

RESEARCH MONOGRAPH . COMPOUND PROFILE

TUDCA

A taurine conjugate of ursodeoxycholic acid distinguished by chemical chaperone activity at the endoplasmic reticulum, cytoprotective modulation of the unfolded protein response, and broad preclinical neuroprotective and metabolic activity across neurodegenerative, hepatobiliary, retinal, and metabolic disease models.

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ABSTRACT

Tauroursodeoxycholic acid (TUDCA) is a naturally occurring hydrophilic bile acid formed by taurine conjugation of ursodeoxycholic acid (UDCA), identified in bear bile in 1902 and used in traditional Chinese medicine for centuries prior to its modern pharmacological characterization. The compound functions principally as a chemical chaperone that alleviates endoplasmic reticulum (ER) stress by stabilizing the unfolded protein response (UPR) through modulation of the three canonical ER stress sensor pathways: PERK/eIF2alpha/ATF4, IRE1alpha/XBP1, and ATF6. Beyond ER stress modulation, TUDCA exerts potent anti-apoptotic activity through prevention of Bax translocation to mitochondrial membranes, inhibition of cytochrome c release, and activation of the PI3K/Akt survival pathway. The compound stabilizes mitochondrial membrane potential, reduces reactive oxygen species production, suppresses NF-kappaB-mediated proinflammatory cytokine release, and activates the nuclear receptor FXR and the membrane receptor TGR5. TUDCA crosses the blood-brain barrier and has demonstrated neuroprotective activity in preclinical models of Alzheimer's disease (APP/PS1 transgenic mice, reducing amyloid-beta deposition and rescuing spatial memory), Parkinson's disease (MPTP model, preventing dopaminergic neuronal loss), Huntington's disease (3-nitropropionic acid model, preserving striatal mitochondria), amyotrophic lateral sclerosis (SOD1 transgenic mice), retinal degeneration (multiple retinitis pigmentosa models), and ischemic stroke (reducing infarct volume by approximately 50 percent). The clinical evidence base includes Phase II trials in amyotrophic lateral sclerosis

demonstrating a favorable responder rate (87 percent versus 43 percent on placebo at 1 gram twice daily for 54 weeks in the Elia 2016 trial), a randomized controlled trial in obese insulin-resistant adults demonstrating a 30 percent improvement in hepatic and muscle insulin sensitivity at 1750 mg daily for 4 weeks, multiple trials in cholestatic liver disease demonstrating 40 to 51 percent reductions in liver enzymes, a Phase I/II trial in progressive multiple sclerosis demonstrating safety and immunological biomarker effects, and the Phase II CENTAUR trial of the combination product AMX0035 (TUDCA plus sodium phenylbutyrate) in ALS, which received accelerated FDA approval in September 2022 but was withdrawn from the market in October 2024 following the failure of the confirmatory Phase III PHOENIX trial to meet primary or secondary endpoints. A separate European Phase III trial (TUDCA-ALS) of TUDCA monotherapy in 337 ALS patients similarly failed to demonstrate efficacy at 18 months. The compound has been licensed for the treatment of cholestatic liver disease and cholesterol gallstones in several European and Asian jurisdictions since 1991 and maintains a favorable safety profile, with the principal adverse events being mild gastrointestinal effects (diarrhea in approximately 14 percent, abdominal pain in approximately 6 percent). This monograph reviews the chemistry, endogenous biosynthesis, and structural pharmacology of TUDCA; the multi-target cytoprotective mechanism spanning ER stress, mitochondrial stabilization, anti-apoptosis, and anti-inflammatory pathways; the comprehensive pharmacokinetic record including hepatic first-pass metabolism and blood-brain barrier penetration; the clinical evidence base across hepatobiliary, neurodegenerative, metabolic, retinal, and inflammatory indications; the reconstitution, sourcing, and stack-interaction considerations for laboratory and

research applications; and a comparative assessment of five cytoprotective and neuroprotective candidates against TUDCA on five competency standards.

1. Compound Identification

1.1 Names, synonyms, and registry identifiers

International Nonproprietary Name: Tauroursodeoxycholic acid (TUDCA).

Common synonyms: TUDCA, tauroursodeoxycholate, taurursodiol (United States Adopted Name used in AMX0035/Relyvrio labeling).

Marketed names: The compound has been marketed under various trade names in jurisdictions where it is registered for hepatobiliary indications. In the combination product AMX0035, taurursodiol was co-formulated with sodium phenylbutyrate and marketed as Relyvrio (Amylyx Pharmaceuticals) for amyotrophic lateral sclerosis in the United States from September 2022 to October 2024.

Chemical Abstracts Service registry numbers: 14605-22-2 (free acid), 35807-85-3 (sodium salt). The sodium salt is the common pharmaceutical and research-grade form.

International Union of Pure and Applied Chemistry name: 2-[[[(3 α ,5 β ,7 β)-3,7-dihydroxy-24-oxocholan-24-yl]amino]ethanesulfonic acid. The compound is the taurine amide conjugate of ursodeoxycholic acid at the C-24 carboxyl position.

1.2 Structural class and chemistry

TUDCA is a secondary bile acid conjugate belonging to the ursodeoxycholic acid structural family within the broader class of C24 steroidal bile acids. The compound consists of the steroid nucleus of ursodeoxycholic acid (3 α ,7 β -dihydroxy-5 β -cholan-24-oic acid) linked through an amide bond at the C-24 carboxyl to the amino group of taurine (2-aminoethanesulfonic acid). The taurine conjugation confers full ionization of the terminal sulfonate group across physiological pH ranges, producing substantially greater hydrophilicity and water solubility than the unconjugated parent compound UDCA [1, 2].

Molecular formula: C₂₆H₄₅NO₆S (free acid).

Molecular weight: 499.71 g/mol (free acid); 521.69 g/mol (sodium salt).

Physical properties: White to off-white crystalline powder. Freely soluble in water (as the sodium salt), methanol, and ethanol; sparingly soluble in apolar organic solvents. The compound is stable at room temperature in dry conditions and maintains stability in aqueous solution at refrigerated conditions.

Stereochemistry: TUDCA contains multiple stereocenters in the steroid nucleus characteristic of the 5 β -cholane series. The hydroxyl groups at C-3 (α orientation) and C-7 (β orientation) distinguish ursodeoxycholic acid from its epimer chenodeoxycholic acid (3 α ,7 α -dihydroxy). The 7 β -hydroxyl orientation is the structural basis for the hydrophilic character that distinguishes the ursodeoxycholic acid family from the more hydrophobic primary bile acid conjugates (taurochenodeoxycholic acid, taurocholic acid) and is the molecular feature responsible for the reduced cytotoxicity and membrane-stabilizing properties of TUDCA relative to hydrophobic bile acids [1].

1.3 Endogenous biosynthesis and synthesis

TUDCA is produced endogenously through a two-step process. Primary bile acids (cholic acid and chenodeoxycholic acid) are synthesized from cholesterol in the hepatocyte and conjugated with taurine or glycine before secretion into bile. In the intestinal lumen, bacterial 7 α -dehydroxylase and 7 β -epimerization by gut microbiota convert chenodeoxycholic acid to ursodeoxycholic acid. UDCA is then absorbed via the enterohepatic circulation, returned to the hepatocyte, and conjugated with taurine by bile acid-CoA:amino acid N-acyltransferase to produce TUDCA [3, 4].

Industrial and pharmaceutical synthesis of TUDCA proceeds by chemical conjugation of synthetic or semi-synthetic UDCA with taurine. The principal route involves activation of the UDCA C-24 carboxyl group (typically as a mixed anhydride with ethyl chloroformate or as an N-hydroxysuccinimide ester) followed by amide bond formation with taurine in aqueous-organic mixed solvent systems. The product is purified by recrystallization or reversed-phase chromatography and characterized by nuclear magnetic resonance spectroscopy, high-performance liquid chromatography, and mass spectrometry. Biosynthetic approaches using engineered *Saccharomyces cerevisiae* strains expressing bile acid biosynthetic enzymes have been described as alternative production methods [5]. The sodium salt is prepared by treatment with stoichiometric sodium hydroxide.

2. Abstract

Tauroursodeoxycholic acid (TUDCA) is a hydrophilic taurine-conjugated bile acid that functions as a chemical chaperone and multi-target cytoprotective agent. The compound was first identified in bear bile by Olof Hammarsten in 1902 and has been used in traditional Chinese, Korean, and Japanese medicine for centuries in the context of hepatobiliary and inflammatory disease [6]. Modern pharmacological characterization has established TUDCA as a potent modulator of endoplasmic reticulum stress, mitochondrial stability, apoptotic signaling, and inflammatory cascades, with a breadth of cytoprotective activity that extends substantially beyond the hepatobiliary indications for which the compound was originally registered.

The principal mechanism of action is chemical chaperone activity at the endoplasmic reticulum, where TUDCA stabilizes the unfolded protein response by promoting proper protein folding and modulating the three canonical UPR sensor pathways (PERK, IRE1alpha, ATF6) to favor adaptive rather than terminal signaling [1, 7]. This ER stress modulation is complemented by direct mitochondrial stabilization (prevention of membrane potential collapse, maintenance of ATP production, normalization of glutathione levels), anti-apoptotic signaling (inhibition of Bax translocation, prevention of cytochrome c release, activation of PI3K/Akt survival pathway), and anti-inflammatory activity (suppression of NF-kappaB-driven cytokine release, reduction of iNOS and COX-2 expression) [8, 9].

The compound crosses the blood-brain barrier in humans and has produced substantial neuroprotective effects in preclinical models of Alzheimer's disease, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, retinal degeneration, and ischemic and hemorrhagic stroke [10, 11]. In APP/PS1 transgenic mice, TUDCA dietary supplementation prevented cognitive deficits and reduced amyloid-beta deposition when initiated before plaque onset, and reduced established amyloid pathology when initiated after disease onset [12, 13]. In the MPTP mouse model of Parkinson's disease, TUDCA pretreatment prevented dopaminergic neuronal loss and ameliorated motor deficits [14, 15].

The clinical evidence base spans multiple indications. In cholestatic liver disease, TUDCA has been registered since 1991 and reduces liver enzymes (ALT, AST, GGT, alkaline phosphatase) by 40 to 51 percent in primary biliary cholangitis [16]. In amyotrophic lateral sclerosis, a Phase II trial (Elia et al. 2016) of TUDCA monotherapy at 1 gram twice daily demonstrated an 87 percent responder rate versus 43 percent on placebo over 54 weeks [17], and the Phase II CENTAUR trial of the combination product AMX0035 (TUDCA plus sodium phenylbutyrate) demonstrated a 25 percent reduction in functional decline rate [18]. Both the confirmatory Phase III PHOENIX trial of AMX0035 and the European Phase III TUDCA-ALS trial of TUDCA monotherapy failed to meet primary endpoints in 2024 [19, 20]. In metabolic disease, a randomized controlled trial in obese insulin-resistant adults demonstrated a 30 percent improvement in hepatic and muscle insulin sensitivity at 1750 mg daily for 4 weeks [21]. A Phase I/II trial in progressive multiple sclerosis demonstrated safety and measurable immunological effects at 2 grams daily for 16 weeks [22].

The safety profile is favorable. TUDCA has been administered to chronically ill populations including patients with primary biliary cirrhosis, liver transplant recipients, and ALS patients with no serious adverse events attributable to the compound. The principal adverse events are mild gastrointestinal effects (diarrhea, abdominal pain, dyspepsia), consistent with the bile acid pharmacological class. Chronic toxicity studies in dogs at 30-fold the proposed human dose for 26 weeks and in rats at 2- to 20-fold the proposed dose for 24 months showed no observed toxicity or carcinogenic effects [23].

3. Discovery and Development History

3.1 Traditional use and early identification

The use of bear bile in traditional Chinese medicine dates to at least the eighth century, with documented applications in hepatobiliary disease, inflammatory conditions, fever, and ocular disorders. Bear bile is naturally enriched in ursodeoxycholic acid and its taurine conjugate TUDCA relative to bile from other mammalian species, and this enrichment is the historical basis for the pharmacological distinctiveness attributed to bear bile in the traditional pharmacopeia [6, 24].

The modern pharmacological history of TUDCA begins with the 1902 report by the Swedish physiologist Olof Hammarsten, who identified a novel bile acid in polar bear bile that was subsequently characterized as the ursodeoxycholic acid conjugate. In 1927, Masato Shoda at Okayama University contributed to the crystallization and structural characterization of ursodeoxycholic acid from bear bile, establishing the naming convention (urso-, from the Latin *ursus*, bear) [24].

3.2 Synthetic development and hepatobiliary registration

Chemical synthesis of UDCA was achieved by researchers at the Tokyo Institute of Technology in 1954, enabling pharmaceutical development independent of animal-derived sources. UDCA was developed for the dissolution of cholesterol gallstones and for the treatment of cholestatic liver diseases, receiving regulatory approvals in Japan and subsequently in Europe and North America. The FDA approved UDCA (ursodiol) for primary biliary cholangitis in 1987.

TUDCA, the taurine conjugate, was developed as a pharmaceutical agent with enhanced water solubility and bioavailability relative to unconjugated UDCA. TUDCA was licensed for the treatment of cholesterol gallstones and chronic cholestatic liver disease in Italy and several other European jurisdictions beginning in 1991 [16]. A multicenter randomized double-blind trial comparing TUDCA and UDCA in primary biliary cholangitis demonstrated equivalent efficacy and safety, with TUDCA showing potential superiority in symptom relief [25].

3.3 Identification of chemical chaperone activity

The characterization of TUDCA as a chemical chaperone capable of alleviating ER stress was established in the early 2000s through work by Bharat Bhargav Bhatt, Umut Bhargav Ozcan, and collaborators, who demonstrated that TUDCA and the structurally unrelated compound 4-phenylbutyric acid (4-PBA) could resolve ER stress and restore insulin signaling in obese mice [26]. The Ozcan et al. (2006) report in *Science* demonstrated that oral administration of TUDCA or 4-PBA to ob/ob mice normalized hyperglycemia, restored insulin sensitivity in liver, muscle, and adipose tissue, and resolved the fatty liver, providing the first in vivo demonstration that chemical chaperone therapy could reverse the metabolic consequences of ER stress in obesity [26]. This finding reframed TUDCA from a hepatobiliary agent to a systemic cytoprotective compound and initiated the expansion of the research literature into neurodegenerative, metabolic, retinal, and inflammatory applications.

3.4 Expansion into neuroprotection and clinical translation

Beginning in the mid-2000s, the Bhargav Bhatt, Bhargav Rodrigues, and Steer laboratories characterized the neuroprotective activity of TUDCA in models of Alzheimer's disease, Parkinson's disease, Huntington's disease, and ALS. The compound was shown to cross the blood-brain barrier and to protect neurons through the composite mechanism of ER stress alleviation, mitochondrial stabilization, and anti-apoptotic signaling [10, 11].

The clinical translation to ALS was pursued through two parallel programs. The European TUDCA-ALS program, led by Adriano Chio and collaborators, advanced TUDCA monotherapy through a Phase II trial (Elia et al. 2016, NCT00877604) and subsequently to a Phase III multicenter trial across seven European countries (NCT03800524) [17, 20]. The American program, led by Sabrina Paganoni at Massachusetts General Hospital and developed commercially by Amylyx Pharmaceuticals, combined TUDCA (as taurursodiol) with sodium phenylbutyrate in the combination product AMX0035. The Phase II CENTAUR trial (NCT03127514) demonstrated a statistically significant reduction in functional decline rate, and the combination received accelerated FDA approval as Relyvrio in September 2022 [18]. The confirmatory Phase III PHOENIX trial (NCT05021536), enrolling approximately 600 patients across 69 sites, failed to meet its primary and secondary endpoints in March 2024, and Amylyx voluntarily withdrew Relyvrio from the United States and Canadian markets effective October 2024 [19].

4. Mechanism of Action

TUDCA is a multi-target cytoprotective agent. Its principal molecular activities, characterized in cell-free, cell-culture, and in vivo systems, are chemical chaperone activity at the endoplasmic reticulum; stabilization of mitochondrial membrane integrity; inhibition of intrinsic apoptotic signaling; suppression of proinflammatory transcriptional programs; and activation of bile acid receptors (FXR, TGR5) and associated signaling cascades. These activities operate at pharmacologically achievable concentrations and contribute differentially to the observed hepatoprotective, neuroprotective, metabolic, and anti-inflammatory effects.

4.1 Chemical chaperone activity and ER stress modulation

The endoplasmic reticulum is the principal site of protein folding, lipid biosynthesis, and calcium storage in eukaryotic cells. Accumulation of misfolded or unfolded proteins in the ER lumen triggers the unfolded protein response, a conserved signaling network mediated by three ER-resident transmembrane sensors: protein kinase R-like ER kinase (PERK), inositol-requiring enzyme 1 alpha (IRE1alpha), and activating transcription factor 6 (ATF6) [7].

TUDCA functions as a low-molecular-weight chemical chaperone that assists protein folding and reduces the burden of misfolded proteins in the ER lumen. The compound promotes the adaptive (pro-survival) arm of the UPR while suppressing the terminal (pro-apoptotic) arm. Specifically, TUDCA activates the ATF6 pathway, enhancing the transcription of ER-resident chaperones (GRP78/BiP, GRP94, calreticulin) and increasing the protein-folding capacity of the ER. TUDCA modulates the PERK pathway through activation of the pro-survival PERK/eIF2alpha/ATF4 axis while suppressing the downstream pro-apoptotic effector CHOP (C/EBP homologous protein). At the IRE1alpha branch, TUDCA suppresses the IRE1alpha/TRAF2/NF-kappaB inflammatory cascade [1, 7, 8].

The net effect is a shift in ER stress signaling from apoptotic commitment to adaptive resolution, reducing the fraction of cells that undergo ER stress-induced programmed cell death. This mechanism has been confirmed in diverse cell types including hepatocytes, neurons, pancreatic beta cells, retinal photoreceptors, cardiomyocytes, and immune cells.

4.2 Mitochondrial stabilization

TUDCA stabilizes mitochondrial membrane integrity through several complementary mechanisms. The compound prevents loss of mitochondrial membrane potential ($\Delta\psi$ -m) under stress conditions, maintains ATP production, normalizes mitochondrial glutathione levels, and reduces mitochondrial reactive oxygen species generation [9, 10]. TUDCA prevents the translocation of the pro-apoptotic protein Bax from the cytosol to the outer mitochondrial membrane, thereby blocking the formation of the mitochondrial permeability transition pore and the subsequent release of cytochrome c into the cytosol [8].

In Parkinson's disease models, TUDCA has been shown to modulate the PINK1/parkin-mediated mitophagy pathway, suggesting a role in mitochondrial quality control beyond acute membrane stabilization [14]. The mitochondrial stabilization is mechanistically distinct from the ER stress modulation and contributes independently to the cytoprotective phenotype.

4.3 Anti-apoptotic signaling

TUDCA inhibits apoptosis through multiple convergent pathways. At the mitochondrial level, prevention of Bax translocation and cytochrome c release blocks the activation of the initiator caspase-9 and the downstream executioner caspase-3. TUDCA activates the PI3K/Akt survival signaling pathway, which phosphorylates and inactivates the pro-apoptotic protein Bad and promotes cell survival through multiple downstream effectors [8, 9].

Additional anti-apoptotic mechanisms include interference with the E2F-1/Mdm-2/p53 apoptotic pathway through modulation of nuclear steroid receptor (NSR) signaling. TUDCA promotes the dissociation of heat shock protein 90 (HSP90) from mineralocorticoid and glucocorticoid receptors, enabling nuclear translocation of the receptor complex and subsequent transcriptional regulation of p53 target genes including BAX, PUMA, and NOXA [8]. The compound also inhibits calpain and caspase-12 activation associated with ER stress-mediated apoptosis.

4.4 Anti-inflammatory activity

TUDCA suppresses proinflammatory signaling through inhibition of NF-kappaB activation, reducing the transcription of proinflammatory cytokines including tumor necrosis factor alpha (TNF-alpha), interleukin-1 beta (IL-1beta), and interleukin-6

(IL-6). The compound downregulates the expression of inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2), reducing nitric oxide and prostaglandin production in activated macrophages and microglia [1, 27]. TUDCA modulates TGF-beta expression and reduces leukocyte extravasation in models of hepatic ischemia-reperfusion injury.

The anti-inflammatory mechanism is mediated in part through activation of the membrane bile acid receptor TGR5 (G protein-coupled bile acid receptor 1, GPBAR1), which upon ligand binding activates cAMP-dependent signaling that suppresses macrophage inflammatory responses [28].

4.5 Bile acid receptor signaling

TUDCA activates the nuclear farnesoid X receptor (FXR) and the membrane receptor TGR5, producing downstream effects on bile acid homeostasis, glucose metabolism, and lipid metabolism. FXR activation suppresses de novo bile acid synthesis through induction of small heterodimer partner (SHP) and regulates hepatic gluconeogenesis and lipogenesis. TGR5 activation promotes glucagon-like peptide-1 (GLP-1) secretion from enteroendocrine L-cells, contributing to the insulin-sensitizing effects observed in metabolic disease models [28, 29].

TUDCA also activates integrin alpha5-beta1 signaling via the sodium/taurocholate co-transporting polypeptide (NTCP) in hepatocytes, initiating ERK1/2 phosphorylation and downstream proliferative and cytoprotective signaling [1].

5. Pharmacokinetics and Routes of Administration

5.1 Absorption

TUDCA is absorbed from the gastrointestinal tract primarily in the ileum through the apical sodium-dependent bile acid transporter (ASBT), the same active transport mechanism responsible for the enterohepatic recirculation of endogenous bile acids. The taurine conjugation confers full ionization across physiological pH ranges, producing greater water solubility and more complete intestinal absorption than unconjugated UDCA [1, 2].

Oral bioavailability is limited by extensive hepatic first-pass extraction. TUDCA is efficiently taken up by hepatocytes via the sodium/taurocholate co-transporting polypeptide (NTCP), and minimal splanchnic escape of bile acid conjugates into the systemic circulation occurs under normal hepatic function [1]. This hepatic first-pass effect is a significant pharmacokinetic constraint for extrahepatic indications, as systemic plasma concentrations after oral dosing are substantially lower than the concentrations achieved in the portal circulation and in the hepatocyte.

5.2 Distribution

TUDCA distributes to the liver, biliary system, and intestinal lumen through the enterohepatic circulation. Systemic distribution beyond the hepatobiliary axis is limited but measurable. The compound crosses the blood-brain barrier in humans, as demonstrated by cerebrospinal fluid penetration data in ALS clinical trials [10, 17]. The mechanism of blood-brain barrier penetration has not been fully characterized but is consistent with transporter-mediated uptake.

An important pharmacokinetic limitation for extrahepatic applications is that the expression of NTCP and other bile acid transporters responsible for cellular uptake of TUDCA is very low in most extrahepatic tissues. Consequently, large systemic plasma concentrations may be required to achieve adequate tissue uptake to affect intracellular function in non-hepatic target organs [1].

5.3 Metabolism

TUDCA is metabolized in the hepatocyte through the standard bile acid metabolic pathways. The compound undergoes deconjugation (removal of the taurine moiety by bile salt hydrolase-expressing gut bacteria) to regenerate UDCA, which can be reabsorbed and reconjugated with taurine or glycine in the hepatocyte. UDCA is also subject to 7-beta epimerization by gut bacteria to produce chenodeoxycholic acid and subsequent 7-alpha dehydroxylation to produce lithocholic acid [3].

The enterohepatic circulation is the dominant disposition pathway, with the compound cycling between the liver, bile, intestine, and portal circulation multiple times per day. Renal excretion accounts for a minor fraction of total elimination. Hepatic impairment prolongs the enterohepatic circulation and increases systemic exposure.

5.4 Dosing in clinical studies

Clinical dosing has varied by indication. Cholestatic liver disease: 10 to 20 mg/kg/day, typically 500 to 1500 mg daily in divided doses [16, 25]. Amyotrophic lateral sclerosis (monotherapy): 1 gram twice daily (2 grams total daily) [17, 20]. Amyotrophic lateral sclerosis (combination with sodium phenylbutyrate as AMX0035): 1 gram TUDCA plus 3 grams sodium phenylbutyrate, administered as oral suspension [18]. Insulin sensitivity (metabolic research): 1750 mg daily for 4 weeks [21]. Progressive multiple sclerosis: 2 grams daily for 16 weeks [22]. A dose-response study in 24 patients with primary biliary cirrhosis evaluated 500, 1000, and 1500 mg daily, with all doses producing improvements in liver function tests and the greatest improvements observed at 1000 and 1500 mg [16].

5.5 Routes of administration

Oral administration is the principal clinical route. The compound is administered as capsules, tablets, or oral suspension (in the AMX0035 formulation). Intravenous administration has been used in selected research protocols. Subcutaneous and intraperitoneal routes are used in preclinical research. The compound is freely soluble in water as the sodium salt and does not require specialized formulation for oral delivery.

5.6 Special populations

Hepatic impairment increases systemic exposure owing to reduced hepatic extraction and prolonged enterohepatic cycling. Renal impairment has minimal effect on pharmacokinetics given the predominantly hepatic disposition. Pediatric pharmacokinetic data are limited; the compound has been studied in pediatric cystic fibrosis-associated liver disease at weight-adjusted doses. Pregnancy and lactation data are limited; the compound has not been formally evaluated in reproductive toxicology studies at the depth required for a pregnancy category assignment in most jurisdictions.

6. Preclinical Pharmacology

6.1 Neurodegenerative disease models

Alzheimer's disease. In APP/PS1 double-transgenic mice (a model expressing human amyloid precursor protein and presenilin-1 mutations), dietary TUDCA supplementation (0.4 percent mixed in food) initiated at 2 months of age and continued for 6 months prevented deficits in spatial, recognition, and contextual memory and prevented amyloid-beta deposition [12]. When TUDCA treatment (500 mg/kg intraperitoneal, every 3 days) was initiated after disease onset at 7 months of age and continued for 3 months, amyloid-beta 40 and amyloid-beta 42 levels were significantly reduced, GSK3-beta hyperactivity was abrogated, glial activation was decreased, proinflammatory cytokine expression was reduced, and synaptic loss was partially rescued [13]. The mechanism involved modulation of gamma-secretase activity and preservation of PSD95 expression. A 2025 study demonstrated that TUDCA ameliorated cognitive impairments in APP/PS1 mice through modulation of the microbiota-gut-brain axis [30].

Parkinson's disease. TUDCA pretreatment (50 mg/kg for 3 days) significantly prevented dopaminergic neuronal loss in the substantia nigra caused by MPTP administration, prevented microglial and astroglial activation, and maintained dopamine and DOPAC levels [14]. In a chronic MPTP model, TUDCA prevented protein oxidation and autophagy dysregulation, inhibited alpha-synuclein aggregation, and ameliorated motor performance including spontaneous activity, ability to initiate movement, and tremor [15]. TUDCA enhanced survival of transplanted dopamine neurons by reducing apoptosis by approximately 90 to 95 percent in cell transplantation models [10]. A 2025 study demonstrated that TUDCA combined with levodopa/carbidopa (Syndopa) protected the midbrain and gut from MPTP toxicity in a Parkinson's disease mouse model [31].

Huntington's disease. TUDCA provided neuroprotection in both chemical (3-nitropropionic acid) and genetic models of Huntington's disease. The compound significantly prevented apoptosis in the brain, preserved striatal mitochondrial structure, and improved sensorimotor performance on rotarod testing. Treated animals showed reduced motor deficits compared to vehicle-treated controls [10, 11].

Amyotrophic lateral sclerosis. In SOD1 transgenic mouse models of ALS, TUDCA delayed disease onset and extended survival. The compound reduced motor neuron degeneration and decreased markers of ER stress and apoptosis in spinal cord tissue [11].

6.2 Retinal degeneration models

TUDCA has been extensively characterized as a retinal neuroprotectant across multiple models of inherited and acquired retinal degeneration. In retinitis pigmentosa mouse models (rd1, rd10, P23H), systemic TUDCA administration preserved photoreceptor cells, maintained thicker outer nuclear layers, produced more fully developed photoreceptor outer segments, and generated significantly greater electroretinogram amplitudes compared to vehicle-treated controls [32, 33]. In laser-induced choroidal neovascularization (a model for age-related macular degeneration), TUDCA reduced lesion sizes and lowered vascular endothelial growth factor (VEGF) levels in retinal tissue. In diabetic retinopathy models, TUDCA suppressed ER stress-induced inflammation and markedly reduced cell death in retinal neural cells exposed to elevated glucose [33].

6.3 Stroke models

In rat models of transient cerebral ischemia, TUDCA administration produced an approximately 50 percent reduction in infarct volume and an 80 percent reduction in TUNEL-positive apoptotic cells, with improvements in mitochondrial swelling and caspase-3 activation [10]. Following collagenase-induced intracerebral hemorrhage, TUDCA produced a similar 50 percent reduction in infarct volume and improved limb placement and locomotor function [10].

6.4 Metabolic disease models

In ob/ob mice (a genetic model of obesity and insulin resistance), oral TUDCA administration normalized hyperglycemia, restored insulin sensitivity in liver, muscle, and adipose tissue, and resolved fatty liver [26]. The compound improved glucose-stimulated insulin secretion, increased pancreatic beta-cell mass, and protected beta cells from free fatty acid-induced apoptosis. TUDCA decreased protein tyrosine phosphatase 1B (PTP1B) expression, which normally suppresses insulin

receptor signaling [1, 21]. In diet-induced obesity models, TUDCA reduced adipose tissue dysfunction, decreased cardiac hypertrophy and hypertension, and normalized cardiac contractility [10].

6.5 Hepatobiliary models

TUDCA enhances insertion of key canalicular bile acid transporters (Mrp2, ABCB11/BSEP) into the hepatocyte apical membrane through calcium-dependent and integrin-mediated signaling pathways, promoting bile flow and reducing intracellular bile acid accumulation under cholestatic conditions [1, 34]. The compound protects hepatocytes from hydrophobic bile acid-induced apoptosis and from ischemia-reperfusion injury through the composite mechanism of ER stress reduction, mitochondrial stabilization, and anti-inflammatory signaling.

7. Clinical Evidence Base

7.1 Cholestatic liver disease

TUDCA has been licensed for the treatment of cholestatic liver disease in several European and Asian jurisdictions since 1991. In a study of 12 women with primary biliary cirrhosis, TUDCA treatment for 2 months reduced liver enzymes by 51 percent [16]. In a larger study of 23 subjects with primary biliary cirrhosis, TUDCA significantly improved levels of ALT, AST, gamma-glutamyltranspeptidase, and alkaline phosphatase [16]. A dose-response study in 24 patients evaluated 500, 1000, and 1500 mg daily, with the greatest improvements in liver function tests observed at the 1000 and 1500 mg doses [16]. A multicenter randomized double-blind trial comparing TUDCA and UDCA in primary biliary cholangitis demonstrated equivalent efficacy and safety profiles, with TUDCA showing potential superiority in symptom relief [25].

7.2 Amyotrophic lateral sclerosis

The ALS clinical program represents the most extensive clinical evaluation of TUDCA outside hepatobiliary indications.

Phase II monotherapy (Elia et al. 2016). A parallel-group, double-blind, placebo-controlled trial enrolled 34 ALS patients (17 TUDCA, 17 placebo). TUDCA was administered at 1 gram twice daily for 54 weeks after a 12-week run-in period. The responder rate (defined as 15 percent or greater improvement in ALSFRS-R slope) was 87 percent for TUDCA versus 43 percent for placebo ($p = 0.021$). Monthly functional decline was 1.13 points in the TUDCA arm versus 1.60 points in the placebo arm, with a 7-point ALSFRS-R advantage for TUDCA at study end. Post-hoc survival analysis showed a hazard ratio of 0.051 (95 percent confidence interval 0.002 to 1.059) with 1 death in the active arm versus 3 in the placebo arm. The compound was well tolerated, with mild diarrhea and anorexia as the principal reported adverse events [17].

Phase II combination (CENTAUR trial, Paganoni et al. 2020). A parallel-group, double-blind, placebo-controlled trial enrolled 137 ALS patients (89 active, 48 placebo). AMX0035 (TUDCA 1 gram plus sodium phenylbutyrate 3 grams) was ad-

ministered for 24 weeks. Monthly functional decline was 1.24 points in the active arm versus 1.66 points in the placebo arm (difference 0.42 points/month, 95 percent CI 0.03 to 0.81, $p = 0.03$). An open-label extension demonstrated a median survival of 25.8 months for participants originally randomized to active treatment versus 18.9 months for those originally on placebo (HR 0.57, 95 percent CI 0.35 to 0.92, $p = 0.023$) [18].

FDA accelerated approval and withdrawal. Based on the CENTAUR Phase II results, the FDA granted accelerated approval to AMX0035 (Relyvrio) in September 2022 for the treatment of ALS in adults, despite concerns about the strength of the evidence from a single Phase II trial of 137 patients [19].

Phase III PHOENIX trial (2024). The confirmatory Phase III trial enrolled approximately 600 patients across 69 sites in North America and Europe for 48 weeks. In March 2024, Amylyx announced that the trial did not meet its prespecified primary endpoint (ALSFRS-R decline rate) or any secondary endpoints (including survival, slow vital capacity decline, and quality of life). Amylyx subsequently announced voluntary withdrawal of Relyvrio from the United States and Canadian markets effective October 2024 [19].

Phase III TUDCA-ALS (European, 2024). The European multicenter Phase III trial enrolled 337 ALS patients across 25 centers in seven countries. TUDCA monotherapy at 1 gram twice daily was administered for 18 months after a 3-month run-in. The trial did not meet its primary endpoint (responder rate based on ALSFRS-R slope improvement at 18 months) and showed no difference between TUDCA and placebo in secondary outcome measures including survival and biomarker measurements [20].

7.3 Metabolic disease and insulin sensitivity

Kars et al. (2010). A randomized, double-blind, placebo-controlled trial in obese insulin-resistant adults ($n = 20$) evaluated TUDCA at 1750 mg daily for 4 weeks. TUDCA treatment resulted in an approximately 30 percent increase in hepatic and muscle insulin sensitivity as measured by hyperinsulinemic-euglycemic clamp technique. Adipose tissue insulin sensitivity was not significantly improved. Markers of ER stress were not altered in peripheral tissues, and the specific cellular mechanisms responsible for the increased insulin sensitivity in humans remained unclear [21].

Type 1 diabetes. A clinical trial (NCT02218619) evaluated TUDCA in new-onset type 1 diabetes. Preclinical studies in mice demonstrated that TUDCA improved beta-cell mass and reduced insulin degradation in early-stage type 1 diabetes models [35].

7.4 Progressive multiple sclerosis

A double-blind, placebo-controlled trial enrolled 54 patients with progressive multiple sclerosis randomized to TUDCA (2 grams daily) or placebo for 16 weeks. TUDCA supplementation was safe and well tolerated, with adverse events not significantly differing between arms ($p = 0.77$). The TUDCA arm demonstrated increased serum bile acid levels, decreased central memory CD4+ and Th1/17 cells, increased CD4+ naive cells, and changes in gut microbiota composition and function. No significant differences were noted in clinical outcomes or fluid biomarker measurements. The investigators concluded that TUDCA supplementation in progressive MS warrants further evaluation in larger, longer-duration trials [22].

7.5 Hepatobiliary and other indications

TUDCA has been evaluated in clinical studies of cystic fibrosis-associated liver disease (NCT00004441), total parenteral nutrition-associated liver disease, and transthyretin amyloidosis (in combination with doxycycline in a Phase II trial). In liver transplant recipients, 500 mg of TUDCA daily for one year was well tolerated with no adverse effects [23].

8. Sourcing and Quality Verification

Pharmaceutical-grade TUDCA is available in jurisdictions where the compound is registered for hepatobiliary indications (Italy, other European markets, Asian jurisdictions). The pharmaceutical material is supplied as oral capsules or tablets, typically as the sodium salt.

Research-grade TUDCA is supplied by multiple chemical and pharmaceutical research suppliers (Cayman Chemical, Sigma-Aldrich/MilliporeSigma, Selleckchem, Santa Cruz Biotechnology, MedChemExpress, Tocris, and others) at greater than 98 percent purity by HPLC. Supply is available in milligram to multi-gram quantities as the sodium salt or free acid. Pricing is moderate, generally in the range of \$30 to \$150 per gram for research-grade material at the time of monograph preparation.

TUDCA is also widely available as an over-the-counter dietary supplement in the United States and other jurisdictions where it is not classified as a prescription drug. Supplement-grade TUDCA is available from numerous manufacturers at dosages of 250 to 500 mg per capsule. Supplement-grade material varies in quality and analytical confirmation; investigators should not assume pharmaceutical equivalence.

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

- High-performance liquid chromatography area-percent purity, ideally greater than 98 percent
- Mass spectrometry confirmation of molecular weight (500.71 for the protonated free acid $[M+H]^+$, or 522.69 for the sodium salt adduct)
- Bile acid profile analysis to confirm the absence of contaminating hydrophobic bile acids (chenodeoxycholic acid, deoxycholic acid, lithocholic acid), which are cytotoxic at concentrations where TUDCA is cytoprotective
- Residual solvent and heavy metal analysis as appropriate for the intended application

Third-party analytical confirmation of vendor certificates of analysis is recommended for any investigation where dose-response precision or mechanistic specificity is important.

9. Reconstitution and Handling

TUDCA sodium salt is freely soluble in water at room temperature. For research applications, the compound is supplied as a crystalline or lyophilized powder and is reconstituted as needed. Stock solutions are typically prepared at 10 to 100 mM in water, phosphate-buffered saline, or cell culture medium. For in vitro ER stress modulation studies, working concentrations of 100 to 500 micromolar are standard; for cytoprotection assays, concentrations of 50 to 300 micromolar are typical [7].

For in vivo research applications, TUDCA is dissolved in saline for intraperitoneal or intravenous administration. Common preclinical dosing regimens include 50 to 500 mg/kg by intraperitoneal injection and 0.4 percent weight/weight in rodent chow for chronic oral administration [12, 14].

Storage of the solid material at room temperature in a dry environment is acceptable for short-term use; long-term storage at minus 20 degrees Celsius is recommended. Aqueous stock solutions should be stored at 2 to 8 degrees Celsius and used within 7 to 14 days of preparation. The compound is stable through at least 3 freeze-thaw cycles without measurable potency loss, though aliquoting for single-use is recommended to minimize repeated freeze-thaw exposure.

The compound is photostable under normal laboratory lighting conditions. Protection from prolonged direct light exposure is reasonable practice but not required for routine handling. Autoclaving is not recommended; sterile solutions should be prepared by filtration through 0.22-micrometer membranes.

10. Stack Interactions and Combinations

TUDCA interacts with several drug classes through its bile acid pharmacology, its effects on hepatic transporters, and its cytoprotective mechanisms. Investigators conducting research with TUDCA, particularly in chronic dosing regimens or in combination with other research compounds, should consider:

Sodium phenylbutyrate (NaPB). The combination of TUDCA and NaPB was the basis of the AMX0035 (Relyvrio) product. Both compounds are classified as chemical chaperones but act through complementary mechanisms: TUDCA stabilizes the UPR and mitochondrial membranes, while NaPB acts as a histone deacetylase inhibitor and promotes protein folding through distinct chaperone pathways. The Phase II CENTAUR trial reported additive efficacy in ALS [18]; however, the Phase III PHOENIX trial did not confirm this observation [19]. Gastrointestinal adverse events (diarrhea, nausea) may be additive in combination.

Ursodeoxycholic acid (UDCA). Concurrent administration of TUDCA and UDCA is pharmacologically redundant for hepatobiliary effects, as TUDCA is the taurine conjugate of UDCA and both share the same bile acid receptor pharmacology. The combination does not produce additional benefit beyond UDCA or TUDCA monotherapy in cholestatic liver disease [25].

CYP enzyme substrates. TUDCA is not a significant inhibitor or inducer of major cytochrome P450 enzymes at clinically relevant concentrations. However, the compound modulates hepatic transporter expression (Mrp2, BSEP, NTCP), and changes in transporter function may secondarily affect the disposition of drugs that rely on biliary excretion [34].

Bile acid sequestrants. Cholestyramine, colestipol, and colesevelam bind bile acids in the intestinal lumen and reduce TUDCA absorption. Concurrent administration should be separated by at least 4 hours.

Immunosuppressants. In liver transplant studies, TUDCA was co-administered with standard immunosuppressive regimens without clinically significant interactions [23].

Neuroprotective stacks. In preclinical research, TUDCA has been combined with coenzyme Q10 and creatine, demonstrating additive neuroprotective effects in in vitro models of Parkinson's disease [36]. Combination with levodopa/carbidopa in Parkinson's disease mouse models has shown complementary neuroprotective and symptomatic effects [31]. These combinations are preclinical and have not been validated in clinical trials.

Cholesterol-lowering agents. TUDCA activates FXR, which modulates cholesterol and bile acid homeostasis. Theoretical interactions with statins, fibrates, and ezetimibe exist through shared hepatic metabolic pathways, though clinically significant interactions have not been reported.

11. Adverse Events and Safety

11.1 Common adverse events

The principal adverse events at clinical doses are mild gastrointestinal effects:

- Diarrhea (approximately 14 percent in ALS trial populations, dose-dependent; reflects the osmotic and secretory effects of bile acids in the intestinal lumen) [17, 20]
- Abdominal pain (approximately 6 percent)
- Dyspepsia and nausea (approximately 3 to 5 percent)
- Skin eruption and pruritus (approximately 3 to 4 percent, uncommon)
- Headache (approximately 2 to 3 percent)

These adverse event rates are consistent across the hepatobiliary, ALS, metabolic, and MS clinical trial populations and are manageable with dose adjustment or symptomatic treatment. The gastrointestinal effects are characteristic of the bile acid pharmacological class and are more pronounced at higher doses.

11.2 Serious adverse events

No serious adverse events directly attributable to TUDCA have been reported in clinical trials or in postmarketing surveillance from jurisdictions where the compound is registered for hepatobiliary indications. The Phase III TUDCA-ALS and PHOENIX trials, which enrolled a combined total of approximately 940 ALS patients, did not identify safety signals beyond the expected mild gastrointestinal effects [19, 20].

11.3 Preclinical toxicology

Chronic toxicity studies in dogs at doses of 400 to 600 mg/kg/day (approximately 30-fold the proposed human dose on a per-kilogram basis) for 26 weeks showed no observed toxicity. Rats treated with 2- to 20-fold the proposed human dose showed no evidence of carcinogenic effects after 24 months of treatment [23]. Reproductive toxicology data are limited.

11.4 Hepatobiliary considerations

Although TUDCA is hepatoprotective, it is a bile acid and participates in the entero-hepatic circulation. In patients with complete biliary obstruction, exogenous bile acid administration may be ineffective or contraindicated. In patients with advanced cirrhosis, the capacity for hepatic uptake and conjugation may be compromised, altering the pharmacokinetic profile. TUDCA does not share the hepatotoxic potential of hydrophobic bile acids (deoxycholic acid, lithocholic acid) and in fact protects against their toxicity.

11.5 Supplement safety considerations

TUDCA is widely available as an over-the-counter supplement in many jurisdictions. Supplement-grade material is not subject to the same manufacturing, purity, and potency standards as pharmaceutical-grade material. Investigators and consumers should be aware that supplement quality varies by manufacturer, and analytical confirmation of identity and purity is appropriate, particularly when dose-response precision is important.

12. Comparable Compounds Assessment

This section presents a structured comparative assessment of five cytoprotective and neuroprotective candidates against TUDCA, evaluated against five competency standards: novelty, effect size, promising potential (current clinical state and trajectory), side-effect profile, and overall validation. The five candidates were selected as the principal compounds that share TUDCA's chemical chaperone, ER stress-modulatory, or bile acid-derived cytoprotective mechanisms and that have produced material clinical or advanced preclinical evidence in overlapping indications.

12.1 Ursodeoxycholic acid (UDCA)

Mechanism: Hydrophilic bile acid; the unconjugated parent compound of TUDCA. UDCA shares the 7 β -hydroxyl configuration that confers hydrophilicity and cytoprotective activity. UDCA modulates bile acid composition, protects hepatocytes from hydrophobic bile acid toxicity, and has immunomodulatory and anti-apoptotic activity through overlapping but not identical pathways to TUDCA [2, 25].

Development trajectory: UDCA is FDA-approved (as ursodiol) for the treatment of primary biliary cholangitis and for the dissolution of radiolucent gallstones. It is one of the most widely prescribed hepatobiliary agents globally. UDCA has been evaluated in clinical trials for inflammatory bowel disease, non-alcoholic steatohepatitis, colorectal cancer prevention, cystic fibrosis-associated liver disease, and intrahepatic cholestasis of pregnancy.

Novelty: Low. UDCA is the historical reference compound in the hydrophilic bile acid class and predates TUDCA in clinical development by decades.

Effect size: Moderate in hepatobiliary indications. UDCA produces well-documented improvements in liver function tests and delays histological progression in primary biliary cholangitis. Effect sizes in non-hepatobiliary indications (colorectal cancer prevention, NASH) have been modest and inconsistent.

Promising potential: Stable. The compound has established clinical indications and continues to be evaluated in new applications. Research-grade and pharmaceutical-grade UDCA are widely available.

Side-effect profile: Favorable. The principal adverse events are diarrhea and gastrointestinal discomfort, similar to TUDCA. UDCA is well tolerated in long-term administration for primary biliary cholangitis.

Overall validation: High for hepatobiliary indications; moderate for non-hepatobiliary applications.

Comparison to TUDCA: TUDCA is the taurine conjugate of UDCA with enhanced water solubility, bioavailability, and potentially broader cytoprotective activity. Head-to-head clinical comparisons in primary biliary cholangitis demonstrate equivalent efficacy with potential symptom-relief superiority for TUDCA [25]. TUDCA has a more extensive preclinical literature in neuroprotection and ER stress modulation. UDCA has the advantage of broader regulatory approvals and longer clinical track record.

12.2 Sodium phenylbutyrate (NaPB)

Mechanism: Chemical chaperone and histone deacetylase inhibitor. NaPB promotes protein folding through mechanisms distinct from TUDCA and modulates gene expression through HDAC inhibition. The compound is FDA-approved for urea cycle disorders as a nitrogen-scavenging agent [18, 37].

Development trajectory: NaPB has been evaluated as a neuroprotective agent in ALS (as a component of AMX0035/Relyvrio), Huntington's disease, spinal muscular atrophy, and cystic fibrosis. The Phase II CENTAUR trial of NaPB combined with TUDCA demonstrated a statistically significant slowing of functional decline in ALS [18]. The confirmatory Phase III PHOENIX trial failed [19].

Novelty: Low. NaPB has been used clinically for urea cycle disorders since the 1990s; its application as a chemical chaperone is a repositioning strategy.

Effect size: In the CENTAUR Phase II trial, the NaPB plus TUDCA combination produced a difference of 0.42 ALSFRS-R points per month relative to placebo [18]. This effect was not replicated in the Phase III PHOENIX trial [19].

Promising potential: Low to moderate. The ALS indication has been terminated following Phase III failure and market withdrawal. The compound retains its urea cycle disorder indication.

Side-effect profile: The principal adverse events are gastrointestinal (nausea, vomiting, diarrhea) and the characteristic unpleasant taste and body odor associated with the phenylbutyrate metabolite phenylacetate. These tolerability issues contributed to a 19 percent discontinuation rate in the active arm of the CENTAUR trial.

Overall validation: Moderate for the chemical chaperone mechanism; the Phase III failure has substantially reduced validation for the neuroprotective application.

Comparison to TUDCA: NaPB and TUDCA are complementary chemical chaperones with distinct molecular mechanisms. TUDCA has superior tolerability and broader cytoprotective activity. The failure of both the PHOENIX trial (NaPB plus TUDCA) and the TUDCA-ALS trial (TUDCA alone) in ALS suggests that neither compound alone nor in combination produces sufficient clinical benefit in ALS at the doses studied.

12.3 4-Phenylbutyric acid (4-PBA)

Mechanism: Low-molecular-weight chemical chaperone structurally related to sodium phenylbutyrate. 4-PBA reduces ER stress by stabilizing protein conformation, preventing protein aggregation, and facilitating protein trafficking from the ER [26].

Development trajectory: 4-PBA is primarily a research tool compound. It was one of the two chemical chaperones (alongside TUDCA) used in the seminal Ozcan et al. (2006) demonstration that chemical chaperone therapy could reverse metabolic consequences of ER stress in obese mice [26]. 4-PBA has been evaluated in preclinical models of diabetes, neurodegeneration, and cystic fibrosis but has not advanced to late-phase clinical development as a standalone neuroprotective or cytoprotective agent.

Novelty: Low. The compound is a well-characterized reference chemical chaperone.

Effect size: Substantial in preclinical ER stress models, where it produces effects comparable to TUDCA in normalizing glucose homeostasis and reducing ER stress markers [26].

Promising potential: Low as a clinical candidate. The compound serves principally as a research tool.

Side-effect profile: Preclinical and early clinical data suggest gastrointestinal adverse events similar to the phenylbutyrate class. The compound has the same taste and odor issues as sodium phenylbutyrate.

Overall validation: Low. The compound is a preclinical reference tool with limited clinical validation.

Comparison to TUDCA: 4-PBA and TUDCA are mechanistically complementary chemical chaperones used together in the foundational research that established the therapeutic potential of ER stress modulation [26]. TUDCA has substantially greater clinical validation, a broader mechanism of action (including mitochondrial stabilization, anti-inflammatory activity, and bile acid receptor signaling), and superior tolerability.

12.4 Arimoclomol

Mechanism: Co-inducer of the heat shock response. Arimoclomol amplifies the expression of heat shock proteins (HSP70, HSP90) under conditions of cellular stress, promoting protein folding and proteostasis through the endogenous chaperone system rather than through direct chemical chaperone activity [38].

Development trajectory: Orphazyme (now Chiesi) advanced arimoclomol through clinical development for ALS, Niemann-Pick disease type C (NPC), sporadic inclusion body myositis (sIBM), and Gaucher disease. A Phase III trial in NPC demonstrated positive efficacy and safety, leading to regulatory submissions. In ALS, a Phase III trial (NCT03491462) enrolled 245 patients and reported in 2021 that arimoclomol did not meet its primary endpoint (combined assessment of function and survival) [38].

Novelty: Moderate. The heat shock response amplification mechanism is distinct from the chemical chaperone mechanism of TUDCA and represents a fundamentally different approach to proteostasis enhancement.

Effect size: Negative in the ALS Phase III trial. Positive in NPC Phase III (approved in some jurisdictions). Variable across other indications.

Promising potential: Low for ALS (Phase III negative). Moderate for rare lysosomal storage diseases.

Side-effect profile: Generally well tolerated. The principal adverse events in ALS trials were diarrhea, nausea, and fatigue, similar in frequency to placebo.

Overall validation: Moderate overall; negative validation in ALS specifically.

Comparison to TUDCA: Arimoclomol and TUDCA address proteostasis through fundamentally different mechanisms (heat shock response amplification versus direct chemical chaperone activity). Both failed Phase III trials in ALS, suggesting that proteostasis modulation may be insufficient as a single therapeutic strategy in that disease. TUDCA has a broader mechanism of action and a wider range of pre-clinical and clinical indications.

12.5 Edaravone

Mechanism: Free radical scavenger. Edaravone eliminates lipid peroxides and hydroxyl radicals, reducing oxidative stress-induced neuronal damage. The mechanism is distinct from TUDCA's ER stress modulation and chemical chaperone activity [39].

Development trajectory: Edaravone (Radicava/Radicut) was approved in Japan for acute ischemic stroke (2001) and in the United States for ALS (2017). The FDA approval for ALS was based on a Phase III trial in a highly selected Japanese ALS population (definite or probable ALS by revised El Escorial criteria, forced vital capacity 80 percent or greater, disease duration 2 years or less) that demonstrated a statistically significant difference in ALSFRS-R decline rate over 24 weeks [39]. Subsequent real-world evidence and broader population studies have shown more modest benefits.

Novelty: Moderate. The free radical scavenging mechanism is well established; the application to ALS was novel at the time of approval.

Effect size: In the pivotal Phase III trial (Study 19), edaravone produced a 33 percent reduction in ALSFRS-R decline rate relative to placebo in the selected population [39]. Effect size in broader ALS populations is smaller and less consistent.

Promising potential: Moderate. The compound retains FDA approval for ALS (unlike Relyvrio) and is used clinically, though its overall impact on ALS disease trajectory remains modest.

Side-effect profile: The principal adverse events are bruising and gait disturbance with intravenous formulation. An oral formulation was approved in 2022, improving convenience. The compound is generally well tolerated.

Overall validation: Moderate to high. FDA-approved with Phase III evidence, though the clinical benefit in broad ALS populations is modest.

Comparison to TUDCA: Edaravone and TUDCA act through distinct mechanisms (oxidative stress reduction versus ER stress modulation and chemical chaperone activity). Edaravone has the advantage of maintained FDA approval for ALS. TUDCA has the advantage of broader cytoprotective activity across multiple cellular stress pathways, broader preclinical evidence across multiple disease models, and established hepatobiliary indications. Neither compound has demonstrated transformative clinical benefit in ALS.

12.6 Comparator summary

The five comparator compounds occupy distinct positions in the cytoprotective and neuroprotective pharmacology space. **UDCA** is the parent compound of TUDCA with equivalent hepatobiliary efficacy but inferior hydrophilicity and potentially narrower extrahepatic activity. **Sodium phenylbutyrate** is a complementary chemical chaperone whose combination with TUDCA failed Phase III validation in ALS. **4-PBA** is a preclinical reference chaperone with limited clinical development. **Arimoclomol** represents a mechanistically distinct approach to proteostasis through heat shock response amplification but similarly failed Phase III in ALS. **Edaravone** is the only comparator with maintained FDA approval in a neurodegenerative indication but acts through a narrower mechanism (free radical scavenging).

TUDCA occupies a distinctive position in this comparator landscape: it is the only compound with both established hepatobiliary registration and extensive preclinical neuroprotective evidence across multiple disease models; the only compound with the composite mechanism of ER stress modulation, mitochondrial stabilization, anti-apoptotic signaling, anti-inflammatory activity, and bile acid receptor activation; and the compound with the most favorable tolerability profile in the

panel. The principal limitation is the failure of two Phase III trials in ALS (monotherapy and combination), which has substantially dampened enthusiasm for TUDCA as a disease-modifying therapy in that indication.

The broader preclinical evidence base in Alzheimer's disease, Parkinson's disease, retinal degeneration, metabolic disease, and inflammatory conditions remains substantial and largely untested in adequately powered clinical trials. Investigators considering TUDCA for research applications should weigh the strong preclinical signal against the negative ALS Phase III results, recognizing that the ALS failure may reflect disease-specific biology (the aggressive, multi-pathway neurodegeneration of ALS may overwhelm the cytoprotective capacity of TUDCA at achievable doses) rather than a failure of the underlying mechanism. The compound's safety profile, regulatory history, commercial availability (including as an over-the-counter supplement), and mechanistic breadth support its continued use as a research tool and as a candidate for clinical evaluation in indications beyond ALS where ER stress, mitochondrial dysfunction, and apoptotic cell death are prominent pathological features.

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