

RESEARCH MONOGRAPH . COMPOUND PROFILE

AVL-3288

An isoxazole-acrylamide chemical entity originally developed at the University of California Irvine as compound CCMI and licensed through multiple owners to Anvylic Therapeutics, representing the most mechanistically distinct alpha-7 nicotinic candidate in clinical development through its Type I positive allosteric modulator mechanism that preserves the spatiotemporal specificity of endogenous cholinergic neurotransmission.

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ABSTRACT

AVL-3288 (also known as UCI-4083, CCMI, Anvylic-3288, and XY-4083) is a small-molecule, orally bioavailable Type I positive allosteric modulator (PAM) of the homopentameric alpha-7 subtype of the neuronal nicotinic acetylcholine receptor (alpha-7 nAChR). The compound is mechanistically distinct from the partial-agonist (tropisetron, encenicline, GTS-21) and full-agonist (bradanicline, PHA-543613) classes that have dominated alpha-7 nicotinic receptor drug development. Type I PAMs bind the alpha-7 receptor at an allosteric site distinct from the orthosteric (acetylcholine) binding site, do not directly activate the receptor in the absence of agonist, and enhance the potency and efficacy of endogenous acetylcholine signaling at the receptor. Critically, Type I PAMs preserve the rapid desensitization kinetics of the alpha-7 channel and therefore preserve the spatiotemporal specificity of cholinergic neurotransmission, in contrast to direct agonists which prolong receptor activation and may produce non-physiological signaling. This mechanistic profile is the principal scientific argument for the AVL-3288 approach as an alternative to direct agonist development in cognitive applications, particularly in light of the September 2015 FDA clinical hold and March 2016 Phase 3 termination of encenicline (a partial agonist) for severe gastrointestinal toxicity. The compound was originated at the University of California Irvine in the laboratory of Kelvin Gee in the early 2000s as part of an academic medicinal-chemistry program for novel alpha-7 nicotinic receptor modulators, was licensed through several commercial owners (Bionomics, Anvylic Therapeutics), and was advanced through a first-in-human Phase 1a single-ascending-dose study in 21 healthy

non-smokers (Gee et al. 2017) and a Phase 1b randomized double-blind placebo-controlled triple-cross-over study in 24 non-smoking medicated outpatients with schizophrenia or schizoaffective disorder (Freedman et al. 2020) at 10 milligrams and 30 milligrams oral doses. The Phase 1a study reported safety, dose-proportional pharmacokinetics, and exploratory cognitive signals at 10 and 30 milligrams. The Phase 1b study in schizophrenia patients reported P50 auditory evoked potential gating biomarker effects at 30 milligrams (consistent with alpha-7 receptor target engagement), exploratory cognitive performance signals, and acceptable tolerability across the studied doses. The compound has not advanced to Phase 2 as of the most recent monograph revision; future development depends on commercial-funding decisions. AVL-3288 represents the most mechanistically novel of the alpha-7 nicotinic receptor candidates and is the principal contemporary alternative therapeutic concept for the alpha-7 nicotinic target. This monograph reviews the chemistry, synthesis, and structural class of AVL-3288; the receptor pharmacology of Type I PAM mechanism in molecular and electrophysiological detail; the limited human pharmacokinetic record from Phase 1a and Phase 1b; the clinical evidence base in healthy volunteers and schizophrenia outpatients; sourcing, reconstitution, and stack-interaction considerations; the safety record; and a structured comparative assessment of five alpha-7 nicotinic acetylcholine receptor candidates against AVL-3288 on the five competency standards.

1. Compound Identification

1.1 Names, synonyms, and registry identifiers

Names: AVL-3288. The compound has been known by multiple synonyms reflecting its development history through several owners: UCI-4083 (the University of California Irvine designation); CCMI (an acronym for the chemical class designation); Anvylic-3288 (the current Anvylic Therapeutics designation); XY-4083 (a Chinese chemical-supplier designation in some catalogs).

Trade names: None. The compound has not advanced to commercial registration.

Chemical Abstracts Service registry number: 917837-54-8 (free base).

International Union of Pure and Applied Chemistry name: (Z)-N-(4-chlorophenyl)-3-((4-chlorophenyl)amino)-2-(3-methylisoxazol-5-yl)acrylamide.

1.2 Structural class and chemistry

AVL-3288 is an isoxazole-acrylamide. The core chemical scaffold comprises a 3-methylisoxazole heterocycle linked to an alpha-aminoacrylamide bearing two 4-chlorophenyl substituents (one at the alpha-amino position, one at the amide nitrogen). This structural class is distinct from:

- The quinuclidine-amide class that includes encenicline (benzothiophene), bradanicline (benzofuran), and PHA-543613 (furopyridine)
- The tropane-indole class represented by tropisetron
- The dimethoxybenzylidene-anabaseine class represented by GTS-21

The structural distinction is the medicinal-chemistry corollary of the mechanistic distinction. The isoxazole-acrylamide scaffold binds the alpha-7 receptor at an allosteric site rather than at the orthosteric acetylcholine-binding site, and the chemical scaffold therefore differs from the orthosteric agonist scaffolds.

Molecular formula: C₁₉H₁₅Cl₂N₃O₂ (free base).

Exact mass: 387.05 g/mol (free base, monoisotopic).

Molecular weight: 388.25 g/mol (free base).

Physical properties: Yellow to off-white crystalline solid. Soluble in dimethyl sulfoxide; sparingly soluble in water; soluble in methanol and ethanol with warming. Stable at room temperature in dry conditions.

Stereochemistry: AVL-3288 is achiral; the compound contains no stereocenters and is not subject to the stereoselectivity considerations that apply to the chiral quinuclidine-amide alpha-7 candidates.

1.3 Synthesis

The published synthesis of AVL-3288 proceeds through condensation of 3-methyl-5-acetylisoxazole with 4-chloroaniline to form an enaminone intermediate, followed by acylation with 4-chlorophenyl isocyanate or with 4-chlorobenzoyl chloride and ammonia to install the amide nitrogen substituent. The geometric isomerism of the acrylamide (the (Z) configuration at the carbon-carbon double bond) is established during the condensation step and is preserved through the acylation. The final compound is purified by recrystallization or chromatography.

The synthesis is substantially simpler than the chiral quinuclidine-amide synthesis of bradanicline or encenicline, contributing to lower research-grade material cost (typically \$100 to \$300 per gram).

2. Abstract

AVL-3288 (UCI-4083, CCMI) is a small-molecule, orally bioavailable Type I positive allosteric modulator of the alpha-7 subtype of the neuronal nicotinic acetylcholine receptor, representing the most mechanistically distinct alpha-7 nicotinic candidate in clinical development through its allosteric (rather than orthosteric) mechanism of action. The compound was originated at the University of California Irvine in the laboratory of Kelvin Gee in the early 2000s as part of an academic medicinal-chemistry program for alpha-7 nicotinic receptor modulators. The compound was licensed to Bionomics in the early 2010s, then to Anvylic Therapeutics, with the academic naming history (UCI-4083, CCMI, Anvylic-3288, AVL-3288) reflecting the multiple owners.

The Type I PAM mechanism is the principal scientific feature of AVL-3288 and the principal differentiator from the orthosteric agonist class (encenicline, bradanicline, tropisetron, GTS-21, PHA-543613). At the molecular level, AVL-3288 binds the alpha-7 receptor at a transmembrane allosteric site identified by electrophysiological and mutagenesis studies as distinct from the orthosteric acetylcholine-binding site at the extracellular domain interface. AVL-3288 does not directly activate the receptor in the absence of agonist (essential criterion for PAM classification) and enhances the potency (leftward shift of the agonist concentration-response curve) and efficacy (increase in maximal response) of endogenous acetylcholine signaling at the receptor [1, 2]. Critically, Type I PAMs preserve the rapid desensitization kinetics of the alpha-7 channel (in contrast to Type II PAMs which slow desensitization, and to direct agonists which prolong receptor activation in a non-physiological manner). Preservation of desensitization kinetics is the molecular basis for the theoretical safety advantage of the Type I PAM mechanism: spatiotemporal specificity of cholinergic neurotransmission is preserved, off-target activation of alpha-7 receptors in tissues with low endogenous acetylcholine (such as enteric tissues and immune cells in basal state) is minimized, and the receptor desensitization that may underlie pathological responses to direct agonists (such as the encenicline gastrointestinal toxicity) is avoided.

The clinical development trajectory comprised:

- Phase 1a single ascending-dose study in 21 healthy non-smokers with single oral doses at 5, 10, and 30 milligrams (Gee et al. 2017) [3]. The study reported safety, dose-proportional pharmacokinetics, and exploratory cognitive signals at 10 and 30 milligrams (positive but non-significant effects on neurocognition assessed by a battery selected for sensitivity to alpha-7 nicotinic mechanism). P50 auditory evoked potential biomarker effects were observed at the higher dose, supporting target engagement.
- Phase 1b randomized double-blind placebo-controlled triple-cross-over study in 24 non-smoking medicated outpatients with schizophrenia or schizoaffective disorder (Freedman et al. 2020) [4]. Each subject received 5 days of AVL-3288 (10 milligrams or 30 milligrams) or placebo across three separate treatment weeks, with cognitive and biomarker testing at the end of each week. The study reported P50 auditory gating effects at 30 milligrams (a biomarker that responds to alpha-7 nicotinic receptor target engagement and that is dysfunctional in schizophrenia), exploratory signals on cognitive performance, and acceptable tolerability across the studied doses. No clinically significant adverse events were observed.

The compound has not advanced to Phase 2 as of the most recent monograph revision. Future clinical development depends on Anvylic's commercial decisions and on funding for a Phase 2 program. The Type I PAM mechanism remains the principal contemporary alternative to the orthosteric agonist class for the alpha-7 nicotinic target, and the favorable safety profile observed in Phase 1 and Phase 1b supports continued investigation.

In preclinical work, AVL-3288 has been characterized in models of attention, working memory, traumatic brain injury cognitive deficits, and Alzheimer disease cognitive deficits [5]. The compound rescued learning and memory deficits in water maze retention and working memory paradigms following traumatic brain injury in rodent models, with effects persisting at 24 hours and 1 month after training. The preclinical pharmacology supports the cognitive enhancement profile that the Phase 1 and Phase 1b studies have begun to translate to humans.

This monograph reviews the chemistry, synthesis, and structural class of AVL-3288; the Type I PAM receptor pharmacology in molecular detail; the limited human pharmacokinetic record from Phase 1a and Phase 1b; the clinical evidence base; the preclinical pharmacology in cognitive and traumatic brain injury models; sourcing and quality verification; reconstitution and handling; stack-interaction considerations including the principal combination-pharmacology research oppor-

tunities with orthosteric agonists; the safety record; and a structured comparative assessment of five alpha-7 nicotinic acetylcholine receptor candidates against AVL-3288.

3. Discovery and Development History

3.1 Origin at University of California Irvine

The AVL-3288 chemistry program was originated in the laboratory of Kelvin W. Gee at the University of California Irvine in the early 2000s as part of an academic medicinal-chemistry program for novel alpha-7 nicotinic receptor modulators. The Gee laboratory had previously contributed substantial work to the GABA-A receptor PAM mechanism and was uniquely positioned to apply allosteric modulator concepts to the alpha-7 nicotinic receptor [1]. The chemistry effort produced multiple isoxazole-acrylamide compounds with PAM activity at alpha-7; CCMI was selected from the series for advanced characterization and ultimately for clinical development. The university designation UCI-4083 was assigned to the lead compound, which was subsequently licensed to commercial development partners and re-branded as AVL-3288 (the name carrying through the Anylyc Therapeutics ownership era).

3.2 Preclinical pharmacology

The preclinical pharmacology of AVL-3288 was developed extensively at UC Irvine and at collaborating laboratories. Key preclinical findings include:

- Type I PAM activity at human and rat alpha-7 nicotinic receptors expressed in heterologous systems, with confirmation that the compound does not directly activate the receptor in the absence of acetylcholine
- Brain penetration in rodent species (brain-to-plasma ratio approximately 5)
- Cognitive enhancement in rodent attention, working memory, and reference memory paradigms
- Rescue of cognitive deficits in models of traumatic brain injury [5]
- Anti-inflammatory effects in models of sepsis and other inflammatory conditions
- Acceptable safety in rodent toxicology and absence of cardiovascular liabilities at clinically relevant doses

3.3 Licensing and commercial development

The UC Irvine-originated chemistry was licensed through several commercial owners. The current owner is Anylyc Therapeutics, which has indicated continued development intent for the compound. The Anylyc naming convention (AVL-3288, Anylyc-3288) is the dominant contemporary designation.

3.4 Phase 1a clinical development

The Gee et al. (2017) Phase 1a first-in-human single-ascending-dose study in 21 healthy non-smokers tested single oral doses at 5, 10, and 30 milligrams [3]. The study was a randomized, double-blind, placebo-controlled design with a parallel-group dose-escalation across the three doses. Each subject received a single dose of AVL-3288 or matching placebo and was assessed for safety, pharmacokinetics, and exploratory cognitive endpoints over 24 to 48 hours after dosing.

Key findings:

- No clinically significant adverse events at any of the studied doses
- Dose-proportional plasma pharmacokinetics across the studied range with peak concentrations achieved approximately 2 to 3 hours after oral administration
- Plasma elimination half-life of approximately 8 to 12 hours
- Indication of positive but non-significant effects on neurocognition at 10 and 30 milligrams (the two doses produced overlapping peak plasma levels, providing the basis for the "two-dose" cognitive response observation)
- Some evidence for effects on inhibition of the P50 auditory evoked potential to repeated stimuli, a biomarker that responds to alpha-7 nicotinic receptor activation

The exploratory positive cognitive signals supported initiation of the Phase 1b study in schizophrenia patients.

3.5 Phase 1b clinical development

The Freedman et al. (2020) Phase 1b randomized double-blind placebo-controlled triple-cross-over study in 24 non-smoking medicated outpatients with schizophrenia or schizoaffective disorder is the principal cognitive-disorder clinical readout

for AVL-3288 [4]. Each subject received 5 days of AVL-3288 (10 milligrams or 30 milligrams) or matching placebo across three separate treatment weeks, with washout periods between treatment weeks and with cognitive and biomarker testing at the end of each week.

Key findings:

- Acceptable tolerability with no clinically significant adverse events at either dose
- P50 auditory evoked potential gating effects at 30 milligrams, consistent with target engagement at the alpha-7 nicotinic receptor in schizophrenia patients
- Exploratory signals on cognitive performance measures (the small sample size precluded definitive efficacy conclusions but the directionality of effect was consistent with the expected procognitive activity)
- No effects on positive or negative symptom scales (an expected finding for short-duration cognitive enhancement)

The Phase 1b study supported continued development interest in AVL-3288 but did not provide definitive efficacy evidence at the magnitude required to justify the substantial investment in a Phase 2 program. The compound has not advanced to Phase 2 as of the most recent monograph revision.

3.6 Current development status

The current development status (Anvylic Therapeutics ownership, Phase 1b complete, Phase 2 not yet initiated) reflects the broader scientific and commercial environment for alpha-7 nicotinic receptor candidates following the encenicline Phase 3 failure and bradanicline Phase 2 confirmatory failure. The Type I PAM mechanism is supported by strong scientific rationale and favorable Phase 1 safety data; future advancement depends on dedicated funding for a Phase 2 program with appropriate sample size and dose-response design.

4. Mechanism of Action

4.1 Type I PAM mechanism at the alpha-7 nicotinic acetylcholine receptor

Type I PAMs of the alpha-7 nicotinic receptor are a distinct class of ligands characterized by:

- Binding at an allosteric site distinct from the orthosteric (acetylcholine) binding site
- Lack of direct receptor activation in the absence of orthosteric agonist
- Enhancement of the potency (leftward shift of the agonist concentration-response curve) and efficacy (increase in maximum response) of orthosteric agonists at the receptor
- Preservation of the rapid desensitization kinetics of the channel (the criterion that distinguishes Type I from Type II PAMs)

AVL-3288 satisfies all four Type I PAM criteria. The allosteric binding site has been characterized through electrophysiological mutagenesis studies as a transmembrane region distinct from the orthosteric site at the extracellular domain interface where acetylcholine and the orthosteric agonists bind [1, 2]. The compound enhances acetylcholine-induced channel currents at concentrations of 0.1 to 10 micromolar without producing detectable channel currents in the absence of acetylcholine.

4.2 Preservation of physiological signaling

The preservation of rapid desensitization kinetics is the principal mechanistic feature that distinguishes the Type I PAM mechanism from direct agonist mechanisms. The alpha-7 nicotinic receptor is normally activated by brief (millisecond-scale) acetylcholine pulses at synapses, with the receptor desensitizing rapidly after the pulse and recovering for the next signaling event. This rapid desensitization is essential for the temporal patterning of cholinergic neurotransmission. Direct agonists with slow dissociation kinetics (encenicline, bradanicline, tropisetron at the alpha-7 site) prolong receptor activation beyond the physiological pulse and can

disrupt the temporal patterning. Type I PAMs operate during the brief acetylcholine pulse to enhance the channel response, but allow the rapid desensitization to proceed normally, preserving the temporal pattern.

The therapeutic implications include:

- Reduced off-target receptor activation in tissues with low endogenous acetylcholine concentrations (basal-state enteric tissue, immune cells in homeostasis, peripheral tissues), which may explain the absence in AVL-3288 Phase 1 of the severe gastrointestinal toxicity that triggered the encenicline Phase 3 clinical hold
- Preservation of cholinergic signaling specificity for cortical and hippocampal cognitive circuits, where the alpha-7 nicotinic mechanism is most relevant
- Reduced receptor downregulation and tachyphylaxis with chronic dosing, since the receptor desensitization kinetics are preserved rather than overridden
- Preserved sensitivity to endogenous cholinergic tone, supporting context-dependent enhancement of the cognitive endpoints that align with the user's natural attention and arousal state

4.3 Downstream signaling

The downstream signaling consequences of alpha-7 nicotinic receptor activation are similar regardless of whether the activation is produced by direct agonist or by PAM-augmented endogenous signaling: calcium-dependent activation of calcium/calmodulin-dependent protein kinase II, ERK1/2 mitogen-activated protein kinase pathway activation, 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 [6]. The PAM mechanism therefore engages the same downstream pathway as the agonist class but with different temporal patterning and different tissue specificity.

4.4 Composite pharmacology

AVL-3288 at the studied clinical doses (10 to 30 milligrams) produces plasma free concentrations in the low-micromolar range, consistent with the in vitro EC₅₀ for PAM activity at human alpha-7 nicotinic receptors. Brain penetration in humans

has not been directly measured but is supported by rodent brain-to-plasma ratio data and by the central nervous system biomarker effects (P50 auditory gating) observed in Phase 1a and Phase 1b. The composite mechanism therefore supports central nervous system target engagement at the studied clinical doses through PAM augmentation of endogenous acetylcholine signaling.

5. Pharmacokinetics and Routes of Administration

5.1 Absorption

AVL-3288 is absorbed from the gastrointestinal tract after oral administration. Time to peak plasma concentration after a single oral dose is approximately 2 to 3 hours [3]. Bioavailability has not been directly measured against an intravenous reference; the dose-proportional plasma concentrations across the 5 to 30 milligram range observed in Phase 1a support adequate absorption [3].

5.2 Distribution

Plasma protein binding has not been precisely characterized in published material. Volume of distribution and tissue distribution in humans have not been directly measured; rodent tissue distribution data support brain-to-plasma ratio of approximately 5.

5.3 Metabolism and elimination

Plasma elimination half-life is approximately 8 to 12 hours [3]. The metabolism is hepatic; the principal cytochrome P450 isoforms involved have not been characterized in published material. Renal excretion of unchanged drug is a minor pathway.

5.4 Routes of administration

Oral administration was the only route used in Phase 1a and Phase 1b clinical development. The compound is supplied in oral capsule formulations.

6. Clinical Evidence Base

6.1 Phase 1a (Gee 2017)

The Phase 1a single ascending-dose study in 21 healthy non-smokers tested 5, 10, and 30 milligrams as single oral doses. Findings: safety; dose-proportional pharmacokinetics; positive but non-significant cognitive signals at 10 and 30 milligrams; P50 auditory evoked potential biomarker effects [3].

6.2 Phase 1b (Freedman 2020)

The Phase 1b triple-cross-over study in 24 non-smoking schizophrenia outpatients tested 10 and 30 milligrams over 5-day treatment weeks. Findings: tolerability; P50 auditory gating effects at 30 milligrams; exploratory cognitive signals; no symptom-scale effects [4].

6.3 Preclinical evidence in traumatic brain injury

Sun et al. (2019) characterized AVL-3288 in a rodent model of traumatic brain injury, demonstrating rescue of water maze retention and working memory deficits and rescue of cue and contextual fear memory at 24 hours and 1 month after training [5]. The traumatic brain injury preclinical evidence supports a potential second indication beyond schizophrenia cognitive impairment.

6.4 Preclinical evidence in Alzheimer disease and inflammation models

Preclinical work in Alzheimer disease and in inflammation models has supported the cognitive enhancement and anti-inflammatory profile expected from the alpha-7 nicotinic Type I PAM mechanism. Definitive clinical translation to these indications has not been established.

7. Reported Research Dose Ranges

7.1 Approved doses

None. AVL-3288 has not received regulatory approval.

7.2 Investigational doses

The Phase 1a and Phase 1b doses ranged from 5 to 30 milligrams as single oral doses or 5-day repeated daily dosing. The 30-milligram dose produced the most pronounced biomarker and cognitive signals in Phase 1b and is the principal candidate dose for a future Phase 2 program.

For research applications using AVL-3288 as an alpha-7 nicotinic Type I PAM tool compound, in vitro concentrations are typically 0.1 to 30 micromolar in heterologous expression systems and primary neuronal culture, and rodent in vivo doses are typically 1 to 30 milligrams per kilogram by oral or intraperitoneal administration.

8. Sourcing and Quality Verification

AVL-3288 has not advanced to commercial registration and is not available as a pharmaceutical-grade preparation. Research-grade AVL-3288 is supplied by multiple chemical suppliers (MedChemExpress, Selleckchem, Tocris, MedKoo, BocSci, InvivoChem, others) at moderate prices, typically \$100 to \$300 per gram of the free base at the time of monograph preparation. The simpler synthesis (no chirality required) supports lower cost than the chiral quinuclidine-amide candidates.

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 (388.06 ± 0.01 for the protonated free base $[M+H]^+$)
- Confirmation of the (Z) geometric isomer (the (E) isomer is inactive)
- Karl Fischer or loss-on-drying analysis for residual water
- Residual solvent analysis

9. Reconstitution and Handling

AVL-3288 is sparingly soluble in water and is typically prepared as stock solutions in dimethyl sulfoxide at 10 to 50 millimolar concentrations. Aqueous formulations for in vivo work require co-solvents (cyclodextrin, polyethylene glycol) or suspension formulations. Refrigerated storage of the solid is appropriate; the compound is stable at room temperature in dry conditions.

10. Stack Interaction Considerations

The combination pharmacology of AVL-3288 with orthosteric alpha-7 nicotinic agonists is the principal opportunity for combination research. Investigators should consider:

Orthosteric alpha-7 agonists (encenicline, bradanicline, tropisetron, GTS-21, PHA-543613): Concurrent administration of AVL-3288 with an orthosteric agonist produces compound effects at the alpha-7 receptor. The PAM mechanism amplifies the agonist signal, potentially producing greater functional response at lower agonist concentrations and avoiding the high-concentration off-target effects that may underlie agonist-class toxicities.

Acetylcholinesterase inhibitors: AVL-3288 augments endogenous acetylcholine signaling at alpha-7 receptors. Combination with acetylcholinesterase inhibitors (donepezil, rivastigmine, galantamine) increases endogenous acetylcholine concentrations available for PAM augmentation, producing potentially larger composite effects than either intervention alone.

Antipsychotics: Concurrent second-generation antipsychotic background in schizophrenia patients was the standard concomitant medication context for the Phase 1b study. No specific pharmacokinetic interaction has been characterized.

Nicotine and tobacco: Tobacco status is a known interactor with alpha-7 nicotinic receptor pharmacology. The Phase 1a and Phase 1b studies enrolled non-smokers specifically; the effect of AVL-3288 in tobacco users has not been characterized.

11. Adverse Events and Safety

11.1 Phase 1 safety profile

AVL-3288 was generally well tolerated in Phase 1a (Gee 2017) and Phase 1b (Freedman 2020) clinical development. No clinically significant adverse events were observed at the studied doses (5 to 30 milligrams). Common adverse events were mild and balanced with placebo [3, 4].

11.2 Mechanistic safety advantages of the Type I PAM approach

The Type I PAM mechanism is theoretically expected to produce a more favorable safety profile than the orthosteric agonist class for several reasons:

- Preservation of receptor desensitization kinetics avoids the prolonged receptor activation that may underlie pathological responses to direct agonists
- Dependence on endogenous acetylcholine for activation reduces off-target receptor activation in tissues with low cholinergic tone
- Preservation of spatiotemporal specificity of cholinergic neurotransmission

These theoretical advantages have been supported by the favorable Phase 1 and Phase 1b safety profiles, but require Phase 2 and Phase 3 confirmation at larger sample sizes and longer treatment durations to establish definitive comparison to the orthosteric agonist class.

11.3 Absence of severe gastrointestinal toxicity

Notably, AVL-3288 Phase 1 and Phase 1b did not produce the severe gastrointestinal toxicity (severe nausea, vomiting, gastrointestinal ulceration, gastrointestinal bleeding) that triggered the September 2015 FDA clinical hold on encenicline Phase 3 trials. The Phase 1 sample sizes (21 healthy volunteers, 24 schizophrenia outpatients) are too small to definitively establish absence of the severe gastrointestinal toxicity at the population level, but the absence in the studied populations is consistent with the theoretical safety advantages of the Type I PAM mechanism.

12. Comparable Compounds Assessment

Five alpha-7 nicotinic acetylcholine receptor candidates are evaluated against AVL-3288 on the five competency standards.

12.1 Tropisetron

Mechanism: Multi-target ligand (5-HT₃ antagonist plus alpha-7 partial agonist plus APP ectodomain binding). Orthosteric mechanism at alpha-7 with 25-40 percent intrinsic activity.

Novelty: Moderate. Multi-target mechanism distinct from pure alpha-7 strategies.

Effect size: Modest in cognitive endpoints; strong in fibromyalgia.

Promising potential: Moderate. Registered antiemetic and fibromyalgia indications.

Side-effect profile: Well characterized; constipation, headache.

Overall validation: Moderate to high.

Comparison to AVL-3288: Tropisetron and AVL-3288 are mechanistically distinct (orthosteric partial agonist plus other targets versus pure allosteric modulator) and clinically distinct (registered indications versus Phase 1b). Combination of the two would produce both orthosteric activation and PAM augmentation; the combination has not been characterized in published research.

12.2 Encenicline

Mechanism: Orthosteric alpha-7 partial agonist (60-70 percent intrinsic activity).

Novelty: Moderate.

Effect size: Phase 2 cognitive signals; Phase 3 missed primary endpoints.

Promising potential: Low. Development terminated.

Side-effect profile: Phase 3 severe gastrointestinal toxicity.

Overall validation: Moderate. Phase 3 advancement.

Comparison to AVL-3288: Encenicline (orthosteric partial agonist) and AVL-3288 (allosteric PAM) are mechanistically distinct in the most fundamental sense for the alpha-7 receptor. The encenicline Phase 3 termination, particularly the severe gastrointestinal toxicity component, has been the principal scientific motivation for continued investigation of the AVL-3288 PAM approach as an alternative path forward. AVL-3288's mechanism-based safety advantages remain to be confirmed in larger-scale studies.

12.3 Bradanicline

Mechanism: Orthosteric alpha-7 full agonist (80-90 percent intrinsic activity).

Novelty: Low.

Effect size: Phase 2 mixed results (positive exploratory, negative confirmatory).

Promising potential: Low for cognitive impairment; ongoing for Tourette syndrome.

Side-effect profile: Well tolerated; did not produce the encenicline gastrointestinal toxicity.

Overall validation: Low to moderate.

Comparison to AVL-3288: Bradanicline (orthosteric full agonist) represents the highest-intrinsic-activity end of the orthosteric agonist spectrum; AVL-3288 represents the allosteric alternative. Combination of the two would test whether allosteric augmentation of full-agonist signaling produces additional benefit beyond either alone. The bradanicline Phase 2 confirmatory failure on cognitive endpoints in schizophrenia is consistent with the limitations of orthosteric agonism at this receptor in this indication; AVL-3288's PAM approach remains an alternative.

12.4 GTS-21 (DMXBA)

Mechanism: Orthosteric alpha-7 partial agonist (30-50 percent intrinsic activity); also alpha-4-beta-2 cross-reactivity.

Novelty: Low. Historical reference compound.

Effect size: Modest in early Phase 2; non-significant in larger Phase 2.

Promising potential: Low.

Side-effect profile: Well tolerated.

Overall validation: Moderate. Long clinical history.

Comparison to AVL-3288: GTS-21 is the historical reference compound for the orthosteric partial agonist class; AVL-3288 represents the allosteric alternative. The two compounds are complementary research tools and could be combined to assess additivity of orthosteric partial agonism and PAM augmentation.

12.5 PHA-543613

Mechanism: Highly selective orthosteric alpha-7 full agonist. Preclinical only.

Novelty: Low to moderate.

Effect size: Substantial in preclinical models. No human data.

Promising potential: Limited as clinical candidate; substantial as research tool.

Side-effect profile: Preclinical only.

Overall validation: Low.

Comparison to AVL-3288: PHA-543613 (orthosteric full agonist research tool) and AVL-3288 (allosteric PAM clinical candidate) are mechanistically distinct. Combination research is a productive line for fundamental alpha-7 nicotinic mechanism studies.

12.6 Comparator summary

The five comparators position AVL-3288 as the principal alternative therapeutic concept for the alpha-7 nicotinic receptor target through its allosteric (rather than orthosteric) mechanism. The encenicline Phase 3 termination and the bradanicline Phase 2 confirmatory failure have made the alpha-7 orthosteric agonist class less attractive for further development; AVL-3288's PAM mechanism preserves the alpha-7 nicotinic target as a research-clinical strategy with a distinct mechanism that addresses some of the apparent limitations of the agonist class. The favorable Phase 1 and Phase 1b safety profile of AVL-3288 supports continued investigation, contingent on commercial funding for a Phase 2 program. AVL-3288 is the only Type I PAM with substantive clinical data in the alpha-7 nicotinic receptor space and is therefore the principal contemporary representative of the PAM mechanism for this target.

13. References

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