMS121 administration with food would increase systemic exposure and potentially improve pharmacological activity.

Specific numeric pharmacokinetic parameters (C_{max}, T_{max}, AUC, terminal half-life, clearance, volume of distribution) at individual dose levels have not been published in the available preprint abstract. The complete pharmacokinetic dataset is referenced in the body of the preprint manuscript, which was not accessible for data extraction at the time of monograph preparation. Investigators requiring detailed human pharmacokinetic parameters should consult the full publication when it appears in peer-reviewed form.

5.3 Routes of administration

CMS121 has been administered by the following routes in published studies:

Oral, dietary admixture (preclinical): 200 to 400 ppm in rodent chow, corresponding to approximately 9.4 to 34 mg/kg/day. This is the standard route for chronic preclinical efficacy studies and achieves sustained brain exposure [2, 3, 6,

8].

Oral, capsule or suspension (clinical): Single doses up to 1800 mg and repeat doses up to 900 mg per day for seven days in the Phase 1 trial. Specific formulation details (capsule composition, suspension vehicle) have not been published [5, 16].

No parenteral administration routes have been reported in the published literature.

6. Preclinical Pharmacology

6.1 Alzheimer's disease: APP^{swe}/PS1^{deltaE9} transgenic mice

The principal Alzheimer's disease efficacy study was reported by Ates, Goldberg, Currais, and Maher (Redox Biology, 2020) [2]. APP^{swe}/PS1^{deltaE9} double transgenic mice on a C57BL/6J background (which express human amyloid precursor protein with the Swedish mutation and presenilin 1 with exon 9 deletion, developing amyloid plaques and cognitive deficits by 9 to 12 months of age [31]) were treated with CMS121 at 400 ppm in diet (approximately 34 mg/kg/day) beginning at 9 months of age for 3 months, with testing at 12 months. Sample size was 12 mice per group (wild-type control diet, transgenic control diet, transgenic CMS121 diet).

Morris Water Maze (spatial memory): On Day 1 (visible platform), no differences in escape latency were observed between groups, confirming equivalent visual acuity and motor function. On Day 2 (hidden platform), untreated transgenic mice took significantly longer to locate the platform than wild-type mice; CMS121-treated transgenic mice performed as well as wild-type mice [2].

Elevated Plus Maze (disinhibition): Untreated transgenic mice spent significantly more time in the open arms compared to wild-type mice, indicating disinhibition characteristic of the amyloid pathology. CMS121-treated transgenic mice showed no significant difference from wild-type controls [2].

Fear Conditioning (contextual memory): Untreated transgenic mice showed significantly lower freezing time than other groups. CMS121-treated transgenic mice did not show this deficiency compared to wild-type controls [2].

Lipid peroxidation: Hippocampal 4-hydroxynonenal (4HNE) protein adduct levels were elevated approximately 50 percent in untreated transgenic mice relative to wild-type. CMS121 treatment decreased hippocampal 4HNE levels to those of untreated wild-type mice ($p < 0.05$ to $p < 0.0001$) [2].

Neuroinflammation: GFAP expression was elevated in untreated transgenic hippocampus; CMS121 treatment decreased GFAP levels ($p < 0.01$ to $p < 0.0001$). 15-lipoxygenase-2 (15LOX2) was similarly elevated and reduced by CMS121 to wild-

type levels ($p < 0.05$) [2].

6.2 Accelerated aging: SAMP8 mice

Currais, Huang, Goldberg, and colleagues (eLife, 2019) treated senescence-accelerated SAMP8 mice (a model for sporadic age-associated dementia characterized by progressive cognitive decline, oxidative stress, inflammation, and tau hyperphosphorylation [32]) with CMS121 beginning at 9 months of age (the last quadrant of the SAMP8 lifespan, median approximately 15 months) for 4 months [3].

Elevated Plus Maze: Thirteen-month-old untreated SAMP8 mice spent significantly more time in the open arms compared to 9-month-old SAMP8 mice, reflecting age-associated disinhibition. CMS121 treatment prevented this increase [3].

Barnes Maze (reversal learning): CMS121 significantly improved learning of the new platform location during the reversal phase, indicating preserved cognitive flexibility [3].

Transcriptomics: Analysis identified 485 differentially expressed genes between 9-month-old and 13-month-old SAMP8 mice; CMS121 modified 684 genes, with significant preservation of mitochondrial-related gene expression in oxidative phosphorylation pathways [3].

Acetyl-CoA and histone acetylation: CMS121 increased acetyl-CoA levels via ACC1 inhibition and increased H3K9 acetylation, a memory-linked epigenetic mark [3].

6.3 Geroprotective effects: SAMP8 brain and kidney

Kepchia, Currais, Dargusch, Finley, Schubert, and Maher (Aging, 2021) treated SAMP8 mice with CMS121 during the last quadrant of their lifespan and assessed both brain and kidney outcomes [7]. Both CMS121 and J147 improved physiological markers for brain and kidney function. Drug treatments restored age-altered protein levels in inflammation, proteostasis, MAPK, mTOR, and AMPK pathways to a more youthful phenotype, with tissue-specific patterns of protein-level restoration in brain and kidney [7].

In *Drosophila melanogaster*, CMS121 extended median lifespan by 8.46 percent ($p = 0.017$) [7].

6.4 Huntington's disease: R6/2 and YAC128 mice

Ates, Taguchi, and Maher (Molecular Neurobiology, 2024) evaluated CMS121 in two complementary Huntington's disease mouse models [6].

R6/2 model (B6CBA-Tg(HDexon1)62Gpb/3J; approximately 120 CAG repeats [33]): Treatment began at 6 weeks of age with CMS121 at 200 and 400 ppm in diet (approximately 17 and 34 mg/kg/day). At 13 weeks, forelimb grip strength was significantly higher in the 200 ppm-treated group compared to untreated R6/2 mice ($p < 0.001$). Median survival was 113 days in untreated R6/2 mice versus 134 days in the 200 ppm group [6]. Transcriptomic analysis revealed that CMS121 partially or fully restored expression of leading-edge genes in the oxidative phosphorylation and proteasome gene sets, with genes downregulated by CMS121 generally reverting toward non-carrier expression levels [6].

YAC128 model (FVB-Tg(YAC128)53Hay/J; approximately 120 mixed CAA/CAG repeats [34]): Treatment began at approximately 1 month after arrival with CMS121 at 200 ppm in diet. At 9 months, forelimb grip strength was significantly higher in treated mice ($p < 0.01$); at 13 months, both fore- and hindlimb grip strength were significantly improved ($p < 0.05$); at 18 months, CMS121-treated mice traveled further, moved more frequently, and spent less time resting than untreated YAC128 mice in the open field [6]. Median lifespan was 540 days (untreated) versus 631 days (treated), representing a 17 percent increase [6].

6.5 Metabolic dysfunction and obesity

Dafre and colleagues (Aging, 2024) treated C57BL/6 wild-type mice with CMS121 beginning at 5 weeks of age for 6 months (200 ppm, equivalent to 9.4 mg/kg/day for weeks 1 to 17; increased to 400 ppm, equivalent to 18.8 mg/kg/day for weeks 18 to 24) [8]. Body weight gain was reduced from 18.8 plus or minus 2.6 grams in control mice to 13.4 plus or minus 2.9 grams in CMS121-treated mice, with increased lean mass and decreased fat mass. Insulin levels were markedly decreased. Free fatty acids and triglycerides were reduced in both liver and blood. The metabolic profile resembled that of caloric restriction or a ketogenic diet, with elevated ketone body metabolites [8].

The db/db leptin receptor deficient mouse model was studied for diabetes and kidney outcomes. CMS121 alleviated diabetes-associated liver inflammation and renal damage [7, 8].

6.6 Age-related hearing loss

A study in SAMP8 mice demonstrated that CMS121 attenuated age-related hearing impairment, with the mechanism attributed to FASN inhibition and preservation of auditory neuron viability through reduction of lipid peroxidation [35].

6.7 Translational validity assessment

The preclinical evidence base for CMS121 is notable for several strengths: (a) efficacy demonstrated across mechanistically distinct disease models (amyloid-driven, tau-associated, polyglutamine repeat, metabolic, and aging), suggesting engagement of a conserved age-associated pathway rather than disease-specific molecular rescue; (b) consistent use of dietary administration at translationally relevant doses; (c) independent replication of the AMPK/ACC1 mechanism by the same laboratory in structurally distinct compounds (CMS121 and J147); and (d) demonstration of both central (brain) and peripheral (kidney, liver, metabolic) geroprotective effects. Limitations include that the preclinical work originates predominantly from a single research group (the Maher/Schubert laboratory at the Salk Institute), that independent laboratory replication by external groups has not been published, and that the compounds have not been tested in non-human primate models.

7. Clinical Evidence Base

The clinical evidence for CMS121 consists of a single completed Phase 1 study. The compound has not been evaluated in efficacy trials in patients with Alzheimer's disease or any other neurodegenerative condition. The following summary is provided for research context only and does not constitute evidence of therapeutic efficacy.

7.1 Phase 1: Safety, pharmacokinetics, and cardiodynamics (NCT05318040)

Study design: Phase 1, randomized, double-blind, placebo-controlled, single ascending dose (SAD) and multiple ascending dose (MAD) study with food effect evaluation, conducted at Celerion (Lincoln, Nebraska) [5, 16].

Sponsor: Virogenics, Inc. (San Diego, California).

Collaborator: National Institute on Aging (NIA Award R01AG074447; \$4.5 million over two years) [17].

Study dates: May 1, 2022 to December 17, 2022 (completed) [16].

Population: Healthy adult volunteers, both male and female, aged 18 years and older, BMI 18.0 to 32.0 kg/m², non-smokers for at least 3 months prior to screening. Excluded: subjects with significant cardiovascular, psychiatric, or renal conditions, and those on medications requiring discontinuation within 14 days of dosing (28 days for CYP inducers) [16].

Study parts:

- Part 1 (SAD): Approximately 48 young subjects randomized to single oral doses of CMS121 or placebo at escalating dose levels up to 1800 mg [5, 16].
- Part 2 (MAD): Approximately 32 young subjects randomized to CMS121 or placebo at doses up to 900 mg per day for 7 days [5, 16].
- Part 3 (Elderly MAD): Approximately 8 elderly subjects receiving multiple doses to assess age-related pharmacokinetic differences [5, 16].

Safety findings: Single doses up to 1800 mg and repeat doses up to 900 mg per day for 7 days were generally well tolerated. The majority of treatment-emergent adverse events (TEAEs) were mild in severity [5]. Specific adverse event types, incidence rates, and ECG/QTc interval findings have not been published in the available preprint abstract.

Pharmacokinetics: As described in Section 5.2. Dose-proportional or slightly greater than dose-proportional kinetics; CMS121-C2 as the major circulating metabolite; minimal urinary excretion; approximately 50 percent increase in exposure with food; higher exposure and longer half-life in elderly subjects [5].

7.2 Clinical development status

As of May 2026, no Phase 2 clinical trial of CMS121 has been registered on ClinicalTrials.gov or publicly announced by Virogenics or the Salk Institute. The compound remains in preclinical and early clinical development. Investigators considering CMS121 for research applications should monitor ClinicalTrials.gov and the Salk Institute for updates on the clinical development trajectory.

8. Sourcing and Quality Verification

CMS121 is not a registered pharmaceutical product and is not available as a prescribed medicine in any jurisdiction. The compound is available exclusively as a research-grade chemical from commercial research suppliers.

Research-grade suppliers: CMS121 is listed in the catalogs of multiple research chemical suppliers, including Cayman Chemical (catalog number 27085), InvivoChem, MedChemExpress, Selleckchem, BocSci, and others. The compound is supplied as the free base in milligram to gram quantities, typically as a solid powder at greater than 98 percent purity by high-performance liquid chromatography [4].

Certificate of analysis: Research-grade CMS121 is supplied with vendor certificates of analysis documenting purity by HPLC, identity by mass spectrometry, and in some cases nuclear magnetic resonance spectroscopy confirmation.

Recommended identity and purity verification: Investigators should confirm compound identity and purity on every lot through:

- High-performance liquid chromatography area-percent purity (target: greater than 98 percent)
- Mass spectrometry confirmation of molecular weight (expected $[M+H]^+ = 322.14$ for $C_{20}H_{19}NO_3$)
- Nuclear magnetic resonance spectroscopy (1H -NMR in DMSO- d_6 or $CDCl_3$) confirmation of the quinoline, catechol, and cyclopentyloxy structural elements
- Karl Fischer analysis or loss-on-drying for residual water content
- Residual solvent analysis by gas chromatography for common synthesis solvents

Third-party analytical confirmation (Janoshik Analytical, Anabolic Lab, or equivalent) is appropriate for any investigation where dose-response precision or mechanism-of-action attribution depends on compound identity. The CMS121 research

supplier market is relatively new (the compound first appeared in commercial catalogs after approximately 2015) and lot-to-lot variability has not been systematically characterized in the literature.

9. Reconstitution and Handling

CMS121 is supplied as a solid powder that is stable under appropriate storage conditions. The following handling recommendations are derived from supplier specifications and published in vivo formulation protocols.

Storage (solid): Powder stored at minus 20 degrees Celsius is stable for up to 3 years. Storage at 4 degrees Celsius is acceptable for up to 2 years. Room temperature storage for short periods during weighing and formulation is acceptable [4].

Solubility and stock solutions:

- Dimethyl sulfoxide (DMSO): approximately 50 mg/mL (approximately 155.6 mM). This is the standard solvent for in vitro work. Stock solutions in DMSO at minus 80 degrees Celsius are stable for up to 6 months.
- In vivo formulation vehicle: at least 2.08 mg/mL in 10 percent DMSO, 40 percent polyethylene glycol 300, 5 percent Tween 80, and 45 percent normal saline. This formulation is appropriate for acute dosing by oral gavage.
- For chronic dietary administration (the route used in most published preclinical studies), CMS121 is mixed directly into rodent chow at 200 to 400 ppm [2, 3, 6, 8].

Light and oxygen sensitivity: Not specifically characterized in published literature. Standard practice for quinoline derivatives recommends protection from light and storage under inert atmosphere (nitrogen or argon) for long-term solution storage.

Aliquoting: Aliquoting of stock solutions for single-use is recommended to avoid repeated freeze-thaw cycles. Freeze-thaw stability has not been formally characterized in published literature for CMS121 specifically.

Aqueous solubility: Limited. Investigators requiring aqueous formulations should use co-solvents (DMSO, polyethylene glycol) or cyclodextrin complexation. Direct dissolution in aqueous buffer at neutral pH is not expected to achieve concentrations sufficient for most in vivo applications.

10. Stack Interaction Considerations

CMS121 interacts with lipid biosynthetic and metabolic pathways that are shared with other research compounds and approved therapies. The following interactions are mechanistically predicted or experimentally supported.

FASN inhibitors: Concurrent administration with other FASN inhibitors (TVB-2640/denifanstat, C75, cerulenin, orlistat at high concentrations) would produce additive inhibition of de novo fatty acid synthesis. The combination has not been studied but is pharmacologically predictable and could produce excessive suppression of hepatic lipogenesis. Investigators using CMS121 in metabolic research should be aware of this interaction potential.

AMPK activators: Compounds that activate AMPK (metformin, AICAR, berberine, resveratrol) would produce additive phosphorylation of ACC1 and synergistic elevation of acetyl-CoA. The combination of CMS121 with metformin is of particular translational interest given the geroprotective literature on both compounds, but has not been formally studied.

Acetyl-CoA carboxylase inhibitors: Direct ACC inhibitors in clinical development for metabolic disease (firsocostat/GS-0976, PF-05221304) would produce pharmacologically redundant ACC1 inhibition. The combination is not recommended in research unless the objective is to characterize the dose-response of ACC1 inhibition specifically.

Other geroneuroprotectors: J147 and CAD031 engage the same AMPK/ACC1 pathway as CMS121 but through structurally distinct upstream targets (J147 targets the alpha subunit of ATP synthase) [3, 14]. Combination studies of CMS121 and J147 have been conducted in the SAMP8 model in the context of shared pathway characterization but not as a combination pharmacology investigation [3].

Fisetin: As the parent compound of CMS121, fisetin shares multiple biological activities (antioxidant, anti-inflammatory, senolytic). Co-administration would be pharmacologically redundant for the shared mechanisms and additive for fisetin-specific activities (senolytic, Nrf2 induction). The combination has not been studied.

CYP interactions: CMS121 metabolism in humans involves at least three metabolites (C1, C2, C3), indicating hepatic cytochrome P450-mediated biotransformation [5]. The specific CYP isoforms responsible for CMS121 metabolism have not been published. Investigators co-administering CMS121 with strong CYP inhibitors or inducers should anticipate potential pharmacokinetic interactions pending publication of the CYP identification data.

Ferroptosis-modulating compounds: Compounds that modulate the ferroptosis pathway, including erastin (inducer), RSL3 (inducer), ferrostatin-1 (inhibitor), and liproxstatin-1 (inhibitor), are commonly used alongside CMS121 as pharmacological controls in mechanistic studies [2]. Co-administration of CMS121 with ferroptosis inducers would produce antagonistic effects; co-administration with ferroptosis inhibitors would be additive or synergistic.

11. Adverse Events and Safety Signal

11.1 Phase 1 human safety data

The Phase 1 trial (NCT05318040) reported that single doses of CMS121 up to 1800 mg and repeat doses up to 900 mg per day for 7 days were generally well tolerated in healthy adult volunteers, with the majority of treatment-emergent adverse events mild in severity [5]. Specific adverse event types, incidence rates, dose-response relationships for adverse events, serious adverse events, laboratory abnormalities, and ECG/QTc interval data have not been published in the available preprint abstract.

The eligibility criteria for the Phase 1 trial excluded subjects with significant cardiovascular, psychiatric, or renal conditions, limiting the generalizability of the safety data to medically complex populations [16].

11.2 Preclinical safety

In all published preclinical studies (APPswe/PS1deltaE9, SAMP8, R6/2, YAC128, db/db, C57BL/6 wild-type), CMS121 administered chronically via dietary admixture at 200 to 400 ppm for durations of 3 to 7 months was well tolerated with no reported dose-limiting toxicities [2, 3, 6, 7, 8]. Body weight, food consumption, and general health were monitored throughout these studies; no significant adverse effects attributable to CMS121 were reported.

IND-enabling toxicology studies were conducted prior to the Phase 1 trial, as described in the Currais, Raschke, and Maher (2024) comprehensive review [4]. The results of these formal toxicology studies supported a sufficient safety margin for human dosing but have not been published in detail in the peer-reviewed literature.

11.3 Theoretical safety considerations

FASN inhibition: Systemic FASN inhibition has the potential to disrupt hepatic de novo lipogenesis, which is an essential metabolic pathway. However, CMS121 is a partial inhibitor of FASN (reducing Vmax in a dose-dependent manner) rather than

a complete pathway blocker [2]. The clinical FASN inhibitor TVB-2640 (denifanstat) demonstrated acceptable safety in the Phase 2a FASCINATE-1 trial in NASH patients at doses that produced meaningful hepatic fat reduction, suggesting that partial FASN inhibition is tolerable in humans [15].

Lipid metabolism perturbation: Chronic suppression of de novo fatty acid synthesis could theoretically alter membrane composition, affect signaling lipid pools, or produce nutritional fatty acid deficiency in prolonged treatment. These concerns are mitigated by the dietary availability of essential fatty acids, but long-term safety monitoring in future efficacy trials should include comprehensive lipid panel assessment.

Age-related exposure increases: The Phase 1 finding of higher systemic exposures and longer elimination half-lives in elderly subjects [5] is relevant because the target population for Alzheimer's disease and aging indications is predominantly elderly. Dose adjustment in elderly subjects may be necessary in future efficacy trials, pending publication of the age-specific pharmacokinetic parameters.

11.4 Limitations of the safety database

The human safety database for CMS121 consists of a single Phase 1 trial in approximately 88 healthy volunteers with maximum exposure duration of 7 days [5, 16]. No efficacy trials in disease populations have been conducted. The safety profile in patients with Alzheimer's disease, Huntington's disease, or other neurodegenerative conditions is unknown. The safety profile under chronic dosing (the anticipated clinical use scenario) is unknown. Investigators should treat the Phase 1 safety data as a preliminary characterization only.

12. Comparable Compounds Assessment

This section presents a structured comparative assessment of five compounds in the same mechanistic or indication space as CMS121, evaluated against five competency standards: novelty, effect size, promising potential (current state and trajectory), side-effect profile, and overall validation. The five compounds were selected to represent the parent natural product (fisetin), two sister geroneuroprotectors from the same research pipeline (J147, CAD031), the most clinically advanced FASN inhibitor (denifanstat/TVB-2640), and the canonical ferroptosis inhibitor research tool (ferrostatin-1).

12.1 Fisetin (3,7,3',4'-tetrahydroxyflavone)

Mechanism: Multi-target flavonoid with direct antioxidant activity, Nrf2/ATF4-mediated glutathione maintenance, ERK/CREB-dependent neurotrophic signaling, anti-inflammatory activity through suppression of NF-kappaB, and senolytic activity (selective elimination of senescent cells) [12, 13, 29, 30]. Fisetin does not directly inhibit FASN; the CMS121-specific FASN inhibitory activity was engineered through the medicinal chemistry optimization [2].

Development trajectory: Fisetin is a widely available dietary supplement and has been the subject of multiple clinical trials for aging-related conditions, including senolytic trials at the Mayo Clinic (NCT03675724 for frail elderly adults; NCT03430037 for diabetic kidney disease). Published preclinical evidence includes efficacy in SAMP8 mice (500 ppm, approximately 25 mg/kg/day for 7 months), where fisetin prevented age-related cognitive decline, reduced inflammatory markers (GFAP, SAPK/JNK), and restored synaptic protein levels (Arc, Homer 1, SAP102) [12]. However, fisetin's neuroprotective EC50 in the glutamate oxytosis assay is in the low micromolar range, approximately 10-fold to 100-fold higher than CMS121 [1].

Novelty: Low. Fisetin is a well-characterized natural product with a large literature spanning cancer, inflammation, neurodegeneration, and senescence. The flavonoid scaffold is non-novel.

Effect size: Moderate in preclinical aging models. In the SAMP8 study, fisetin produced significant cognitive improvement and reduced multiple aging biomarkers [12]. Fisetin's low oral bioavailability limits the achievable plasma and brain concentrations in humans.

Promising potential: Moderate. Clinical trials are ongoing for senolytic applications. Neuroprotective clinical trials have not been conducted. The poor bioavailability remains a fundamental limitation for CNS applications.

Side-effect profile: Favorable. Fisetin is a dietary constituent with extensive human consumption history. No significant safety concerns have emerged from clinical trials at doses up to 20 mg/kg [13].

Overall validation: Moderate. Extensive preclinical evidence but limited clinical validation for neuroprotection specifically. The senolytic clinical program is the most advanced translational application.

Comparison to CMS121: CMS121 was designed to overcome fisetin's pharmacokinetic limitations while retaining its biological activities. CMS121 achieves 10-fold to 100-fold greater neuroprotective potency, improved oral pharmacokinetic profile, demonstrated brain penetration, and has progressed to Phase 1 clinical testing. Fisetin retains the advantage of widespread availability, extensive safety history, and additional mechanisms (senolytic, Nrf2 induction) that CMS121 may or may not fully replicate.

12.2 J147

Mechanism: Synthetic curcumin derivative that targets the alpha subunit of mitochondrial ATP synthase, engaging AMPK activation and downstream ACC1 inhibitory phosphorylation. The resulting elevation of acetyl-CoA and suppression of de novo fatty acid synthesis parallels CMS121's metabolic mechanism, though the upstream target is distinct [3, 14]. J147 is effective in the same oxytosis/ferroptosis phenotypic screening cascade used to discover CMS121 [10].

Development trajectory: Developed at the Salk Institute by the same Maher/Schubert laboratory. J147 has been tested in over a dozen rodent models of neurodegeneration and memory impairment, with consistent efficacy [10, 23, 24]. Brain pharmacokinetics in mice showed approximately 600 nM brain concentrations at 2 hours following a 20 mg/kg oral dose, with a brain-to-blood ratio of approximately 0.5 and 28 percent oral bioavailability [23]. Acute toxicity studies were

negative for oral toxicity at maximum testable dose, hERG, CYP450 inhibition, and Ames assays [23]. J147 entered Phase 1 clinical trials for Alzheimer's disease; the trial has been completed, though results have not been fully published in peer-reviewed form as of the present monograph date.

Novelty: Moderate. The ATP synthase alpha subunit target was novel at the time of identification and provides a mechanistic distinction from the direct FASN/ACC1 targeting of CMS121.

Effect size: Moderate to substantial in preclinical models. Consistent cognitive improvement across multiple animal models. Phase 1 results not yet published.

Promising potential: Moderate. Phase 1 complete; Phase 2 trajectory uncertain.

Side-effect profile: Preclinical safety profile favorable. Phase 1 safety data not published in detail.

Overall validation: Moderate. More extensively tested in preclinical models than CMS121; Phase 1 data pending publication.

Comparison to CMS121: J147 and CMS121 are sister geroneuroprotectors from the same laboratory, sharing the AMPK/ACC1 convergent pathway but differing in upstream targets (ATP synthase alpha subunit versus FASN) and structural class (curcumin derivative versus fisetin derivative). Both have completed Phase 1 trials. J147 has a more extensive preclinical literature but CMS121 has Phase 1 pharmacokinetic data in the public domain [5]. The two compounds are complementary research tools for dissecting the contribution of upstream target identity versus shared downstream metabolic mechanism.

12.3 CAD031

Mechanism: Derivative of J147 with maintained neuroprotective and anti-inflammatory properties and additional neurogenic activity (stimulation of nerve stem cell division) [10]. CAD031 engages the AMPK/ACC1 pathway, consistent with the shared mechanism of the Salk geroneuroprotector series. In SAMP8 mice, CAD031 extended median lifespan by approximately 30 percent and maintained mitochondrial homeostasis by regulating acetyl-CoA and fatty acid metabolism [9].

Development trajectory: Preclinical. CAD031 has been evaluated in SAMP8 mice with transcriptomic, metabolomic, and lifespan endpoints [9]. No IND application or clinical trial has been reported.

Novelty: Low to moderate. The compound is a structural derivative of J147 with an additional neurogenic mechanism.

Effect size: The approximately 30 percent lifespan extension in SAMP8 mice is the largest reported for any compound in the Salk geroneuroprotector series and exceeds the lifespan extensions observed with CMS121 (8.46 percent in *Drosophila*, 17 percent in YAC128 mice) [7, 9].

Promising potential: Low to moderate. Preclinical only; no clinical development pathway has been initiated.

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

Overall validation: Low. Limited to a single comprehensive preclinical study in SAMP8 mice.

Comparison to CMS121: CAD031 shows greater lifespan extension in the SAMP8 model than CMS121 and adds neurogenic activity. CMS121 has the advantage of completed Phase 1 human testing, identified molecular target (FASN), broader pre-clinical evidence base (Alzheimer's, Huntington's, metabolic disease), and established research-grade supplier availability.

12.4 Denifanstat (TVB-2640)

Mechanism: First-in-class selective FASN inhibitor that binds the ketoacylreductase (KR) domain of FASN, blocking NADPH consumption and palmitate synthesis [15]. Denifanstat was designed for metabolic disease (nonalcoholic steatohepatitis) rather than neurodegeneration, but it is the most clinically advanced compound targeting the same enzyme (FASN) as CMS121, providing a clinical reference for the safety and feasibility of FASN inhibition in humans.

Development trajectory: Sagimet Biosciences (formerly 3-V Biosciences) advanced denifanstat through Phase 1 in solid tumors (first-in-human study published 2021) and Phase 2a in NASH (FASCINATE-1 trial, published in *Gastroenterology* 2021) [15]. In the FASCINATE-1 trial, 99 patients with NASH were randomized to placebo, 25 mg, or 50 mg of denifanstat once daily for 12 weeks. The

50 mg cohort achieved a least squares mean reduction in liver fat of 28.0 percent (95 percent CI: minus 44.5 to minus 11.6; $p = 0.001$), and 61 percent of the 50 mg group achieved at least 30 percent relative liver fat reduction versus 11 percent on placebo ($p < 0.001$). Improvements were observed in metabolic, pro-inflammatory, and fibrotic biomarkers [15]. Denifanstat was subsequently advanced to Phase 2b/3 studies for NASH.

Novelty: High for the FASN inhibition mechanism in a clinical context. Denifanstat validates that pharmacological FASN inhibition is clinically feasible and tolerable.

Effect size: Clinically significant in NASH (28 percent liver fat reduction, improvement in inflammatory and fibrotic biomarkers) [15].

Promising potential: Moderate to high for NASH; no development for neurodegeneration.

Side-effect profile: Well tolerated in Phase 2a; adverse events were mostly mild and balanced among groups [15].

Overall validation: Moderate to high. Phase 2a positive data with clinical endpoints in NASH.

Comparison to CMS121: Denifanstat and CMS121 both inhibit FASN but through potentially different binding sites and with different downstream pharmacological profiles. Denifanstat validates the safety of FASN inhibition in humans, which de-risks CMS121's mechanism. CMS121 has the advantage of CNS penetration, the additional AMPK/ACC1/acetyl-CoA epigenetic mechanism, and the neuroprotective phenotypic activity that denifanstat has not been evaluated for. The two compounds are complementary: denifanstat provides clinical validation of the FASN target in peripheral metabolic disease, while CMS121 extends the FASN mechanism to CNS neurodegeneration.

12.5 Ferrostatin-1

Mechanism: Canonical small-molecule ferroptosis inhibitor that traps lipid peroxyl radicals and forms a complex with ferrous iron, reducing labile iron levels in cells [19, 20]. Ferrostatin-1 inhibits ferroptosis more efficiently than phenolic antioxidants through a unique iron-complexation mechanism [20]. It is the standard pharmacological control for ferroptosis inhibition in mechanistic studies.

Development trajectory: Research tool compound. Ferrostatin-1 has not been advanced to clinical development due to poor oral bioavailability, rapid metabolism, and limited pharmacokinetic suitability for in vivo applications beyond acute parenteral dosing in rodents [19]. The compound is used extensively as a positive control in ferroptosis research.

Novelty: Moderate at the time of its identification by Dixon and colleagues (2012); now a well-established pharmacological tool [19].

Effect size: Robust in vitro ferroptosis inhibition and in acute in vivo models (cerebral ischemia-reperfusion, intracerebral hemorrhage, spinal cord injury) when administered by direct injection [19, 20]. Not suitable for chronic oral dosing studies due to pharmacokinetic limitations.

Promising potential: Low as a clinical candidate; high as a research tool.

Side-effect profile: Not characterized in humans. Preclinical safety in acute studies is acceptable.

Overall validation: High as a mechanistic tool; low as a therapeutic candidate.

Comparison to CMS121: CMS121 and ferrostatin-1 both protect against ferroptotic cell death, but through fundamentally different mechanisms. CMS121 operates upstream by reducing the substrate pool for lipid peroxidation (via FASN inhibition); ferrostatin-1 operates downstream by directly scavenging lipid peroxyl radicals and chelating iron. CMS121 has the decisive advantages of oral bioavailability, brain penetration, chronic dosing suitability, and a multi-target pharmacological profile that ferrostatin-1 lacks. Ferrostatin-1 has the advantage of well-characterized, specific ferroptosis inhibition that makes it a cleaner mechanistic tool for dissecting the contribution of ferroptosis to a given pathological phenotype. The two compounds are frequently used together in mechanistic studies, with ferrostatin-1 as the reference inhibitor and CMS121 as the translationally relevant candidate [2].

12.6 Comparator summary

The five comparators illuminate CMS121's positioning from distinct angles. **Fisetin** is the parent compound from which CMS121 was derived, demonstrating that the medicinal chemistry optimization produced meaningful improvements in potency and pharmacokinetics while retaining the core biological activities. **J147** is the closest structural and programmatic peer, sharing the AMPK/ACC1 convergent pathway

from a distinct upstream target and an equivalent clinical development stage. **CAD031** represents the next-generation geroneuroprotector from the same pipeline, with stronger lifespan extension data but no clinical development. **Denifanstat** validates the clinical feasibility of FASN inhibition in humans, de-risking CMS121's principal molecular mechanism. **Ferrostatin-1** provides the mechanistic contrast, operating downstream of CMS121 in the ferroptosis pathway with high specificity but no translational potential.

CMS121 occupies a unique position as the only compound in this panel that combines direct FASN inhibition, AMPK/ACC1 pathway engagement, demonstrated CNS penetration and neuroprotective efficacy across multiple disease models, and completed Phase 1 human pharmacokinetic data. Its principal limitation relative to the comparator set is that the preclinical and mechanistic evidence originates predominantly from a single research group, and independent external replication has not been published. The clinical development trajectory beyond Phase 1 remains uncertain.

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Investigators should obtain analytical confirmation of identity and purity on every lot. The Phase 1 clinical trial data referenced in this monograph derive from a pre-print (medRxiv) that has not undergone peer review at the time of monograph preparation; pharmacokinetic parameters from this source should be treated as preliminary pending peer-reviewed publication.