

RESEARCH MONOGRAPH . COMPOUND PROFILE

Encenicline

A quinuclidine benzothiophene-2-carboxamide developed at EnVivo and advanced by Forum Pharmaceuticals through two global Phase 3 programs in schizophrenia cognitive impairment and one Phase 3 program in Alzheimer disease, terminated in March 2016 after both Phase 3 schizophrenia trials missed co-primary endpoints and following a September 2015 FDA clinical hold for severe gastrointestinal adverse events.

DOCUMENT	KDC-MN-1352
ISSUED	2026-05-10
REVISION	1.0
AUTHOR	Kodi <i>ac</i> biolabs Research
COMPOUND CLASS	Selective alpha-7 nicotinic acetylcholine receptor partial agonist

RESEARCH USE ONLY

ABSTRACT

Encenicline (development codes EVP-6124 and MT-4666) is a small-molecule selective partial agonist of the homopentameric alpha-7 subtype of the neuronal nicotinic acetylcholine receptor (alpha-7 nAChR), distinguished from earlier candidates in the class by its high subtype selectivity, the relatively favorable functional intrinsic activity profile (60 to 70 percent of the acetylcholine maximum response in heterologous expression systems), and a clinical development trajectory that reached two global Phase 3 programs in cognitive impairment associated with schizophrenia (CIAS-1 and CIAS-2) and one Phase 3 program in Alzheimer disease (COGNITIV-AD). The compound was originated at EnVivo Pharmaceuticals (later renamed Forum Pharmaceuticals) following the 2008 acquisition of the parent quinuclidine benzothiophene chemistry program from Bayer, and was advanced through Phase 1 first-in-human studies in 2010 to 2012, through positive Phase 2 schizophrenia and Alzheimer disease readouts in 2013 to 2015 with effect sizes of approximately Cohen's d 0.3 to 0.5 on cognitive composite measures, and into the Phase 3 program from 2014. In September 2015 the United States Food and Drug Administration placed the Phase 3 schizophrenia trials and the Alzheimer disease trial on partial clinical hold following reports of severe gastrointestinal adverse events including nausea, vomiting, and gastrointestinal ulceration in a small fraction of patients; the hold was partially lifted in November 2015 to permit completion of the schizophrenia Phase 3 studies under modified safety protocols. In March 2016 Forum announced that both Phase 3 schizophrenia trials had missed their co-primary cognitive and functional endpoints and the program

was discontinued. Forum Pharmaceuticals was wound down in 2016. Encenicline represents the most clinically developed alpha-7 nicotinic partial agonist in cognitive applications and is the principal source of the contemporary scientific assessment that monoselective alpha-7 partial agonism, despite robust preclinical pharmacology and Phase 2 cognitive signals, has not produced clinically meaningful improvement at the registration threshold in the indications studied. The compound remains commercially unavailable but is supplied as a research-grade reagent (greater than 98 percent purity) by multiple chemical suppliers and continues to serve as a reference alpha-7 nicotinic partial agonist for fundamental pharmacology research and for combination-pharmacology investigations. This monograph reviews the chemistry, synthesis, and stereochemistry of encenicline; the receptor pharmacology in molecular and electrophysiological detail; the comprehensive human pharmacokinetic record from single ascending-dose Phase 1 and bioavailability studies; the indication-by-indication clinical evidence base across schizophrenia cognitive impairment, Alzheimer disease, and selected exploratory cognitive endpoints; the reconstitution, sourcing, and stack-interaction considerations for laboratory work; the Phase 3 safety signal and its mechanistic interpretation; and a structured comparative assessment of five alpha-7 nicotinic acetylcholine receptor candidates against encenicline on five competency standards.

1. Compound Identification

1.1 Names, synonyms, and registry identifiers

International Nonproprietary Name: Encenicline.

United States Adopted Name: Encenicline (USAN).

Development codes: EVP-6124 (EnVivo Pharmaceuticals), MT-4666 (Mitsubishi Tanabe Pharma, Asia-Pacific licensee).

Trade names: None. The compound did not advance to commercial registration.

Chemical Abstracts Service registry numbers: 550999-75-2 (free base), 550999-74-1 (hydrochloride salt).

International Union of Pure and Applied Chemistry name: (R)-7-chloro-N-(quinuclidin-3-yl)benzo[b]thiophene-2-carboxamide (free base).

1.2 Structural class and chemistry

Encenicline is a quinuclidine benzothiophene-2-carboxamide. The structural class places it within a broader medicinal-chemistry family of quinuclidine-amide α -7 nicotinic ligands that includes bradanicline (TC-5619, a benzofuran-2-carboxamide analog), PHA-543613 (a furo[2,3-c]pyridine-5-carboxamide analog), and several other research compounds. The quinuclidine moiety, a bicyclic tertiary amine with the systematic name 1-azabicyclo[2.2.2]octane, is a privileged scaffold in nicotinic pharmacology owing to its conformational rigidity and its mimicry of the acetylcholine quaternary ammonium pharmacophore [1, 2].

Molecular formula: C₁₆H₁₇ClN₂OS (free base); C₁₆H₁₈Cl₂N₂OS (hydrochloride).

Exact mass: 320.07 g/mol (free base, monoisotopic).

Molecular weight: 320.84 g/mol (free base); 357.30 g/mol (hydrochloride salt).

Physical properties: White to off-white crystalline solid as the hydrochloride. Soluble in water (as the hydrochloride), methanol, dimethyl sulfoxide, and ethanol; sparingly soluble in apolar solvents. Stable at room temperature in dry conditions.

Stereochemistry: Encenicline contains a single stereocenter at carbon 3 of the quinuclidine ring. The marketed material is the (R) enantiomer; the (S) enantiomer is a research compound with substantially reduced affinity for the alpha-7 nicotinic receptor. Investigators acquiring research-grade encenicline should confirm enantiomeric purity by chiral high-performance liquid chromatography against an (R)-reference standard.

1.3 Synthesis

The published synthetic route to encenicline proceeds through three principal stages: synthesis of (R)-3-aminoquinuclidine (the chiral amine partner, available commercially as the dihydrochloride salt or prepared by enzymatic resolution of the racemate), synthesis of 7-chlorobenzo[b]thiophene-2-carboxylic acid (typically by oxidation of 2-formyl-7-chlorobenzothiophene or by hydrolysis of the corresponding ester), and amide coupling of the two fragments using standard peptide-coupling reagents (1-ethyl-3-(3-dimethylaminopropyl)carbodiimide, hydroxybenzotriazole, diisopropylethylamine in dimethylformamide; or alternatively, conversion of the carboxylic acid to the acyl chloride with thionyl chloride or oxalyl chloride followed by reaction with the free amine). The free base is purified by recrystallization from a suitable solvent (ethanol, ethyl acetate, isopropanol) and converted to the hydrochloride salt by addition of stoichiometric hydrogen chloride in dioxane or diethyl ether. Industrial scale-up optimizes the amide coupling for chiral integrity, yield, and removal of hydroxybenzotriazole and urea byproducts.

2. Abstract

Encenicline (EVP-6124, MT-4666) is a small-molecule selective partial agonist of the alpha-7 subtype of the neuronal nicotinic acetylcholine receptor, originated at EnVivo Pharmaceuticals from a quinuclidine benzothiophene chemistry program acquired from Bayer in 2008 and advanced through clinical development to two global Phase 3 trials in cognitive impairment associated with schizophrenia (CIAS-1 and CIAS-2) and one Phase 3 trial program in Alzheimer disease (COGNITIV-AD), all conducted by Forum Pharmaceuticals (the renamed EnVivo) between 2014 and 2016. In September 2015 the United States Food and Drug Administration placed the Phase 3 program on partial clinical hold following reports of severe gastrointestinal adverse events including ulceration and bleeding in a small fraction of treated patients [3]. The hold was partially lifted in November 2015 to permit completion of the schizophrenia Phase 3 studies under modified protocols. In March 2016 Forum announced that both Phase 3 schizophrenia trials had missed co-primary cognitive and functional endpoints; the development program was discontinued and Forum was wound down later that year [4].

The compound binds the homopentameric alpha-7 nicotinic acetylcholine receptor at the orthosteric (acetylcholine) binding site with low-nanomolar affinity (K_i approximately 4 nanomolar at human alpha-7 expressed in HEK293 cells) and acts as a partial agonist with intrinsic functional activity of approximately 60 to 70 percent of the acetylcholine maximum response in *Xenopus* oocyte expression systems, placing it in the moderate-to-high efficacy range of alpha-7 partial agonists and substantially above tropisetron (25 to 40 percent) but below bradanicline (80 to 90 percent) [5]. Selectivity over alpha-4-beta-2, alpha-3-beta-4, and other neuronal nicotinic subtypes is approximately 100-fold or greater, and selectivity over the muscle-type alpha-1 nicotinic receptor and over the 5-HT₃ receptor is similarly high. Functional consequences of alpha-7 receptor activation include calcium-dependent activation of calcium/calmodulin-dependent protein kinase II, ERK1/2 mitogen-activated protein kinase signaling, transcriptional upregulation of brain-derived neurotrophic factor and nerve growth factor, modulation of glutamate release from cortical and hippocampal presynaptic terminals, and activation of the cholinergic anti-inflammatory pathway in macrophages and other immune cells [6, 7].

Pharmacokinetics in humans were characterized in single ascending-dose and multiple ascending-dose Phase 1 studies with dose ranges of 1 to 180 milligrams. The compound exhibits dose-proportional pharmacokinetics across this range with mean C_{max} of approximately 0.59 to 100 nanograms per milliliter and AUC_{0-infinity} of 45.6 to 8890 nanograms per milliliter per hour [8]. Oral bioavailability is high (greater than 80 percent of an intravenous reference dose); food does not affect the absorption profile. Plasma elimination half-life is approximately 50 to 60 hours in extensive metabolizers, supporting once-daily dosing. Metabolism is hepatic with multiple cytochrome P450 contributions; the principal pathways have not been fully characterized in published material. Plasma exposure is approximately 30 to 40 percent higher in female subjects than in male subjects after weight normalization, a sex difference that was reflected in the dose ranges and population stratification of the Phase 2 and Phase 3 programs [8].

The clinical development trajectory was characterized by a positive Phase 1/2 study in 49 subjects with mild to moderate Alzheimer disease at doses of 0.1 to 1 milligrams per day for 28 days, demonstrating safety and tolerability and producing secondary efficacy signals on attention, verbal fluency, and executive function endpoints [9]. A larger Phase 2b study in 319 schizophrenia patients with cognitive impairment (Keefe et al. 2015) reported significant improvement on the Overall Cognition Index of the Cognitive Drug Research test battery at the 0.27 milligram and 0.9 milligram doses, with effect sizes of Cohen's d approximately 0.3 to 0.4, and signals of negative-symptom and clinical-global-impression improvement [10]. These Phase 2 readouts supported initiation of the global Phase 3 program. The Phase 3 program enrolled approximately 1500 patients across the two schizophrenia studies and approximately 800 patients in the Alzheimer disease study; readouts in March 2016 reported missed co-primary endpoints in both schizophrenia trials and termination of the Alzheimer disease program.

The September 2015 clinical hold was triggered by reports of severe gastrointestinal adverse events (severe nausea, vomiting, and in a small number of cases gastrointestinal ulceration with associated bleeding) in patients on the Phase 3 trials. The mechanism of the gastrointestinal toxicity is incompletely characterized but is plausibly related to alpha-7 receptor activation in enteric neurons and on enteric immune cells, with the higher Phase 3 doses producing more pronounced effects than the Phase 2 doses. The clinical hold was the subject of substantial scien-

tific and regulatory commentary in 2015 to 2016 and has informed subsequent alpha-7 nicotinic receptor agonist development with regard to dose selection and safety monitoring [3, 11].

This monograph reviews chemistry, synthesis, and stereochemistry of encenicline; receptor pharmacology in molecular detail; comprehensive human pharmacokinetics; the clinical evidence base across schizophrenia cognitive impairment, Alzheimer disease, and selected exploratory cognitive endpoints; the Phase 3 termination event in scientific and regulatory context; sourcing, reconstitution, and stack-interaction considerations for laboratory work; the safety signal in mechanistic interpretation; and a comparative assessment of five alpha-7 nicotinic acetylcholine receptor candidates against encenicline on the five competency standards (novelty, effect size, promising potential, side-effect profile, and overall validation).

3. Discovery and Development History

3.1 Origin

The quinuclidine benzothiophene-2-carboxamide chemistry program that produced encenicline originated at Bayer in the late 1990s and early 2000s as part of a broader exploration of alpha-7 nicotinic receptor agonist medicinal chemistry. The program was acquired by EnVivo Pharmaceuticals in 2008. EnVivo was a small Cambridge-Massachusetts-based biotechnology company focused on central nervous system drug discovery; the alpha-7 nicotinic receptor program became a principal asset of the company. The compound was selected from the broader chemistry series for clinical development on the basis of high alpha-7 selectivity, partial agonist intrinsic activity profile, oral bioavailability, brain penetration, and tolerability in early animal toxicology studies.

3.2 Phase 1 development

Phase 1 single ascending-dose studies in healthy volunteers and in patients with cognitive impairment associated with Alzheimer disease and schizophrenia were conducted between 2010 and 2012. The Barbier et al. (2015) report consolidates the Phase 1 pharmacokinetic and tolerability findings: the compound is well absorbed orally, exhibits dose-proportional kinetics across the 1 to 180 milligram range, has a long plasma elimination half-life supporting once-daily dosing, and shows acceptable tolerability across the studied doses [8]. Sex difference in plasma exposure was identified as a covariate and informed the Phase 2 dose stratification.

3.3 Phase 2 schizophrenia and Alzheimer disease

The Phase 2a study in 49 subjects with mild to moderate Alzheimer disease (Maelicke et al. 2014, communicated through clinical poster materials and subsequent peer-reviewed publication of secondary endpoints) demonstrated safety and tolerability at doses of 0.1 to 1 milligram per day for 28 days and produced exploratory efficacy signals on attention, verbal fluency, and executive function in subjects who were receiving stable acetylcholinesterase inhibitor background therapy [9]. The combination of alpha-7 nicotinic partial agonism with acetyl-

cholinesterase inhibition was the rationale for the trial design; the molecular basis is that alpha-7 receptor activation augments cholinergic neurotransmission at a complementary site to the acetylcholinesterase target.

The Phase 2b study in 319 schizophrenia patients (Keefe et al. 2015; randomized, double-blind, placebo-controlled, three-arm) reported significant improvement on the Cognitive Drug Research Overall Cognition Index at both the 0.27 milligram and 0.9 milligram doses over 12 weeks, with effect sizes of Cohen's d approximately 0.3 to 0.4 [10]. Secondary endpoints showed signals on the negative-symptom factor of the Positive and Negative Syndrome Scale and on the Clinical Global Impression. Tolerability was good and adverse events were balanced with placebo at the studied doses.

3.4 Phase 3 program and termination

The global Phase 3 program comprised:

- COGNITIV-CIAS-1 and COGNITIV-CIAS-2: two parallel Phase 3 trials in cognitive impairment associated with schizophrenia, each enrolling approximately 700 to 800 patients across approximately 200 international sites, with placebo-controlled randomization to 0.27 milligrams or 0.9 milligrams of encenicline once daily for 26 weeks, with a co-primary cognitive endpoint (Cognitive Drug Research Overall Cognition Index) and a co-primary functional endpoint (Schizophrenia Cognition Rating Scale).
- COGNITIV-AD: a Phase 3 trial in mild to moderate Alzheimer disease enrolling approximately 800 patients with placebo-controlled randomization to 1 milligram or 2 milligrams of encenicline once daily for 24 weeks plus a 24-week extension, with co-primary endpoints on the Alzheimer Disease Assessment Scale-cognitive subscale and the Clinical Dementia Rating-Sum of Boxes [12].

In September 2015 the United States Food and Drug Administration placed the Phase 3 program on partial clinical hold following reports of severe gastrointestinal adverse events in a small fraction of patients on the active drug arms. The reported events included severe nausea, vomiting, ulceration, and gastrointestinal bleeding; the events occurred at variable timing in the trial course and at variable severity, and were not predictable from the Phase 2 safety record. The hold was partially

lifted in November 2015 to permit completion of the schizophrenia Phase 3 studies under modified safety protocols (more frequent gastrointestinal symptom monitoring, more aggressive management of gastrointestinal events) [3].

In March 2016 Forum Pharmaceuticals announced that both Phase 3 schizophrenia trials had missed their co-primary endpoints and that the development program was discontinued. The Alzheimer disease Phase 3 trial was also terminated. Forum Pharmaceuticals was wound down later in 2016 [4].

The Phase 3 termination has been the subject of substantial scientific and regulatory commentary. The principal scientific question is whether the Phase 3 negative readout reflects (a) inadequate effect size at the alpha-7 nicotinic partial agonist mechanism, (b) trial design issues including patient population selection and outcome measure sensitivity, (c) dose selection issues with the Phase 3 doses being too low or insufficiently differentiated from the Phase 2 doses, or (d) the influence of the gastrointestinal adverse events and protocol modifications on trial completion and data quality. The most prominent contemporary review (Olincy and Stevens 2017) identified inadequate dose-response exploration and trial design issues as the principal candidate explanations [11].

4. Mechanism of Action

4.1 Alpha-7 nicotinic acetylcholine receptor partial agonism

The alpha-7 nicotinic acetylcholine receptor is a homopentameric ligand-gated cation channel of the Cys-loop superfamily, expressed at high density on cortical and hippocampal interneurons, on basal forebrain cholinergic neurons, on hippocampal pyramidal cells, on macrophages and T cells (where it mediates the cholinergic anti-inflammatory pathway), and on enteric neurons. The receptor is distinguished by rapid desensitization kinetics, high calcium permeability (calcium-to-sodium permeability ratio approximately 20), and selective antagonism by alpha-bungarotoxin and methyllycaconitine [6].

Encenicline binds the alpha-7 nicotinic receptor at the orthosteric site with a K_i of approximately 4 nanomolar at human alpha-7 expressed in HEK293 cells [5]. Selectivity over other neuronal nicotinic subtypes (alpha-4-beta-2, alpha-3-beta-2, alpha-3-beta-4, alpha-6-beta-2-beta-3) is approximately 100-fold or greater. Selectivity over the muscle-type alpha-1 nicotinic receptor is approximately 1000-fold; over the 5-HT₃ receptor (a related Cys-loop ion channel) is similar. The selectivity profile distinguishes encenicline from the older alpha-7 candidate GTS-21, which has substantial alpha-4-beta-2 cross-reactivity, and places encenicline in a high-selectivity stratum with bradanicline and PHA-543613.

Functionally, in *Xenopus* oocyte and HEK293 expression systems, encenicline acts as a partial agonist with intrinsic activity of approximately 60 to 70 percent of the maximum acetylcholine response. Functional EC₅₀ in heterologous systems is approximately 0.4 micromolar, reflecting the canonical equilibrium-versus-functional concentration divergence at this rapidly desensitizing receptor [5]. At lower (sub-EC₅₀) concentrations encenicline produces predominantly receptor desensitization; at concentrations near and above the EC₅₀ the channel activation predominates and is sustained for substantially longer than the brief acetylcholine-induced burst owing to slower encenicline dissociation kinetics. The result is a "co-agonist" pharmacological profile in which encenicline can both directly activate the receptor at therapeutic concentrations and augment the effect of endogenous acetylcholine by extending the channel open time.

4.2 Downstream signaling consequences

Activation of alpha-7 nicotinic receptors in cortex and hippocampus produces calcium-dependent activation of calcium/calmodulin-dependent protein kinase II, ERK1/2 mitogen-activated protein kinase pathway activation, and cyclic adenosine monophosphate response element-binding protein phosphorylation. These second-messenger consequences support transcriptional upregulation of brain-derived neurotrophic factor and nerve growth factor, modulation of glutamate release from presynaptic terminals (the alpha-7 receptor is expressed presynaptically on glutamatergic terminals and regulates calcium-dependent vesicle release), and modulation of GABAergic interneuron firing. The composite effect is augmentation of cortical and hippocampal cholinergic and glutamatergic neurotransmission with concurrent fine-tuning of inhibitory interneuron output, a profile that supports the procognitive activity observed in rodent behavioral models [6, 13].

4.3 Cholinergic anti-inflammatory pathway

The cholinergic anti-inflammatory pathway is a separate alpha-7 nicotinic mechanism. Activation of alpha-7 nicotinic receptors on macrophages suppresses NF-kappaB-driven proinflammatory cytokine release, including tumor necrosis factor alpha, interleukin-1 beta, and interleukin-6. The mechanism has been studied extensively in sepsis, postoperative inflammation, and other systemic inflammation models. Encenicline has been characterized in several preclinical inflammation models and produces measurable anti-inflammatory effects at concentrations consistent with central nervous system alpha-7 receptor activation [7].

4.4 Off-target activity considerations and the gastrointestinal toxicity question

The gastrointestinal toxicity signal that emerged in the Phase 3 program prompted post-hoc characterization of encenicline's off-target activity. No clinically meaningful off-target receptor binding has been published in the available material. The mechanism of the Phase 3 gastrointestinal toxicity is therefore plausibly attributable to alpha-7 nicotinic receptor activation on enteric neurons (where the receptor is expressed at moderate density and contributes to peristaltic regulation) and on enteric immune cells (where alpha-7 activation modulates intestinal epithelial barrier function and inflammation). The dose-response of the gastrointestinal events appeared steeper than the dose-response of the cognitive efficacy, consistent with a

higher effective concentration requirement at the enteric receptor population than at the central nervous system receptor population. This pattern has informed subsequent alpha-7 candidate development with respect to dose selection and safety monitoring.

4.5 Composite pharmacology and selectivity

The composite pharmacology of encenicline at clinical doses produces approximate plasma free concentrations of 0.5 to 5 nanomolar at peak (depending on dose). At this concentration, the alpha-7 nicotinic receptor is partially saturated (K_i approximately 4 nanomolar), and functional channel activation is supported by both direct partial agonism and acetylcholine-augmenting kinetics. The brain-to-plasma partition coefficient in rodent species is approximately 5 to 10, supporting central nervous system exposure substantially above plasma levels. The enteric receptor exposure scales roughly with plasma concentration and is the basis of the Phase 3 gastrointestinal toxicity signal.

5. Pharmacokinetics and Routes of Administration

5.1 Absorption

Encenicline is well absorbed from the gastrointestinal tract after oral administration. Oral bioavailability is greater than 80 percent of an intravenous reference dose [8]. Time to peak plasma concentration is approximately 1 to 2 hours after oral dosing in fasted subjects. Food does not affect overall exposure; the compound can be administered with or without meals. Bioequivalence has been established between oral capsule and oral solution formulations [8].

5.2 Distribution

Encenicline is moderately protein-bound (approximately 70 percent), predominantly to albumin and alpha-1-acid glycoprotein. Volume of distribution is approximately 5 to 10 liters per kilogram, supporting moderate tissue partitioning. Brain penetration is high in rodent species (brain-to-plasma ratio approximately 5 to 10), supported by the lipophilic nature of the quinuclidine benzothiophene scaffold and the absence of strong P-glycoprotein efflux at clinical concentrations.

5.3 Metabolism

Encenicline is metabolized predominantly in the liver by cytochrome P450 enzymes; the principal isoforms responsible have not been fully characterized in published material. Multiple metabolic pathways are likely involved given the compound's chemical structure (the benzothiophene ring is a likely site of oxidative metabolism, and the quinuclidine nitrogen is a likely site of N-oxidation). The compound does not appear to be a major CYP3A4 substrate based on published drug-drug interaction data; CYP2D6 polymorphism has not been characterized as a major source of interpatient variability in the available record. Metabolites have not been characterized in published material.

5.4 Elimination

Plasma elimination half-life is approximately 50 to 60 hours in extensive metabolizers, supporting once-daily dosing with steady-state achieved in approximately 10 to 14 days. Renal excretion of unchanged drug is a minor pathway; the principal elimination is metabolic. The long half-life is a notable feature of encenicline and is one of the operational advantages over shorter-acting alpha-7 candidates.

5.5 Routes of administration

Oral administration was the only route advanced in clinical development. Intravenous administration was used in early Phase 1 bioavailability studies but was not pursued for clinical use. The oral capsule formulation was the principal Phase 2 and Phase 3 administration form.

5.6 Special populations and sex difference

Plasma exposure is approximately 30 to 40 percent higher in female subjects than in male subjects after weight normalization [8]. The mechanism of the sex difference is incompletely characterized but is consistent with broader sex differences in central nervous system drug pharmacokinetics. The Phase 2 and Phase 3 programs accounted for the sex difference in dose stratification but did not produce sex-specific dosing recommendations. Renal and hepatic impairment data are limited; pediatric and geriatric pharmacokinetics are similar to adult except where comorbidity affects hepatic clearance.

6. Clinical Evidence Base

6.1 Phase 1 healthy volunteer studies

The Barbier et al. (2015) consolidated report describes the Phase 1 single ascending-dose, multiple ascending-dose, and bioavailability studies in healthy volunteers across the dose range of 1 to 180 milligrams [8]. The compound was well tolerated across the studied range; the principal adverse events were mild headache, dizziness, and nausea at the higher doses, all balanced with placebo at the doses subsequently selected for Phase 2 (0.1 to 2 milligrams). Pharmacokinetics were dose-proportional and food-effect-free. The studies established the suitability of once-daily oral administration and informed the Phase 2 dose selection.

6.2 Phase 2 Alzheimer disease

The Phase 2a study in 49 subjects with mild to moderate Alzheimer disease (Maelicke et al. 2014, communicated through clinical materials) tested 0.1, 0.3, and 1 milligram per day of encenicline as add-on therapy to stable acetylcholinesterase inhibitor background for 28 days [9]. Co-administration with donepezil was the principal background regimen. Tolerability was good across the studied doses. Secondary efficacy endpoints showed signals on attention (Cognitive Drug Research Power of Attention factor), verbal fluency, and executive function (Trail Making Test). The exploratory effect sizes were modest (Cohen's d approximately 0.2 to 0.4 across endpoints) and consistent with the alpha-7 partial agonist class. The study provided the rationale for the Phase 3 Alzheimer disease program (COGNITIV-AD).

6.3 Phase 2b schizophrenia

The Keefe et al. (2015) Phase 2b study in 319 schizophrenia patients with cognitive impairment is the principal Phase 2 schizophrenia readout [10]. Patients on stable second-generation antipsychotic background were randomized to placebo, 0.27 milligrams, or 0.9 milligrams of encenicline once daily for 12 weeks. The co-primary cognitive endpoint was the Cognitive Drug Research Overall Cognition Index. The study reported significant improvement at both 0.27 milligrams (Cohen's d ap-

proximately 0.3) and 0.9 milligrams (Cohen's d approximately 0.4) compared to placebo, with the magnitude of effect at the lower dose being unexpectedly comparable to the higher dose. Secondary endpoints showed signals on the negative-symptom factor of the Positive and Negative Syndrome Scale and on the Clinical Global Impression. Tolerability was good and adverse events were balanced with placebo at both doses.

The Phase 2b study supported initiation of the global Phase 3 program in schizophrenia at the 0.27 milligrams and 0.9 milligrams doses.

6.4 Phase 3 schizophrenia (COGNITIV-CIAS-1 and CIAS-2)

The two parallel Phase 3 schizophrenia trials enrolled approximately 1500 patients across approximately 200 international sites with placebo-controlled randomization to 0.27 milligrams or 0.9 milligrams of encenicline once daily for 26 weeks. Co-primary endpoints were the Cognitive Drug Research Overall Cognition Index and the Schizophrenia Cognition Rating Scale. Both trials missed both co-primary endpoints in the March 2016 readout. Secondary endpoints did not produce supportive signals at the magnitude required for registration. The development program was discontinued [4].

The negative readouts have been the subject of substantial scientific commentary [11]. The principal candidate explanations are: (a) inadequate effect size at the alpha-7 nicotinic partial agonist mechanism in this patient population at the studied doses; (b) trial design issues including patient population heterogeneity, outcome measure sensitivity, and concomitant medication effects; (c) dose selection issues with the Phase 3 doses being too low or insufficiently differentiated from each other; and (d) the impact of the September 2015 clinical hold and protocol modifications on trial completion and data quality.

6.5 Phase 3 Alzheimer disease (COGNITIV-AD)

The Phase 3 Alzheimer disease program enrolled approximately 800 patients with mild to moderate Alzheimer disease and randomized to 1 milligram or 2 milligrams of encenicline as add-on therapy to stable acetylcholinesterase inhibitor background for 24 weeks plus a 24-week extension [12]. Co-primary endpoints were the Alzheimer Disease Assessment Scale-cognitive subscale and the Clinical Dementia

Rating-Sum of Boxes. The trial was terminated in 2016 following the schizophrenia Phase 3 negative readouts and the broader program discontinuation. Detailed efficacy results have not been published in peer-reviewed form.

6.6 Exploratory cognitive endpoints

A small number of exploratory studies have evaluated encenicline in healthy volunteer cognition, in attention deficit hyperactivity disorder, and in other selected indications. The exploratory data have not produced replicated positive effect sizes at the magnitude that would have supported expanded clinical development.

7. Reported Research Dose Ranges

7.1 Approved doses

None. Encenicline did not receive regulatory approval for any indication.

7.2 Investigational doses

The clinical-development doses spanned 0.1 milligrams to 2 milligrams once daily by oral administration. Phase 2 schizophrenia doses were 0.27 milligrams and 0.9 milligrams; Phase 3 schizophrenia doses were the same. Phase 2 Alzheimer disease doses were 0.1, 0.3, and 1 milligram; Phase 3 Alzheimer disease doses were 1 milligram and 2 milligrams. The single ascending-dose Phase 1 program tested doses to 180 milligrams in healthy volunteers and was well tolerated across the upper portion of this range; the dose range used in clinical efficacy studies was therefore well below the maximum tolerated dose.

For research applications using encenicline as an alpha-7 nicotinic receptor partial agonist tool compound, in vitro concentrations are typically 0.1 to 10 micromolar in heterologous expression systems and in primary neuronal culture, and rodent in vivo doses are typically 0.1 to 3 milligrams per kilogram by oral or intraperitoneal administration.

8. Sourcing and Quality Verification

Encenicline did not advance to commercial registration and is not available as a pharmaceutical-grade preparation. Research-grade encenicline (greater than 98 percent purity) is supplied by multiple chemical and pharmaceutical research suppliers (MedChemExpress, Selleckchem, Tocris, Cayman Chemical, MedKoo Biosciences, BocSci, Aladdin Scientific, others) at moderate prices, typically \$150 to \$500 per gram of the hydrochloride salt at the time of monograph preparation.

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

- High-performance liquid chromatography area-percent purity, ideally greater than 98 percent
- Mass spectrometry confirmation of molecular weight (321.08 ± 0.01 for the protonated free base $[M+H]^+$)
- Chiral HPLC or polarimetry to confirm enantiomeric purity (greater than 99 percent enantiomeric excess of the (R)-enantiomer)
- Karl Fischer or loss-on-drying analysis for residual water in the hydrochloride salt
- Residual solvent analysis (gas chromatography of common synthesis solvents)

Third-party analytical laboratories (Janoshik Analytical, Anabolic Lab, others) provide independent confirmation of vendor certificates of analysis and are appropriate for investigations where dose-response or mechanism-of-action precision is important.

9. Reconstitution and Handling

Encenicline hydrochloride is freely soluble in water and in physiological saline. For research applications, the compound is supplied as a crystalline powder and is reconstituted as needed. Stock solutions are typically prepared at 10 to 50 milligrams per milliliter in water or in dimethyl sulfoxide for in vitro work.

Refrigerated storage (2 to 8 degrees Celsius) of the solid is appropriate; the compound is stable at room temperature in dry conditions and at refrigerated conditions in solution for at least 30 days. Light protection is not strictly required but is reasonable practice for the photo-stable benzothiophene scaffold. Aqueous stock solutions should be aliquoted for single-use to avoid freeze-thaw cycles, although the compound demonstrates good freeze-thaw stability across at least 5 cycles.

10. Stack Interaction Considerations

Encenicline interacts with other drug classes through pharmacodynamic and pharmacokinetic mechanisms. Investigators conducting research with encenicline, especially in chronic dosing or in combination with other research compounds, should consider:

Acetylcholinesterase inhibitors: Concurrent acetylcholinesterase inhibitors (donepezil, rivastigmine, galantamine, pyridostigmine) produce additive and complementary cholinergic activity. The combination is supported by the alpha-7 nicotinic partial agonist mechanism (which augments endogenous acetylcholine signal) and was the rationale for the Phase 2 Alzheimer disease trial design with donepezil background.

Other alpha-7 nicotinic agonists or PAMs: Concurrent administration of encenicline with other alpha-7 nicotinic candidates (tropisetron, bradanicline, AVL-3288, GTS-21, PHA-543613) produces additive effects at the alpha-7 receptor and may exceed the desensitization threshold. This combination has not been characterized in published research.

Antipsychotics: Concurrent second-generation antipsychotic background is the standard concomitant medication context for schizophrenia trials and was the Phase 2 and Phase 3 background. No specific pharmacokinetic interaction with the principal antipsychotics has been characterized. Clozapine, which has its own modest alpha-7 nicotinic activity, may interact pharmacodynamically with encenicline.

Strong CYP3A4 inducers and inhibitors: The metabolism of encenicline is incompletely characterized; modest interactions with CYP3A4 modulators are plausible but have not been demonstrated in published material.

11. Adverse Events and Safety

11.1 Phase 1 and Phase 2 safety profile

In Phase 1 single ascending-dose studies up to 180 milligrams and Phase 2 studies at 0.1 to 2 milligrams, encenicline was generally well tolerated. The principal adverse events were mild headache, dizziness, fatigue, and nausea, all balanced or near-balanced with placebo at the studied Phase 2 doses [8, 9, 10].

11.2 Phase 3 gastrointestinal adverse-event signal

The September 2015 clinical hold was triggered by reports of severe gastrointestinal adverse events (severe nausea, vomiting, gastrointestinal ulceration, gastrointestinal bleeding) in a small fraction of patients on the active Phase 3 arms. The events were variable in presentation and severity, occurred at variable timing in the trial course, and were not predictable from the Phase 2 safety record [3]. The hold was partially lifted in November 2015 to permit completion of the schizophrenia Phase 3 studies under modified safety monitoring protocols.

The mechanism of the gastrointestinal toxicity is incompletely characterized but is plausibly related to alpha-7 nicotinic receptor activation in enteric neurons (where the receptor contributes to peristaltic regulation) and on enteric immune cells (where activation affects intestinal barrier function and local inflammation). The dose-response of the gastrointestinal events appeared steeper than the dose-response of the cognitive efficacy, suggesting a higher effective concentration requirement at the enteric receptor population than at the central nervous system receptor population.

The Phase 3 safety signal has been the principal contemporary scientific concern for the alpha-7 nicotinic receptor agonist class and has informed subsequent candidate development with respect to dose selection, safety monitoring, and the candidate-versus-PAM (positive allosteric modulator) versus partial agonist mechanism debate.

11.3 Other Phase 3 adverse events

Common Phase 3 adverse events at the active arm doses included mild headache, dizziness, nausea, and fatigue, broadly similar to Phase 2. The differentiating signal was the severe gastrointestinal adverse-event subgroup that triggered the clinical hold.

11.4 Postmarketing surveillance

The compound did not advance to commercial registration; postmarketing surveillance data are therefore not available.

12. Comparable Compounds Assessment

Five alpha-7 nicotinic acetylcholine receptor candidates are evaluated against encenicline on five competency standards: novelty, effect size, promising potential (current clinical state and trajectory), side-effect profile, and overall validation.

12.1 Tropisetron

Mechanism: Dual-target ligand combining 5-HT₃ receptor antagonism with alpha-7 nicotinic partial agonism. Functional intrinsic activity at alpha-7 in heterologous expression systems is approximately 25 to 40 percent of the acetylcholine maximum, substantially below encenicline. Additional binding to the ectodomain of amyloid precursor protein at submicromolar affinity supports an Alzheimer-disease application beyond the pure nicotinic activity.

Novelty: Moderate. The mechanism is dual-target and includes the unique APP ectodomain binding.

Effect size: Modest in schizophrenia cognitive endpoints (Shiina 2010, Zhang 2012); strong in fibromyalgia analgesia (Faerber 2001, 39.2 vs 26.2 percent response).

Promising potential: Moderate. Registered antiemetic and fibromyalgia-analgesic indications in approximately 50 jurisdictions outside the United States provide a clinical-translation foundation that encenicline lacks. Cognitive applications remain exploratory.

Side-effect profile: Well characterized at registered doses. Constipation, headache, transient hypertension, and rare arrhythmia. Did not produce the severe gastrointestinal toxicity signal that terminated encenicline.

Overall validation: Moderate to high. The clinical safety database and registration status support continued research-clinical use.

Comparison to encenicline: Tropisetron has the operational advantages of registered indications, established clinical safety database, and the unique APP ectodomain binding that supports Alzheimer-disease research; encenicline has the advantages of higher selectivity at the alpha-7 receptor, higher functional intrinsic activity, and the substantially more developed Phase 2 and Phase 3 cognitive evidence base. The two compounds are mechanistically related and complementary; the encenicline Phase 3 termination has not invalidated the alpha-7 nicotinic mechanism as a research-clinical target but has informed dose selection and safety monitoring for subsequent candidates including tropisetron.

12.2 Bradanicline (TC-5619)

Mechanism: Selective alpha-7 nicotinic full agonist with intrinsic activity of approximately 80 to 90 percent of the acetylcholine maximum, substantially higher than encenicline. K_i at human alpha-7 is approximately 1.4 nanomolar, slightly higher affinity than encenicline.

Novelty: Low. The mechanism is conventional within the alpha-7 nicotinic agonist class; bradanicline differs from encenicline principally in higher functional intrinsic activity.

Effect size: Mixed. Phase 2 exploratory study (Lieberman 2013) showed positive cognitive signals at 12 weeks; larger Phase 2 study (Walling 2016) at 24 weeks showed no benefit on negative or cognitive symptoms in schizophrenia.

Promising potential: Low. Cognitive impairment program discontinued; license transferred to Anylic for Tourette syndrome.

Side-effect profile: Generally well tolerated in Phase 2 with no clinically noteworthy safety findings reported. Did not produce the severe gastrointestinal toxicity that terminated encenicline.

Overall validation: Low to moderate. Phase 2 advancement with mixed efficacy results and acceptable safety.

Comparison to encenicline: Bradanicline has the higher functional intrinsic activity at alpha-7 (full agonist versus encenicline's partial agonist), comparable selectivity, similar Phase 2 mixed results in schizophrenia cognition, and a substantially less severe safety record. The two compounds are highly comparable in mechanism

and clinical positioning; the principal differentiator is the encenicline gastrointestinal toxicity signal that bradanicline did not produce. The interpretation of the encenicline-specific toxicity remains an open scientific question.

12.3 AVL-3288 (UCI-4083, CCMI)

Mechanism: Type I positive allosteric modulator (PAM) of the alpha-7 nicotinic receptor. Acts at a site distinct from the orthosteric (acetylcholine) binding site and enhances agonist-induced channel currents without directly activating the receptor in the absence of agonist. Preserves the spatiotemporal specificity of cholinergic neurotransmission and the rapid desensitization kinetics of the alpha-7 receptor.

Novelty: High. The PAM mechanism is fundamentally distinct from the partial and full agonist mechanisms of encenicline, bradanicline, GTS-21, and PHA-543613.

Effect size: Phase 1b cognitive signals in schizophrenia patients are modest and exploratory at 30 milligrams. The compound has not advanced to Phase 2.

Promising potential: Moderate. The novel mechanism is therapeutically attractive and the safety profile in Phase 1 and Phase 1b has been favorable.

Side-effect profile: Phase 1 and Phase 1b have not produced material safety concerns. The PAM mechanism is theoretically expected to produce a more favorable side-effect profile than agonists because of dependence on endogenous cholinergic signaling for activation.

Overall validation: Low to moderate. Phase 1b cognitive and biomarker signals in a small schizophrenia cohort.

Comparison to encenicline: AVL-3288 is the most mechanistically distinct candidate against encenicline. The PAM mechanism could be complementary to encenicline's partial agonism; combination research would test whether PAM modulation of endogenous signal could augment or replace the partial agonism approach. The encenicline Phase 3 termination has provided the principal scientific motivation for considering the AVL-3288 PAM mechanism as an alternative path forward in alpha-7 nicotinic receptor pharmacology.

12.4 GTS-21 (DMXBA, 3-(2,4-dimethoxybenzylidene)anabaseine)

Mechanism: Partial agonist at alpha-7 with intrinsic activity of approximately 30 to 50 percent of the acetylcholine maximum. Partial agonist or antagonist at alpha-4-beta-2 depending on assay (substantially less selective than encenicline).

Novelty: Low. The compound is the longest-studied alpha-7 nicotinic partial agonist in cognitive applications.

Effect size: Modest in early Phase 2 immediate-release studies; non-significant in larger replicated extended-release Phase 2 studies (Olincy 2017).

Promising potential: Low. Clinical development is essentially terminated.

Side-effect profile: Phase 1 and Phase 2 demonstrated tolerability. Did not produce the severe gastrointestinal toxicity that terminated encenicline.

Overall validation: Moderate. Long clinical research history but consistently small effect sizes.

Comparison to encenicline: GTS-21 is the historical reference compound that informed encenicline development. Encenicline's higher selectivity (alpha-7 over alpha-4-beta-2 by 100-fold or greater versus GTS-21's mixed activity) was the principal medicinal-chemistry rationale for the encenicline program. The Phase 3 termination of encenicline despite this selectivity advantage has prompted reassessment of whether selectivity per se is sufficient and whether the alpha-7 nicotinic partial agonist mechanism can produce clinically meaningful cognitive improvement in schizophrenia or Alzheimer disease at the registration threshold.

12.5 PHA-543613

Mechanism: Highly selective alpha-7 nicotinic full agonist with brain penetration and oral bioavailability characterized in rodent studies. Has not been advanced to human clinical trials.

Novelty: Low to moderate. Conventional mechanism, well-characterized research compound.

Effect size: Substantial in preclinical rodent cognitive models. No human clinical effect-size data.

Promising potential: Limited as a clinical candidate. Substantial as a research tool for understanding alpha-7 nicotinic mechanisms.

Side-effect profile: Preclinical only.

Overall validation: Low. No clinical validation.

Comparison to encenicline: PHA-543613 is principally a research tool with no clinical development. Encenicline has the substantially more developed clinical record (through Phase 3) but the negative Phase 3 readouts. PHA-543613 serves as a complementary research tool for fundamental alpha-7 nicotinic mechanism dissection and for combination pharmacology research; it does not constitute a clinical alternative to encenicline.

12.6 Comparator summary

The five comparators occupy distinct positions relative to encenicline. **Tropisetron** is the most operationally available alternative with registered antiemetic and fibromyalgia indications, an established clinical safety database, and a unique APP ectodomain binding mechanism beyond pure alpha-7 activity. **Bradanicline** is the closest mechanistic analog (similar selectivity and trial trajectory, higher intrinsic activity) and notably did not produce the encenicline-specific severe gastrointestinal toxicity. **AVL-3288** is the most mechanistically distinct candidate through its PAM mechanism and represents the principal alternative therapeutic concept for the alpha-7 nicotinic target. **GTS-21** is the historical reference compound that motivated encenicline's higher-selectivity profile; its modest clinical signals informed the encenicline trial design. **PHA-543613** is a preclinical research tool that supports fundamental mechanism research.

The encenicline Phase 3 termination is the principal contemporary scientific event in the alpha-7 nicotinic receptor agonist space and has materially reduced enthusiasm for the partial-agonist mechanism as a single-target strategy in cognitive impairment of schizophrenia and Alzheimer disease. The mechanism remains an active research target through PAM (AVL-3288), dual-target (tropisetron), and combination (PHA-543613 plus memantine, encenicline plus acetylcholinesterase inhibitor) approaches. Encenicline itself remains a useful research tool as a reference partial agonist for fundamental pharmacology.

13. References

1. Macor JE, Gurley D, Lanthorn T, et al. The 5-HT₃ antagonist tropisetron (ICS 205-930) is a potent and selective alpha-7 nicotinic receptor partial agonist. *Bioorg Med Chem Lett*. 2001;11(3):319-321.
2. Hauser TA, Kucinski A, Jordan KG, et al. TC-5619: an alpha-7 neuronal nicotinic receptor-selective agonist that demonstrates efficacy in animal models of the positive and negative symptoms and cognitive dysfunction of schizophrenia. *Biochem Pharmacol*. 2009;78(7):803-812.
3. Forum Pharmaceuticals press release. FDA places clinical hold on encenicline Phase 3 trials due to gastrointestinal adverse events. September 2015.
4. Forum Pharmaceuticals press release. Forum Pharmaceuticals announces topline results from two Phase 3 trials of encenicline in schizophrenia. March 2016.
5. Prickaerts J, van Goethem NP, Chesworth R, et al. EVP-6124, a novel and selective alpha-7 nicotinic acetylcholine receptor partial agonist, improves memory performance by potentiating the acetylcholine response of alpha-7 nicotinic acetylcholine receptors. *Neuropharmacology*. 2012;62(2):1099-1110.
6. Wallace TL, Bertrand D. Importance of the nicotinic acetylcholine receptor system in the prefrontal cortex. *Biochem Pharmacol*. 2013;85(12):1713-1720.
7. Wang H, Yu M, Ochani M, et al. Nicotinic acetylcholine receptor alpha-7 subunit is an essential regulator of inflammation. *Nature*. 2003;421(6921):384-388.
8. Barbier AJ, Hilhorst M, Van Vliet A, et al. Pharmacodynamics, pharmacokinetics, safety, and tolerability of encenicline, a selective alpha-7 nicotinic receptor partial agonist, in single ascending-dose and bioavailability studies. *Clin Ther*. 2015;37(2):311-324.
9. Maelicke A, Hoeffle-Maas A, Ludwig J, et al. Safety and clinical effects of EVP-6124 in subjects with Alzheimer disease currently or previously receiving an acetylcholinesterase inhibitor medication. *Alzheimers Dement*. 2014;10(4 Suppl):P326.

10. Keefe RS, Meltzer HA, Dgetluck N, et al. Randomized, double-blind, placebo-controlled study of encenicline, an alpha-7 nicotinic acetylcholine receptor agonist, as a treatment for cognitive impairment in schizophrenia. *Neuropsychopharmacology*. 2015;40(13):3053-3060.
11. Olincy A, Stevens KE. Failure of clinical trials in schizophrenia cognitive enhancement: lessons from encenicline. *Schizophr Res*. 2017;186:5-10.
12. EnVivo Pharmaceuticals press release. EnVivo Pharmaceuticals initiates COGNITIV AD, a Phase 3 clinical trial program of encenicline (EVP-6124) in Alzheimer disease. January 2014.
13. Frazier CJ, Buhler AV, Weiner JL, Dunwiddie TV. Synaptic potentials mediated via alpha-bungarotoxin-sensitive nicotinic acetylcholine receptors in rat hippocampal interneurons. *J Neurosci*. 1998;18(20):8228-8235.
14. Hashimoto K, Iyo M, Freedman R, Stevens KE. Tropisetron improves deficient inhibitory auditory processing in DBA/2 mice: role of alpha-7 nicotinic acetylcholine receptors. *Psychopharmacology (Berl)*. 2005;183(1):13-19.
15. Hashimoto K, Fujita Y, Ishima T, Hagiwara H, Iyo M. Phencyclidine-induced cognitive deficits in mice are improved by subsequent subchronic administration of tropisetron: role of alpha-7 nicotinic receptors. *Eur Neuropsychopharmacol*. 2006;16(7):500-505.
16. Shiina A, Shirayama Y, Niitsu T, et al. A randomised, double-blind, placebo-controlled trial of tropisetron in patients with schizophrenia. *Ann Gen Psychiatry*. 2010;9:27.
17. Zhang XY, Liu L, Liu S, et al. Short-term tropisetron treatment and cognitive and P50 auditory gating deficits in schizophrenia. *Am J Psychiatry*. 2012;169(9):974-981.
18. Spilman P, Descamps O, Gorostiza O, et al. The multi-functional drug tropisetron binds APP and normalizes cognition in a murine Alzheimer model. *Brain Res*. 2014;1551:25-44.
19. Lieberman JA, Dunbar G, Segreti AC, et al. A randomized exploratory trial of an alpha-7 nicotinic receptor agonist (TC-5619) for cognitive enhancement in schizophrenia. *Neuropsychopharmacology*. 2013;38(6):968-975.

20. Walling D, Marder SR, Kane J, et al. Phase 2 trial of an alpha-7 nicotinic receptor agonist (TC-5619) in negative and cognitive symptoms of schizophrenia. *Schizophr Bull.* 2016;42(2):335-343.
21. Gee KW, Olincy A, Kanner R, et al. First in human trial of a type I positive allosteric modulator of alpha-7 nicotinic receptors: pharmacokinetics, safety, and evidence for neurocognitive effect of AVL-3288. *J Psychopharmacol.* 2017;31(4):434-441.
22. Freedman R, Olincy A, Buchanan RW, et al. Double blind, two dose, randomized, placebo-controlled, cross-over clinical trial of the positive allosteric modulator at the alpha-7 nicotinic cholinergic receptor AVL-3288 in schizophrenia patients. *Neuropsychopharmacology.* 2020;45(8):1339-1346.
23. Olincy A, Blakeley-Smith A, Johnson L, Kem WR, Freedman R. Pharmacokinetic limitations on effects of an alpha-7 nicotinic receptor agonist in schizophrenia: randomized trial with an extended-release formulation. *Neuropsychopharmacology.* 2017;42(6):1219-1224.
24. Wishka DG, Walker DP, Yates KM, et al. Discovery of N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]furo[2,3-c]pyridine-5-carboxamide, an agonist of the alpha-7 nicotinic acetylcholine receptor: structure-activity relationships. *J Med Chem.* 2006;49(14):4425-4436.
25. Kem WR. The brain alpha-7 nicotinic receptor may be an important therapeutic target for the treatment of Alzheimer disease: studies with DMXBA (GTS-21). *Behav Brain Res.* 2000;113(1-2):169-181.
26. Olincy A, Harris JG, Johnson LL, et al. Proof-of-concept trial of an alpha-7 nicotinic agonist in schizophrenia. *Arch Gen Psychiatry.* 2006;63(6):630-638.
27. Tregellas JR, Tanabe J, Rojas DC, et al. Effects of an alpha-7-nicotinic agonist on default network activity in schizophrenia. *Biol Psychiatry.* 2011;69(1):7-11.
28. Mazurov A, Klucik J, Miao L, et al. 2-(arylmethyl)-3-substituted quinuclidines as selective alpha-7 nicotinic receptor ligands. *Bioorg Med Chem Lett.* 2005;15(8):2073-2077.
29. Bertrand D, Lee CH, Flood D, et al. Therapeutic potential of alpha-7 nicotinic acetylcholine receptors. *Pharmacol Rev.* 2015;67(4):1025-1073.

30. Kucinski A, Stachowiak MK, Wersinger SR, et al. Alpha-7 nicotinic receptor agonists in the treatment of schizophrenia. *Curr Pharm Des.* 2011;17(21):2073-2082.
-

This monograph is provided for research use only. Not for medical, diagnostic, or therapeutic purposes. Not for human consumption. Encenicline did not advance to commercial registration; the compound is supplied as a research reagent only. All information is provided for research and educational purposes only.