

RESEARCH MONOGRAPH . COMPOUND PROFILE

Bradanicline

A quinuclidine benzofuran-2-carboxamide developed at Targacept as a selective alpha-7 nicotinic full agonist with a binding affinity of 1.4 nanomolar at the human alpha-7 receptor, advanced through Phase 2 development for cognitive impairment and negative symptoms of schizophrenia with a positive 12-week exploratory trial followed by a negative larger 24-week confirmatory trial, subsequently licensed to Anylyc Therapeutics for Tourette syndrome and other indications.

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ABSTRACT

Bradanicline (development codes TC-5619 and ATA-101) is a small-molecule, highly selective full agonist of the homopentameric alpha-7 subtype of the neuronal nicotinic acetylcholine receptor (alpha-7 nAChR), originated at Targacept Pharmaceuticals (Winston-Salem, North Carolina) from a quinuclidine benzofuran-2-carboxamide chemistry program in the mid-2000s and advanced through Phase 1 and Phase 2 clinical development for cognitive impairment associated with schizophrenia. The compound binds the human alpha-7 nicotinic receptor with a K_i of approximately 1.4 nanomolar, slightly higher affinity than encenicline (K_i approximately 4 nanomolar) and substantially higher affinity than tropisetron at the alpha-7 site, and exhibits functional intrinsic activity of approximately 80 to 90 percent of the acetylcholine maximum response in heterologous expression systems, placing it in the high-efficacy stratum of alpha-7 ligands as a full agonist rather than the partial-agonist class that encenicline and tropisetron occupy. The full-agonist intrinsic activity is the principal medicinal-chemistry differentiator of bradanicline within the broader quinuclidine-amide chemical class. Selectivity over alpha-4-beta-2, alpha-3-beta-4, alpha-3-beta-2, and other neuronal nicotinic subtypes is approximately 100-fold or greater. The compound was advanced through an exploratory Phase 2 trial in 185 schizophrenia patients (Lieberman et al. 2013) at 5 milligrams once daily for 12 weeks, with statistically significant improvement on the Groton Maze Learning Task and on the Scale for Assessment of Negative Symptoms compared to placebo, and a statistically significant drug effect on working memory in the tobacco-using subgroup. A

larger confirmatory Phase 2 trial (Walling et al. 2016) in 477 schizophrenia outpatients across 64 sites at 5 or 50 milligrams once daily for 24 weeks did not support a benefit on negative or cognitive symptoms compared to placebo. Targacept terminated the cognitive impairment program in 2013 and the compound was subsequently licensed to Catalyst Biosciences and to Anvylic Therapeutics for Tourette syndrome and selected other neurological indications. The compound represents a useful research-clinical reference for the alpha-7 nicotinic full-agonist class and for the assessment of whether higher functional intrinsic activity at the receptor produces greater clinical benefit. Bradanicline did not produce the severe gastrointestinal toxicity that triggered the September 2015 FDA clinical hold on encenicline; the safety profile in Phase 2 was well-tolerated with no clinically noteworthy findings reported. The compound 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 full agonist for fundamental pharmacology research. This monograph reviews the chemistry, synthesis, and stereochemistry of bradanicline; the receptor pharmacology in detail; the human pharmacokinetic record; the indication-by-indication clinical evidence base; and a structured comparative assessment of five alpha-7 nicotinic acetylcholine receptor candidates against bradanicline on five competency standards.

1. Compound Identification

1.1 Names, synonyms, and registry identifiers

International Nonproprietary Name: Bradanicline.

Development codes: TC-5619 (Targacept), ATA-101 (Anvylic Therapeutics, the licensee for Tourette syndrome development).

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

Chemical Abstracts Service registry numbers: 639489-84-2 (free base), 1111941-90-2 (hydrochloride salt).

International Union of Pure and Applied Chemistry name: N-[(2S,3R)-2-(pyridin-3-ylmethyl)quinuclidin-3-yl]benzofuran-2-carboxamide (free base).

1.2 Structural class and chemistry

Bradanicline is a quinuclidine benzofuran-2-carboxamide bearing a (2S)-pyridin-3-ylmethyl substituent at the 2-position of the quinuclidine ring. The structural class is the same quinuclidine-amide medicinal-chemistry family that includes encenicline (a quinuclidine benzothiophene-2-carboxamide) and PHA-543613 (a quinuclidine furo[2,3-c]pyridine-5-carboxamide). Within the family, bradanicline is distinguished by:

- The benzofuran heterocycle (versus benzothiophene in encenicline and furo[2,3-c]pyridine in PHA-543613)
- The unique 2-(pyridin-3-ylmethyl) substituent on the quinuclidine ring (the encenicline and PHA-543613 quinuclidines are unsubstituted at this position)
- Two stereocenters (at quinuclidine 2 and 3) versus the single stereocenter at quinuclidine 3 in encenicline and PHA-543613

The 2-(pyridin-3-ylmethyl) group is the principal medicinal-chemistry feature responsible for the high alpha-7 nicotinic selectivity and the full-agonist intrinsic activity profile. The pyridine nitrogen is positioned to interact with the alpha-7 recep-

tor binding pocket in a manner that promotes channel opening rather than receptor occupancy without activation.

Molecular formula: C₂₂H₂₃N₃O₂ (free base); C₂₂H₂₄ClN₃O₂ (hydrochloride).

Exact mass: 361.18 g/mol (free base, monoisotopic).

Molecular weight: 361.45 g/mol (free base); 397.91 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. Stable at room temperature in dry conditions.

Stereochemistry: Bradanicline contains two stereocenters (quinuclidine carbons 2 and 3) and is supplied as the single (2S,3R) diastereomer. The other three stereoisomers (2R,3S; 2S,3S; 2R,3R) are research compounds with substantially reduced affinity for the α -7 nicotinic receptor. Investigators acquiring research-grade bradanicline should confirm diastereomeric purity by chiral high-performance liquid chromatography against a (2S,3R)-reference standard.

1.3 Synthesis

The published synthesis of bradanicline proceeds through asymmetric construction of the (2S)-3-aminoquinuclidine bearing the (3R)-pyridin-3-ylmethyl substituent (the chiral diamine partner, prepared by enantioselective alkylation of the quinuclidine and subsequent functional-group manipulation), synthesis of benzo-furan-2-carboxylic acid (commercially available), and amide coupling of the two fragments using standard peptide-coupling reagents. The two-stereocenter chiral synthesis is more complex than the encenicline single-stereocenter route and is the principal reason bradanicline has higher manufacturing cost than encenicline at equivalent quality. The hydrochloride salt is prepared by addition of stoichiometric hydrogen chloride.

2. Abstract

Bradanicline (TC-5619, ATA-101) is a small-molecule, highly selective full agonist of the alpha-7 subtype of the neuronal nicotinic acetylcholine receptor, originated at Targacept Pharmaceuticals from a quinuclidine benzofuran-2-carboxamide chemistry program. The compound is distinguished within the broader quinuclidine-amide medicinal-chemistry family (encenicline, PHA-543613) by the presence of a (2S)-pyridin-3-ylmethyl substituent at the 2-position of the quinuclidine ring, which produces full-agonist intrinsic activity at the alpha-7 receptor (approximately 80 to 90 percent of the acetylcholine maximum response in heterologous expression systems) versus the partial-agonist intrinsic activity of encenicline (60 to 70 percent) and tropisetron (25 to 40 percent) at the same receptor. The Hauser et al. (2009) report consolidates the in vitro receptor pharmacology, the rodent behavioral pharmacology, and the safety pharmacology that supported clinical development [1].

The compound binds the human alpha-7 nicotinic receptor with a K_i of approximately 1.4 nanomolar against [3H]-methyllycaconitine. Selectivity over alpha-4-beta-2, alpha-3-beta-4, alpha-3-beta-2, and other neuronal nicotinic subtypes is approximately 100-fold or greater; selectivity over the muscle-type alpha-1 nicotinic receptor and over the 5-HT₃ receptor is similar. The receptor pharmacology supports a procognitive, anti-inflammatory, and antinegative-symptom profile characterized in animal models of schizophrenia and Alzheimer disease [1, 2].

The clinical development trajectory comprised an exploratory Phase 2 trial in 185 schizophrenia patients (Lieberman et al. 2013) at 5 milligrams of bradanicline once daily for 12 weeks, with statistically significant improvement on the Groton Maze Learning Task (a hippocampally-mediated spatial learning task) and on the Scale for Assessment of Negative Symptoms compared to placebo, and a statistically significant drug effect on working memory in the tobacco-using subgroup [3]. A larger confirmatory Phase 2 trial (Walling et al. 2016) in 477 schizophrenia outpatients randomized to placebo, 5 milligrams, or 50 milligrams of bradanicline once daily for 24 weeks across 64 sites did not support a benefit on negative or cognitive symptoms compared to placebo [4]. The discrepancy between the exploratory and the confirmatory Phase 2 results has been the subject of substantial scientific commentary and represents a recurring pattern in alpha-7 nicotinic agonist clinical development.

Targacept terminated the cognitive impairment program in 2013 following the negative confirmatory readout. The compound was subsequently licensed to Catalyst Biosciences and to Anylic Therapeutics for Tourette syndrome and selected other neurological indications. The Tourette syndrome program rationale is supported by the alpha-7 nicotinic receptor's expression on cortical interneurons and basal ganglia output neurons and by the cholinergic anti-inflammatory pathway, both of which are implicated in tic disorder pathophysiology. Clinical evidence in this indication is preliminary as of the most recent monograph revision.

The compound was generally well tolerated in the Phase 2 program with no clinically noteworthy safety findings reported [3, 4]. Notably, bradanicline did not produce the severe gastrointestinal toxicity that triggered the September 2015 FDA clinical hold on encenicline. The mechanism of the differential gastrointestinal safety is incompletely characterized and is one of the principal residual scientific questions for the alpha-7 nicotinic agonist class.

This monograph reviews the chemistry, synthesis, and stereochemistry of bradanicline; the dual-stereocenter receptor pharmacology in detail; the limited published human pharmacokinetic record; the clinical evidence base across schizophrenia cognitive impairment and the more recent Tourette syndrome positioning; sourcing, reconstitution, and stack-interaction considerations for laboratory work; the safety record in Phase 2; and a structured comparative assessment of five alpha-7 nicotinic acetylcholine receptor candidates against bradanicline on the five competency standards.

3. Discovery and Development History

3.1 Origin

The quinuclidine benzofuran-2-carboxamide chemistry program that produced bradanicline was developed at Targacept Pharmaceuticals (Winston-Salem, North Carolina), a small biotechnology company specializing in nicotinic acetylcholine receptor drug discovery. Targacept was founded as a spin-out from R.J. Reynolds Tobacco's research program (the parent company had operated nicotine-receptor research as an adjunct to its tobacco business in the 1980s and 1990s). The Targacept platform addressed multiple nicotinic receptor subtypes including α -7, α -4-beta-2, and others.

The bradanicline program was selected from the broader α -7 chemistry effort on the basis of high α -7 selectivity, full-agonist intrinsic activity, brain penetration, and oral bioavailability. The compound was advanced through preclinical safety pharmacology and into Phase 1 development in approximately 2007 to 2008.

3.2 Phase 1 development

The Phase 1 program comprised single ascending-dose and multiple ascending-dose studies in healthy volunteers and in selected patient populations. Detailed Phase 1 pharmacokinetic data have not been published in peer-reviewed form; the available record consolidates the Phase 1 findings within the Phase 2 reports and describes good oral bioavailability, a plasma elimination half-life supporting once-daily dosing, and acceptable tolerability across the studied dose range [3].

3.3 Phase 2 schizophrenia (exploratory)

The Lieberman et al. (2013) Phase 2a study is the principal early-phase clinical readout [3]. The study randomized 185 schizophrenia patients in the United States and India on stable antipsychotic background to placebo or bradanicline 5 milligrams once daily for 12 weeks. Cognitive endpoints included a battery selected for sensitivity to α -7 nicotinic mechanism (the CogState computerized battery,

with the Groton Maze Learning Task as the principal cognitive outcome). Negative symptom endpoints included the Scale for Assessment of Negative Symptoms (SANS).

Results showed:

- Statistically significant improvement on the Groton Maze Learning Task at week 12 (effect size Cohen's d approximately 0.4, $p < 0.05$)
- Statistically significant improvement on the SANS total score ($p < 0.05$)
- Statistically significant working memory improvement in the tobacco-using subgroup (a pre-specified analysis based on the established interaction of nicotine with alpha-7 nicotinic receptor function in schizophrenia)
- Acceptable tolerability with no clinically noteworthy safety findings

The exploratory Phase 2a study results supported initiation of the larger confirmatory Phase 2 trial.

3.4 Phase 2 schizophrenia (confirmatory)

The Walling et al. (2016) Phase 2b study randomized 477 schizophrenia outpatients across 64 sites to placebo, bradanicline 5 milligrams, or bradanicline 50 milligrams once daily for 24 weeks [4]. The 50 milligram dose was a 10-fold escalation from the 5 milligram dose tested in the Lieberman study and was selected to test for dose-response and for the possibility that the Lieberman 5 milligram dose was at the bottom of the effective range.

Results did not support a benefit on the cognitive or negative-symptom co-primary endpoints at either dose. The discrepancy with the Lieberman exploratory study has been attributed by various commentators to:

- Larger sample size with greater statistical power exposing a true small-or-zero effect that the exploratory study had inflated
- Different patient populations (multinational versus US/India), different antipsychotic background, different concomitant medication patterns
- Different cognitive batteries with different sensitivity to alpha-7 nicotinic mechanism
- Treatment duration (24 weeks versus 12 weeks) with possible tachyphylaxis or compensation mechanisms

- The 50-milligram dose introducing a dose-response deviation through receptor desensitization or off-target activity not present at 5 milligrams

The confirmatory negative readout led to termination of the schizophrenia cognitive impairment program by Targacept in late 2013 (the Targacept commercial pipeline overall was wound down in 2013-2014 following the Phase 3 failure of varenicline in nicotine cessation).

3.5 Subsequent licensing and Tourette syndrome program

The bradanicline asset was subsequently licensed to Catalyst Biosciences and then to Anylic Therapeutics for Tourette syndrome and selected other neurological indications. The Tourette syndrome program rationale draws on the alpha-7 nicotinic receptor's expression on cortical interneurons and on basal ganglia output neurons and on the cholinergic anti-inflammatory pathway, both of which are implicated in tic disorder pathophysiology. Anylic conducted a Phase 1b study and has indicated continued development; clinical evidence in this indication is preliminary as of the most recent monograph revision.

4. Mechanism of Action

4.1 Alpha-7 nicotinic acetylcholine receptor full agonism

Bradanicline binds the alpha-7 nicotinic receptor at the orthosteric (acetylcholine) binding site with a K_i of approximately 1.4 nanomolar at human alpha-7 expressed in cell-line systems against [3H]-methyllycaconitine [1]. The binding affinity is slightly higher than encenicline (K_i approximately 4 nM) and substantially higher than the alpha-7 partial agonists tropisetron (K_i approximately 7 nM, but 25-40 percent intrinsic activity) and GTS-21.

Functionally, in *Xenopus* oocyte and HEK293 expression systems, bradanicline acts as a full agonist with intrinsic activity of approximately 80 to 90 percent of the maximum acetylcholine response. The functional EC_{50} in heterologous systems is in the low-micromolar range. The full-agonist intrinsic activity profile distinguishes bradanicline from the partial-agonist class (encenicline at 60-70 percent, tropisetron at 25-40 percent, GTS-21 at 30-50 percent) and supports the medicinal-chemistry hypothesis that higher intrinsic activity at the alpha-7 receptor would translate to greater clinical efficacy in cognitive applications.

The clinical translation of this hypothesis has been mixed. The Lieberman et al. (2013) exploratory Phase 2 study demonstrated cognitive improvement consistent with the full-agonist intrinsic activity profile. The Walling et al. (2016) confirmatory Phase 2 study did not. The discrepancy raises the question of whether higher functional intrinsic activity at the receptor is associated with greater clinical benefit; the answer in the bradanicline program appears to be "not necessarily," and informs the broader scientific assessment of whether the alpha-7 nicotinic agonist mechanism is sensitive to the partial-versus-full agonist distinction at clinical doses.

4.2 Selectivity profile

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 selec-

tivity profile is high and is comparable to encenicline; both compounds substantially exceed GTS-21 (which has alpha-4-beta-2 cross-reactivity) in receptor selectivity.

4.3 Downstream signaling and behavioral pharmacology

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 transcriptional upregulation of brain-derived neurotrophic factor and nerve growth factor. The cholinergic anti-inflammatory pathway is the second principal alpha-7 mechanism, with activation of alpha-7 nicotinic receptors on macrophages suppressing NF-kappaB-driven proinflammatory cytokine release [5].

In rodent behavioral models, bradanicline reverses scopolamine-induced and apomorphine-induced cognitive deficits, improves novel object recognition memory, attenuates phencyclidine-induced behavioral deficits relevant to schizophrenia (sensorimotor gating, social withdrawal), and produces antidepressant-like effects in the forced swim and tail suspension tests [1]. The composite preclinical pharmacology supported the schizophrenia cognitive impairment program rationale.

4.4 Composite pharmacology

The composite pharmacology of bradanicline at clinical doses (5 to 50 milligrams) produces plasma free concentrations in the low-nanomolar range. At this concentration, the alpha-7 nicotinic receptor is partially saturated (K_i approximately 1.4 nanomolar), and functional channel activation is supported by full-agonist intrinsic activity that produces near-maximum channel currents at occupied receptors. Brain penetration is high (brain-to-plasma ratio approximately 5 to 10 in rodent species), supporting central nervous system exposure.

5. Pharmacokinetics and Routes of Administration

5.1 Absorption

Bradanicline is well absorbed from the gastrointestinal tract after oral administration. Detailed published pharmacokinetic data are limited; the available record describes good oral bioavailability and dose-proportional kinetics across the studied range [3, 4].

5.2 Distribution

Plasma protein binding has not been precisely characterized in published material; tissue distribution in rodent species supports moderate brain penetration. Volume of distribution and brain-to-plasma ratio are similar to other quinuclidine-amide alpha-7 ligands.

5.3 Metabolism

Bradanicline is metabolized hepatically by cytochrome P450 enzymes; the principal isoforms have not been fully characterized in published material. The compound is unlikely to be a major CYP2D6 substrate based on the chemical structure. CYP3A4 contribution is plausible.

5.4 Elimination

Plasma elimination half-life supports once-daily oral dosing. Specific half-life values have not been published in detail in peer-reviewed form; the registered Phase 2 dosing was once daily oral administration for 12 to 24 weeks.

5.5 Routes of administration

Oral administration was the route advanced through Phase 2 clinical development. Intravenous and other parenteral routes were not pursued for clinical use.

6. Clinical Evidence Base

6.1 Phase 1

Limited published Phase 1 data. The Phase 1 program characterized single ascending-dose pharmacokinetics, multiple ascending-dose pharmacokinetics, and tolerability across the 1 to approximately 100 milligram dose range. Tolerability was good across the studied range and informed the Phase 2 dose selection of 5 milligrams.

6.2 Phase 2 schizophrenia (Lieberman 2013)

The exploratory Phase 2 study in 185 schizophrenia patients on stable antipsychotic background, randomized to placebo or bradanicline 5 milligrams once daily for 12 weeks, reported [3]:

- Significant improvement on the Groton Maze Learning Task at week 12 (Cohen's d approximately 0.4)
- Significant improvement on the Scale for Assessment of Negative Symptoms total score
- Significant working memory improvement in the tobacco-using subgroup (n approximately 80)
- No safety findings of concern

The pattern of cognitive benefit (with the Groton Maze, a hippocampally-mediated learning task, the most affected) was consistent with the expected alpha-7 nicotinic mechanism contribution to hippocampal function. The selective benefit in tobacco users is consistent with the established interaction of nicotine and the alpha-7 receptor in schizophrenia and was a pre-specified subgroup analysis.

6.3 Phase 2 schizophrenia (Walling 2016)

The larger confirmatory Phase 2 study in 477 schizophrenia outpatients across 64 sites randomized to placebo, bradanicline 5 milligrams, or bradanicline 50 milligrams once daily for 24 weeks, did not support a benefit on negative or cognitive

symptoms compared to placebo at either dose [4]. The negative readout led to termination of the schizophrenia cognitive impairment program by Targacept in 2013.

The discrepancy with the Lieberman exploratory study has been the subject of substantial scientific commentary. The principal candidate explanations are:

- Sample size and statistical power: The Lieberman study (n=185) had limited power; the Walling study (n=477) had substantially greater power. A small or zero true effect could be inflated to apparent significance in the smaller exploratory study and not replicated in the larger confirmatory study.
- Patient population heterogeneity: The Walling study was multinational across 64 sites with diverse patient populations and antipsychotic backgrounds, possibly diluting any true effect.
- Cognitive battery sensitivity: Different cognitive batteries with different sensitivity to alpha-7 nicotinic mechanism were used.
- Treatment duration: The 24-week Walling duration may produce tachyphylaxis or compensation that the 12-week Lieberman duration did not.
- Dose response: The 50-milligram dose may have introduced receptor desensitization or off-target activity that compromised the cognitive benefit at the higher dose.

The negative confirmatory readout, in conjunction with the encenicline Phase 3 failure two years later, has been a principal scientific event in the alpha-7 nicotinic agonist class's contemporary trajectory.

6.4 Tourette syndrome

The Anvylic Therapeutics Tourette syndrome program has been initiated; clinical evidence is preliminary as of the most recent monograph revision.

7. Reported Research Dose Ranges

7.1 Approved doses

None. Bradanicline has not received regulatory approval for any indication.

7.2 Investigational doses

The clinical-development doses spanned 5 milligrams to 50 milligrams once daily by oral administration. The Lieberman 2013 study used 5 milligrams; the Walling 2016 study used 5 and 50 milligrams. The Phase 1 single ascending-dose program tested doses up to approximately 100 milligrams in healthy volunteers and was well tolerated.

For research applications using bradanicline as an alpha-7 nicotinic receptor full agonist tool compound, in vitro concentrations are typically 0.1 to 10 micromolar in heterologous expression systems and rodent in vivo doses are typically 0.3 to 10 milligrams per kilogram by oral or intraperitoneal administration.

8. Sourcing and Quality Verification

Bradanicline has not advanced to commercial registration and is not available as a pharmaceutical-grade preparation. Research-grade bradanicline (greater than 98 percent purity) is supplied by multiple chemical suppliers (MedChemExpress, Selleckchem, Tocris, MedKoo Biosciences, BocSci, others) at moderate-to-higher prices than encenicline owing to the more complex two-stereocenter chiral synthesis. Pricing is in the range of \$300 to \$800 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 (362.19 ± 0.01 for the protonated free base $[M+H]^+$)
- Chiral HPLC to confirm diastereomeric purity (greater than 99 percent of the (2S,3R)-diastereomer)
- Karl Fischer or loss-on-drying analysis for residual water in the hydrochloride salt
- Residual solvent analysis

9. Reconstitution and Handling

Bradanicline hydrochloride is freely soluble in water. 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. Refrigerated storage 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.

10. Stack Interaction Considerations

Bradanicline may interact with other drug classes through pharmacodynamic mechanisms. Investigators conducting research should consider:

Acetylcholinesterase inhibitors: Concurrent administration produces additive cholinergic activity. The combination has not been formally characterized in published research but is plausible for combination cognitive enhancement applications.

Other alpha-7 nicotinic agonists or PAMs: Concurrent administration with other alpha-7 candidates produces additive effects at the alpha-7 receptor and may exceed the desensitization threshold. The combination has not been characterized.

Antipsychotics: Concurrent second-generation antipsychotic background was the standard concomitant medication context for the Phase 2 trials. No specific pharmacokinetic interaction has been characterized.

Nicotine and tobacco: The Lieberman 2013 study identified a tobacco-using subgroup with statistically significant working memory improvement on bradanicline that was not observed in non-tobacco users. The interaction of nicotine and the alpha-7 receptor is well established and supports tobacco status as a stratification variable in alpha-7 nicotinic agonist research.

11. Adverse Events and Safety

11.1 Phase 1 and Phase 2 safety profile

Bradanicline was generally well tolerated in Phase 1 and Phase 2 clinical development. The Lieberman 2013 and Walling 2016 reports describe acceptable tolerability with no clinically noteworthy safety findings reported [3, 4]. Common adverse events were mild and balanced with placebo at the studied doses.

11.2 Comparison to encenicline gastrointestinal safety signal

Notably, bradanicline 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 mechanism of the differential gastrointestinal safety between the two structurally similar alpha-7 selective agonists is incompletely characterized and is one of the principal residual scientific questions for the alpha-7 nicotinic agonist class. Candidate explanations include:

- Different intrinsic activity profiles (bradanicline full agonist 80-90 percent; encenicline partial agonist 60-70 percent) producing different effective concentrations at enteric receptors
- Different off-target receptor profiles not yet fully characterized
- Different metabolic profiles producing different gastrointestinal exposures relative to central nervous system exposure
- Different patient populations and dose ranges in the respective Phase 3 programs

The differential safety profile is the principal contemporary scientific argument for continued investigation of bradanicline-class compounds despite the encenicline Phase 3 failure.

12. Comparable Compounds Assessment

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

12.1 Tropisetron

Mechanism: Dual-target ligand (5-HT3 antagonist plus alpha-7 partial agonist) with additional APP ectodomain binding. Alpha-7 intrinsic activity 25-40 percent of the acetylcholine maximum, substantially below bradanicline's 80-90 percent.

Novelty: Moderate. Multi-target mechanism distinct from the pure alpha-7 agonist class.

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

Promising potential: Moderate. Registered antiemetic and fibromyalgia indications outside the United States.

Side-effect profile: Well characterized. Constipation, headache, transient hypertension. Did not produce severe gastrointestinal toxicity.

Overall validation: Moderate to high.

Comparison to bradanicline: Tropisetron's lower alpha-7 intrinsic activity (partial agonist) and dual-target mechanism (5-HT3 antagonism, APP binding) are mechanistically distinct from bradanicline's high-intrinsic-activity selective alpha-7 full agonism. The compounds are complementary research tools; tropisetron's clinical registration provides operational availability that bradanicline lacks.

12.2 Encenicline

Mechanism: Selective alpha-7 partial agonist with intrinsic activity of approximately 60 to 70 percent of the acetylcholine maximum, intermediate between tropisetron and bradanicline.

Novelty: Moderate.

Effect size: Phase 2 cognitive signals (Cohen's d 0.3-0.4); Phase 3 missed primary endpoints.

Promising potential: Low. Development terminated.

Side-effect profile: Phase 3 severe gastrointestinal toxicity triggered FDA clinical hold; did not occur in bradanicline development.

Overall validation: Moderate. Phase 3 advancement.

Comparison to bradanicline: Encenicline is the closest mechanistic comparator. The differential intrinsic activity (encenicline partial agonist; bradanicline full agonist) and the differential safety profile (encenicline gastrointestinal toxicity; bradanicline acceptable safety) are the principal differentiators. The combined Phase 3 failure (encenicline) and Phase 2 confirmatory failure (bradanicline) on cognitive endpoints in schizophrenia have materially reduced enthusiasm for the alpha-7 nicotinic agonist class as a single-target strategy.

12.3 AVL-3288

Mechanism: Type I positive allosteric modulator (PAM) of alpha-7. Acts at allosteric site distinct from the orthosteric (acetylcholine) site; enhances agonist-induced channel currents without direct receptor activation in the absence of agonist.

Novelty: High. Mechanistically distinct from all the agonist comparators.

Effect size: Phase 1b cognitive signals are modest and exploratory.

Promising potential: Moderate. Novel mechanism with theoretical safety advantages.

Side-effect profile: Phase 1 and Phase 1b favorable.

Overall validation: Low to moderate.

Comparison to bradanicline: AVL-3288 is the most mechanistically distinct comparator. The PAM mechanism is theoretically expected to preserve endogenous cholinergic signal patterning that bradanicline's full agonism does not.

Combination of bradanicline (agonist) and AVL-3288 (PAM) is a plausible research strategy that could produce greater functional alpha-7 receptor activation at lower individual-component concentrations.

12.4 GTS-21 (DMXBA)

Mechanism: Partial agonist at alpha-7 with intrinsic activity 30-50 percent; partial agonist or antagonist at alpha-4-beta-2 (substantially less selective than bradanicline).

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 in Phase 1 and Phase 2.

Overall validation: Moderate. Long clinical research history.

Comparison to bradanicline: GTS-21 is the historical reference compound that predates bradanicline. Bradanicline's higher selectivity (alpha-7 over alpha-4-beta-2 by 100-fold or greater versus GTS-21's mixed activity) and higher intrinsic activity (full agonist versus partial agonist) were medicinal-chemistry refinements over the GTS-21 baseline. The clinical results have not validated these refinements as producing greater clinical benefit at the registration threshold.

12.5 PHA-543613

Mechanism: Highly selective alpha-7 full agonist (similar to bradanicline). Brain penetration and oral bioavailability characterized in rodent species. Has not been advanced to human clinical trials.

Novelty: Low to moderate. Conventional mechanism.

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

Promising potential: Limited as a clinical candidate. Substantial as a research tool.

Side-effect profile: Preclinical only.

Overall validation: Low.

Comparison to bradanicline: PHA-543613 is the closest preclinical analog to bradanicline by intrinsic activity (both are high-intrinsic-activity selective alpha-7 agonists) and by chemical structure (both are quinuclidine-amides). The principal differentiator is clinical development: bradanicline has Phase 2 clinical data (positive exploratory, negative confirmatory); PHA-543613 has only preclinical data. PHA-543613 serves as a complementary research tool for fundamental mechanism research.

12.6 Comparator summary

The five comparators position bradanicline within the alpha-7 nicotinic full-agonist class with distinct mechanistic and clinical features. The principal scientific contribution of bradanicline to the broader class is the demonstration that high alpha-7 selectivity and high functional intrinsic activity at the receptor are not sufficient to produce reproducible clinical benefit in schizophrenia cognitive impairment at the studied doses. The combined Phase 2 confirmatory failure of bradanicline (Walling 2016) and the Phase 3 failure of encenicline (March 2016) constitute the principal contemporary scientific evidence against the selective alpha-7 nicotinic agonist mechanism as a sufficient strategy for schizophrenia cognitive enhancement. The mechanism remains an active research target through PAM (AVL-3288), dual-target (tropisetron), and combination (PHA-543613 plus memantine) approaches; the bradanicline Tourette syndrome program through Anvylic Therapeutics is the principal continuation of the bradanicline development trajectory in a different therapeutic context.

13. References

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